Morpholine
Processing

Identification

Chemical Name(s):
Tetrahydro-2*H*-1,4-oxazine

CAS Number:
110-91-8

Other Names:
Tetrahydro-1,4-oxazine; tetrahydro-*p*-oxazine
diethylene oxamide, diethylene imidoxide

Other Codes:
RTECS QD6475000
DOT ID 2054 29
NIOSH Registry Number: QD6475000
UN/ID Number: UN2054

Summary of Advised Recommendation[*]

Synthetic / Non-Synthetic:	Allowed or Prohibited:	Suggested Annotation:
Synthetic	*Prohibited*	*None.*

Characterization

Composition:
C_4H_9NO

Properties:
Classified as a lower aliphatic secondary amine (Turcotte and Johnson, 1992). A mobile, hygroscopic liquid, with a characteristic amine odor, morpholine is miscible in water with the formation of some heat (Budavari, 1996). Forms a strong base in aqueous solution that is volatile with steam. The mixture of morpholine and water does not have a constant boiling point. Therefore morpholine in aqueous solution is not easily separable by distillation or entraining. Flash point: 100°F. (38°C.). Melting point: -4.9° C. Boiling point at 760mm pressure: 128.9°C. Surface tension at 20°C: 37.5 dynes/cm. Viscosity at 20°C: 2.23cp. (Budavari, 1996).

How Made:
First prepared in 1898 by dehydration of diethanolamine (Budavari, 1996). Also produced by reaction of diethylene glycol and ammonia (Ashford, 1995).

Specific Uses:
The petitioned use is as a boiler chemical. It is also used as a post-harvest fungicide in fruit waxes (Lewis, 1989), a systemic fungicide for field use (Meister, 2000). Other FDA approved uses include as an adhesive; a fungicidal coating for paper and cardboard; a defoaming agent for pulp and paper; and a corrosion inhibitor for steel and tinplate (See Table 1). Solvent for casein, dyes, resins and waxes (Budavari, 1996). Morpholine has many derivatives including the production of insecticides and herbicides (IPCS, 1996), to produce pharmaceuticals such as anesthetics and antiseptics. It is a rubber accelerator; component of waxes and polishes; optical brightener for detergents; preservative for book paper; organic intermediate; antioxidant (NTP, 2001).

---

[*] *This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the requirements of the Organic Foods Production Act to the best of the investigator's ability, and has been reviewed and commented on by experts on the TAP. The substance is evaluated against the criteria found in section 2119(m) of the OFPA (7 USC 6517(m)). The information and advice presented to the NOSB is based on the technical evaluation against that criteria, and is not intended to incorporate commercial availability, socio-economic impact, or any other factor that the NOSB and the USDA may want to consider in making their decisions.*

Table 1	
FDA Approved Uses of Morpholine	
Use	**21 CFR**
Food coating (wax)	172.235
Boiler water additive	173.310
Adhesive	175.105
Paper coating	176.180
Defoaming agent (paper)	176.210
Corrosion inhibitor	178.3300
Source: EAFUS, 2001.	

Action:
Neutralizes carbonic acid in steam and steam condensates.

Combinations:
Morpholine is a highly versatile industrial chemical with hundreds of applications and is found in many product combinations. Used as a boiler water additive in conjunction with cyclohexylamine and diethylaminoethanol. Also used in systems with octadecylamine. Used as a preservative in fruit wax. Used as a coating in various waxed cardboard boxes.

Status

OFPA
Equipment cleaner [7 USC 6517(c)(1)(B)(I)].

Regulatory

EPA -
Morpholine is on the 1996 Master Test List for the Toxic Substances Control Act. (61 *Fed. Reg.* 65936, 13 Dec 1996; 57 *Fed. Reg.* 61240, 23 Dec 1992). It is also covered under the proposal Report On Volume, Exposure (45 *Fed. Reg.* 13646, 29 Feb 1980). EPA proposed to require manufacturers and processors of morpholine to report production and exposure-related data, which will be used for ranking substances for investigation and for preliminary risk assessments (45 *Fed. Reg.* 13646, 29 Feb. 1980), and was removed from this list in 1982 (47 *Fed Reg.* 38780).

Morpholine is designated a Volatile Organic Compound (VOC) subject to compliance with the emission standards set forth in subpart VV of the Clean Air Act (40 CFR Part 60.489).

Morpholine is an EPA registered pesticide and also appears on EPA Inert Ingredients List 3.

NIEHS - National Toxicology Program Data (2001).

Toxicity
Acute Toxicity: (abbreviations)

dose	mode	specie	amount	unit
LD50	orl	rat	1,050	mg/kg
LC50	ihl	rat	8,000	ppm/8H
LD50	orl	mus	1,200	mg/kg
LC50	ihl	mus	1,320	mg/m3
LD50	ipr	mus	413	mg/kg
LD50	skn	rbt	500	mg/kg
LD50	orl	mam	1,220	mg/kg
LD50	ihl	mam	12,000	mg/m3

AQTX/TLM96: 1000-100 ppm

Sax Toxicity Evaluation:
THR: High via dermal and moderate via oral routes. Irritant to skin, eyes, and mucous membrane.

Carcinogenicity: Not available.

Tumorigenic Data: Not available.

TDLo: orl-mus 2560 mg/kg/Y-C
Review: IARC Cancer Review: Animal Inadequate Evidence
IARC: Not classifiable as a human carcinogen (Group 3)

Mutagenicity: Not available

Teratogenicity: Not available

Other Toxicity Data:
Skin and Eye Irritation Data:
        skn-rbt 995 mg/24H SEV
        skn-rbt 500 mg open MOD
        eye-rbt   2 mg SEV
 Review: Toxicology Review
 Status: "NIOSH Manual of Analytical Methods" Vol. 3 S150
        Reported in EPA TSCA Inventory, 1980
        EPA TSCA 8(a) Preliminary Assessment Information Proposed Rule

Hazard Class: 3   Subsidiary Risk: None   Packing Group: III

Labels Required: Flammable liquid

Packaging: Passenger: Pkg. Instr.: 309, Y309   Maximum Quantity: 60 L, 10 L
            Cargo: Pkg. Instr.: 310   Maximum Quantity: 220 L

Special Provisions: None

Handling Procedures
Acute/Chronic Hazards: This compound is an irritant and is corrosive.

Minimum Protective Clothing: If Tyvek-type disposable protective clothing is not worn during handling of this chemical, wear disposable Tyvek-type sleeves taped to your gloves.

Recommended Glove Materials: Recommended Glove Type For Use With Neat (Undiluted) Chemical: Recommendations based on permeation test results are made for handling the neat (undiluted) chemical. If this chemical makes direct contact with your glove, or if a tear, puncture or hole develops, replace them at once.

Suggested Glove Type(s) (RAD): Butyl rubber, PVA (to 360 minutes)

Recommended Respirator: Where the neat test chemical is weighed and diluted, wear a NIOSH-approved half face respirator equipped with an organic vapor/acid gas cartridge (specific for organic vapors, HCl, acid gas and SO_2) with a dust/mist filter. Splash proof safety goggles should be worn while handling this chemical. Alternatively, a full face respirator, equipped as above, may be used to provide simultaneous eye and respiratory protection.

Storage Precautions: You should store this chemical under refrigerated temperatures, and protect it from moisture. STORE AWAY FROM SOURCES OF IGNITION.

Spills And Leakage: If you should spill this chemical, use absorbent paper to pick up all liquid spill material. Seal the absorbent paper, as well as any of your clothing which may be contaminated, in a vapor-tight plastic bag for eventual disposal. Wash any surfaces you may have contaminated with a soap and water solution. Do not reenter the contaminated area until the Safety Officer (or other responsible person) has verified that the area has been properly cleaned.

Disposal And Waste Treatment: You should dispose of all waste and contaminated materials associated with this chemical as specified by existing local, state and federal regulations concerning hazardous waste disposal. It is suggested that your contaminated materials should be destroyed by incineration in a special, high temperature (>2000 degrees F), chemical incinerator facility.

Skin Contact:
IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently wash all affected skin areas thoroughly with soap and water.
IMMEDIATELY call a hospital or poison control center even if no symptoms (such as redness or irritation) develop.
IMMEDIATELY transport the victim to a hospital for treatment after washing the affected areas.

Inhalation:
IMMEDIATELY leave the contaminated area; take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital. Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used; if not available, use a level of protection greater than or equal to that advised under Respirator Recommendation.

Eye Contact:
First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician.
IMMEDIATELY transport the victim after flushing eyes to a hospital even if no symptoms (such as redness or irritation) develop.

Ingestion:
DO NOT INDUCE VOMITING. Corrosive chemicals will destroy the membranes of the mouth, throat, and esophagus and, in addition, have a high risk of being aspirated into the victim's lungs during vomiting which increases the medical problems. If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center.
IMMEDIATELY transport the victim to a hospital.
If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. Transport the victim IMMEDIATELY to a hospital.

Symptoms: Symptoms of exposure to this compound may include irritation of the eyes, skin, nose, mucous membranes and respiratory tract, nausea, headache, difficult breathing, visual disturbances and coughing.

Other sources –
US Department of Transportation (DOT) Hazardous Materials Table (59 *Fed. Reg.*67395, 29 Dec 1994) [UN2054] [Flammable liquid]

OSHA Permissable Exposure Levels (PEL): 20 ppm, 70 mg/m^3
Skin designation: X (29 CFR 1910.1000).

FDA
Approved by FDA 21CFR 173.310 not to exceed 10 ppm in steam and not approved for contact with milk and milk products.

Status Among U.S. Certifiers

Not allowed by any U.S. Certifier. See the discussion regarding boiler water additives in general in the background paper, Steam Generation in Organic Food Processing Systems (Steam Paper).

International

In a United Nations sponsored review of the environmental and health impacts of morpholine, the United States was the only country mentioned as permitting food additive applications, including application to boiler water. The only other country mentioned in the study was Germany, which forbids the use of morpholine in water-repellent packaging (IPCS, 1996).

Canada – Not included in the list of permitted non-organic additives substances for organic food products (CGSB, 1999).

CODEX- Not in Annex 2, Table 4, 'Processing Aids' (FAO/WHO, 1999).

EU 2092/91 – Not in Annex VI, 'Processing Aids' (EU 2092/91).

IFOAM – Not on Appendix IV, approved processing aids and other products (IFOAM, 2000).

Japan — Not on the list of approved food additives (Woolsey, 2000).

OFPA 2119(m) Criteria

(1)   The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems.
As this is a processing material, the substance is not used in organic farming systems. Chemical interactions within a processing environment are discussed in the Steam Paper.

(2)   The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment.
See processor criteria (3) below.

(3)   The probability of environmental contamination during manufacture, use, misuse or disposal of such substance.
This is considered below under item (2).

(4)   The effect of the substance on human health.
This is considered in the context of the effect on nutrition (3) below as well as the consideration of GRAS and residues (5) below.

(5)   The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock.
Morpholine is not being reviewed for applications where it is released into the agroecosystem, there is no direct effect.

(6)   The alternatives to using the substance in terms of practices or other available materials.
See discussion of alternatives in the Steam Paper.

(7)   Its compatibility with a system of sustainable agriculture.
This is considered more specifically below in the context of organic handling in (6) below.

Criteria from the February 10, 1999 NOSB Meeting

A PROCESSING AID OR ADJUVANT may be used if;

1. *It cannot be produced from a natural source and has no organic ingredients as substitutes.*
   Morpholine cannot be produced from natural sources and has no organic ingredients as substitutes. When considering chemical means to condition steam lines in boiler systems, the additives to the steam lines must be volatile, so that they purposely travel along with the steam. There are no known non-synthetic boiler additives that can serve this purpose. However, steam can be produced from water without the addition of boiler water additives. A list of substances that are FDA approved for boiler water contact is attached. While these are not direct substitutes, these are available options. The NOSB has already recommended that several of these be listed. See the Steam Paper for more discussion.

2. *Its manufacture, use, and disposal do not have adverse effects on the environment and are done in a manner compatible with organic handling.*
   Produced from ammonia and diethylene glycol. The environmental consequences of the manufacture of ammonia is discussed in the TAP review of ammonium hydroxide. Diethylene glycol is manufactured from ethylene oxide and glycol, a fatty acid alcohol. Ethylene glycol is listed as a hazardous material under EPCRA (40 CFR 355 Appendix A). Production of morpholine requires energy input to drive the synthetic reactions needed to make the material. In the case of synthesis from diethylene glycol and ammonia, energy input is also needed.

   NIOSH and IPCS recommends a variety of protective measures for persons working with this material, including skin and eye protection, and good ventilation (OSHA, 1978; IPCS, 1993) or (by certain manufacturers) respirators (Air Products & Chemicals). Short-term exposure can result in irritation of the skin, lungs, throat, eyes, and nose (OSHA, 1978; IPCS, 1993; Mallinkrodt Baker). Potential hazards of overexposure are visual disturbance, nose irritation, coughing, respiratory irritation, eye and skin irritation, and liver and/or kidney damage (Budavari, Mallinkrodt Baker). It has been shown to cause chronic respiratory disease, liver disease, kidney disease, eye disease (corneal edema), and hypersensitization of the skin (OSHA, 1978). Morpholine is chemically stable in the biosphere, and is not expected to degrade in water environments. Special attention should be given to water organisms (OSHA, 1978; IPCS, 1996).

   Morpholine is flammable and a very dangerous fire hazard when exposed to flame, heat, or oxidizers, and can react with oxidizing materials. Toxic gases and vapors may be released in a fire involving morpholine; when heated to decomposition it emits toxic fumes of nitrogen oxides (Lewis, 1989). The vapor may travel considerable distance to sources of ignition and flash back.

3. *If the nutritional quality of the food is maintained and the material itself or its breakdown products do not have adverse effects on human health as defined by applicable Federal regulations.*
   Morpholine is miscible with water, and forms an azeotrope. Morpholine is rated as very toxic (Gosselin, Smith, and Hodge, 1984). Animals exposed to morpholine showed liver and kidney damage (OSHA, 1978). Morpholine by itself is not considered carcinogenic (NTP, 2001). However, morpholine is a secondary amine known to form nitrosamines (Turcotte and Johnson, 1992). When reacted with nitrates and nitrites, morpholine will form N-nitrosoamines, such as N-nitrosomorpholine (NMOR) (IPCS, 1996). N-nitrosamines are either known or suspected carcinogens, and NMOR is considered a possible human carcinogen by the IARC and an anticipated human carcinogen by the National Toxicology Program (NTP, 2001). Morpholine will also form carbamates under conditions that appear to be antagonistic to forming NMOR (Kirsch, et al., 2000).

4. *Its primary purpose is not as a preservative or used only to recreate/improve flavors, colors, textures, or nutritive value lost during processing except in the latter case as required by law.*
   The primary use is to prevent corrosion of equipment. Because it forms an azeotrope, morpholine will carry over in the steam and will come into direct contact with food exposed to live steam that has been treated with morpholine as an additive. Morpholine is also used as a preservative, primarily with fruit waxes. It is also used in waxed boxes. It is not used to recreate/improve flavors, colors, textures, or nutritive value lost during processing.

5. *Is Generally Recognized as Safe (GRAS) by FDA when used in accordance with Good Manufacturing Practices (GMP), and contains no residues of heavy metals or other contaminants in excess of FDA tolerances.*
   Morpholine is not Generally Recognized as Safe (GRAS). The FDA sets a threshold for its use in steam that is in contact with food because of its toxicity. Morpholine is on the FDA Priority-Based Assessment of Food Additives (PAFA) File (CFSAN, 1998).

   Food Chemicals Codex (1996) specifications for Morpholine require the following:

   Assay: Not less than 99.0%
   Distillation range: Between 126.0° and 130.0° C.
   Heavy metals (as Pb): Not more than 1 mg/kg
   Refractive index: Between 1.454 and 1.455 at 20° C.
   Specific gravity: Between 0.994 and 0.997 at 20° C.

6. *Its use is compatible with the principles of organic handling.*
   Organic standards are precautionary when evaluating synthetic substances used in food. Volatile amines in general, and morpholine in particular, do not appear to be compatible with the principles of organic handling. They are synthetic, toxic, and are not necessary to produce any food. Given the environmental impacts of the manufacturing process and the adverse health effects from exposure, they do not fit within organic principles. Food processors generated and used steam for a long time without these chemicals. Many organic food processors have already adopted viable and practical ways to address corrosion.

7. *There is no other way to produce a similar product without its use and it is used in the minimum quantity required to achieve the process.*
   Culinary steam can be produced without the use of this chemical. See the Steam Paper and reviewers' comments for a further discussion.

TAP Reviewer Discussion*

<u>*Reviewer 1 [Food Science and Nutrition Professor with inspection and certification experience]*</u>
Morpholine is a neutralizing type of boiler additive that is a volatile amine type. Review of the available literature indicates that it is a neutralizing volatile amine type and is a common component of boiler additives used to maintain steam efficiency and reduce corrosion of non-stainless steel steam lines.

Morpholine is a secondary amine, chemically, which has been shown to form N-nitrosomorpholine at physiological pH in a variety of mammalian cells. N-nitrosomorpholine is in a class of powerful carcinogens known as nitrosamines which have been well studied in the literature and whose carcinogenicity is unquestioned. Additionally, morpholine has been shown to cause pulmonary edema, liver necrosis and renal tubular degeneration at vapor levels of concentration. It has also been reported that persons with a history of chronic respiratory, liver, kidney, eye or skin disease may be at increased risk from exposure.

I feel the literature is replete with substantial evidence that morpholine presents a worker safety risk as well as the ability to be converted metabolically in cells to nitrosamines. This is not consistent with the basis of the scientific principles of organic food processing. It is interesting to note that the United States is the only country permitting the use of morpholine in boilers which produce steam for food processing plants in a UN sponsored review. Additionally it is not a GRAS compound as determined by FDA.

---

* *OMRI's information is enclosed in square brackets in italics. Where a reviewer corrected a technical point (e.g., the word should be "intravenous" rather than "subcutaneous"), these corrections were made in this document and are not listed here in the Reviewer Comments. The rest of the TAP Reviewer's comments are edited for identifying comments, redundant statements, and typographical errors. Any text removed is identified by ellipses [. . .] Statements expressed by reviewers are their own, and do not reflect the opinions of any other individual or organization.*

Furthermore, no US certifier allows its use. Overall because of its toxicity and potential to be converted *in vivo* to nitrosamines it is not compatible with any system of sustainable agriculture.

There are a number of alternatives that processors may consider in lieu of using volatile amines such as morpholine.

    A. Install an in-line lock out valve that shuts down the feed line of the boiler additive followed by a purge of the steam line prior to organic processing. This approach may be appropriate for those processing companies who conduct organic processing on an intermittent annual basis.

    B. Mechanical deaereation of boiler feed water to remove soluble gasses such as O_2 and Co_2.

    C. Pumping boiler feed water through ion exchange systems to remove carbonate and bicarbonate hardness components to reduce the rate and amount of CO_2 and H_2CO_3 generated which may preclude the need for a neutralizing amine.

    D. Install stainless steel steam lines which are much more resistant to corrosion.

Therefore exclusion of morpholine should not present any undue hardship for companies certified to produce organic products.

I agree that morpholine is synthetic and should be prohibited from operations where there is direct steam to food contact. I justify this annotation on the basis that if steam is used to indirectly heat food through a heat exchange system then the steam is in a closed loop design and presents minimal risk to the food as well as to plant personnel.

<u>Advised Recommendation to NOSB</u>
1.   Synthetic
2.   Prohibited
3.   Suggested annotation: for processing operations where there is direct steam to food contact.

Reviewer 2 [Consultant to organic certifiers]

Morpholine is a synthetic material . . . *[used]* as an additive to steam *[that]* comes into direct contact with organic foods during processing. The function of the morpholine is to neutralize carbonic acid which forms from the steam generation system; neutralization of the acidic condensate stream reduces corrosion of boiler equipment, most notably steam lines.

Morpholine is also used as an ingredient in waxes and polishes and as a component of protective coatings on fresh fruits and vegetables (Winter, 1994). These uses will not be substantively covered in this review, as this is not the petitioners' request, but it could be deduced from the arguments below that these uses do not meet with acceptability under the OFPA and NOSB criteria for organic foods production.

<u>Comments Based on the Criteria</u>
While it is likely that not all processing conditions may result in the formation of carbamates or nitrosamines, it is currently not possible to categorically exclude certain manufacturing processes or product formulations to ensure that these toxic by-products will be avoided.

Historically, NOSB recommendations have been against the contact of any synthetic boiler additives with organic foods. All organic production and processing standards are in agreement that toxic substances should not contaminate organic foods. Organic certifiers in the United States, if they take a position at all on this issue, are consistent in repeating the prohibition recommended by the NOSB.

Live steam can be and is produced in many processing systems without the use of any boiler additives that carry over onto the food products. Boiler water can be treated in advance of use in the system by a variety of methods to soften, deionize, filter, and otherwise purify it. These steps reduce the need for addition of synthetic materials not on the National List to the boiler system. In some applications, the steam or heating system for the food may be changed to one where live steam is not the active agent, but rather heating (of food contents directly, or of steam in contact with food) is done via a heat exchange system. The wide variety and individuality of processing systems which exist is indicative of the many ways in which the full range of processed food products can be made, without the need for toxic boiler additives to be used in contact with

organic foods. This reviewer does not know of any food product type that absolutely requires morpholine in steam which contacts organic food.

Justification of use of morpholine by the petitioners is based on the constraints of their particular boiler and steam systems as they currently exist, and on the financial and/or logistical challenges involved with changing those systems so as to avoid contact of the organic food by the morpholine. However, economic considerations are clearly not one of the criteria— either in OFPA or the final NOP rule— for determining the suitability of materials used in organic production systems.

History shows that quite often it has been the case that an organic operator (producer or handler) has had to make substantial changes to their system in order to be compliant with organic standards. These changes often involved redesigning of systems, practices, and techniques. In many cases, such changes resulted in the need for financial investment, as well as an investment in time. Some creativity on the part of the operator was often needed, to devise a new system. This has indeed been the case for certain processors, who made adjustments to their boiler systems or manufacturing practices in order to comply with the prohibition of contact of organic foodstuffs by synthetic boiler chemicals. The inconvenience of having to retool or readjust systems should not be the determining factor in whether or not such materials are added to the National List.

For certain processors, where organic processing events are not frequent, the boiler may be operated without the morpholine for a limited time, without significant affect on the boiler or steam line system. For these operations, no retooling may be needed; instead, a procedure can be designed whereby it is verifiable that the volatile boiler chemical has been exhausted from the system prior to handling the organic goods.

For processors who intend to process frequently enough, or for long enough run times, redesigning of the system will be necessary, in one way or another. Prohibition on the use of volatile boiler chemicals can exist without consigning processors to premature deterioration of their equipment. It is often the case in industry that the creative process involved in redesigning systems has unpredicted benefits (short- and long-term) to the operator and the environment, in terms of long-tern cost-effectiveness and sustainability; efforts in this direction should be encouraged, especially if not doing so results in a compromise of organic principles.

In fact, running boiler equipment designed for use with synthetic additives without the additives in place does lead to deterioration, and consequently lower efficiency of the system, which generally means greater energy consumption (Kohan, 1997). While greater efficiency of energy consumption seems undoubtedly to be desirable (both economically and ecologically), energy balance as a whole has not been considered as factor by the NOSB or certifiers when making determinations on the compatibility or allowability of materials or methods. To use such a factor as a criterion in the case for the volatile boiler additive is therefore inconsistent with the rest of the paradigm, and should not be a determining factor at this time.

<u>Advised Recommendations to the NOSB</u>
Morpholine should be deemed a synthetic, prohibited material, and not be added to the National List for any purpose.

<u>*Reviewer 3 [University staff in Food Science with inspection, consulting, and certification experience]*</u>
Morpholine is petitioned for use as a steam additive chemical to reduce corrosion in pipes. There could be direct food contact in many processing operations when steam is used to cook or heat food, such as in a blancher, cooker, canner, or other operations. Morpholine has no functionality toward the food. Morpholine is rated as very toxic. This would make its use of concern to the organic industry. While morpholine is not rated as carcinogenic, the formation of N-nitrosomorpholine (NMOR) upon reaction with nitrites and nitrates is of serious concern. There is sufficient evidence of potential adverse effects that precautionary action does not warrant allowing its use.

The justification for use of morpholine is no different than trying to justify the use of a synthetic herbicide like Round-Up for organic farming, just because it provides a cheaper alternative to weed control and does not leave any detectable residue. Organic handling isn't about economics or end product testing, it's the process that's critical when evaluating compatibility with organic principles. Food processors generated and used steam for a long time without these chemicals. Many organic food processors have already adopted viable and practical ways to address corrosion without the use of morpholine.

There are other solutions that could be used to produce the desired result (no corrosion of piping). To summarize many of the citations reviewed, 'use of stainless steel piping completely solves the problem of corrosion.' The justification statement in the petition and the alternative control methods do not mention this as a possible solution. They do mention the costs of capital equipment and provide anecdotal evidence of the life expectancy and replacement needs should boiler water additives not be used, but provide no data to support this. There are numerous tests that can and should be performed periodically to determine the corrosion rates, (even with the use of inhibitors) to insure that equipment is being operated and maintained in a safe and efficient manner. Without confirming studies to show the differences in corrosion rates with and without the use of corrosion inhibitors, it appears that these petitioners are using anecdotal evidence to justify their continued use of cheap toxic chemicals instead of more expensive, but viable alternatives. There are several cited alternatives: stainless steel piping (suitable for all operations); discontinued use during organic processing (some operations); steam to steam heat exchanger (suitable for some operations); secondary boiler for food contact application only (suitable for all operations) that could be used. None of these are necessarily cheap, but all offer a viable alternative to the use of toxic chemicals.

Advised Recommendations to NOSB
Morpholine should not be approved for use as a boiler chemical for organic production.

Conclusion

The reviewers unanimously consider morpholine to be synthetic, and unanimously advise the NOSB to not add morpholine to the National List. Use should remain prohibited in organic handling.

References

See the Steam Paper.

Vol. 2

ind M.

l M. R.

'ilming-

c Co.).

nnel, J.

iational

ʒ. 15, 51

ʒ(2), 565

I, W. A.

c., New

ʒr, New

VE
s, Inc.

AMINES

M o R

K+h Othmer 4th Ed.
© 1992

LOWER ALIPHATIC AMINES

Lower aliphatic amines are derivatives of ammonia with one, two, or all three of the hydrogen atoms replaced by alkyl groups of five carbons or less. Amines with higher alkyl groups are known as fatty amines. The name, chemical formula, molecular weight, CAS Registry Number, and common name or abbreviation of commercially important amines are given in Table 1. Amines are toxic, colorless gases or liquids, highly flammable, and have strong odors. Lower mol wt amines are water soluble and are sold as aqueous solutions and in pure form. Amines react with water and acids to form alkylammonium compounds analogous to ammonia. The base strengths in water of the primary, secondary, and tertiary amines and ammonia are essentially the same, as shown by the equilibrium constants. Values of K_b for some individual amines are given in Table 2.

$$RNH_2 + H_2O \rightleftharpoons RNH_3^+ + OH^-$$

Primary and secondary amines can also act as very weak acids ($K_a \sim 10^{-33}$). They react with acyl halides, anhydrides, and esters with rates depending on the size of the alkyl group(s). With carbon disulfide and carbon dioxide, these amines form alkyl ammonium salts of dithiocarbamic and carbamic acid, respectively, and with isocyanic acid and alkyl or aryl isocyanates, substituted ureas. Reaction with isothiocyanate gives the corresponding thioureas. Primary amines give alcohols with nitrous acid, secondary amines give highly toxic nitrosamines (see N-NITROSAMINES). The lower aliphatic amines are widely used as intermediates in the manufacture of medicinal, agricultural, textile, rubber, and plastic chemicals.

Physical Properties

Table 2 lists the physical properties of the commercially important alkylamines. The fishy odor of methylamines increases from mono- to trimethylamine. In high concentrations, they all have the odor of ammonia. On cooling aqueous solutions, the crystalline hydrates, $CH_3NH_2 \cdot 3H_2O$, $(CH_3)_2NH \cdot 7H_2O$, and $(CH_3)_3N \cdot 10H_2O$ are formed. Methylamine solutions are good solvents for many inorganic and organic compounds. At atmospheric pressure, trimethylamine forms minimum-boiling azeotropes with ammonia and other methylamines. With increasing pressure, the trimethylamine content of the azeotrope decreases and none is formed above 2652 kPa (370 psig). At atmospheric pressure, trimethylamine boils lower than dimethylamine; this order is reversed at about 446 kPa (50 psig).

Table 1. Commercial Alkylamines

Alkylamine	CAS Registry Number	Molecular formula	mol wt	Synonym or common abbreviation
methylamine	[74-89-5]	CH_5N	31.06	monomethylamine, aminomethane, MMA
dimethylamine	[120-40-3]	C_2H_7N	45.08	DMA
trimethylamine	[75-50-3]	C_3H_9N	59.11	N,N-dimethylmethanamine, TMA
ethylamine	[74-04-7]	C_2H_7N	45.08	monoethylamine, aminoethane, MEA
diethylamine	[109-89-7]	$C_4H_{11}N$	73.14	Diethanamine, N-ethylethanamine, DEA
triethylamine	[121-44-8]	$C_6H_{15}N$	101.19	TEA
n-propylamine	[107-10-8]	C_3H_9N	59.11	mono-n-propylamine, 1-amino-propane, propanamine, MNPA
di-n-propylamine	[142-84-7]	$C_6H_{15}N$	101.19	N-propyl-1-propanamine, DNPA
tri-n-propylamine	[102-69-2]	$C_9H_{21}N$	143.27	N,N-dipropyl-1-propanamine, TNPA
isopropylamine	[75-31-0]	C_3H_9N	59.11	2-aminopropane, MIPA
diisopropylamine	[108-18-9]	$C_6H_{15}N$	101.19	N-(1-methylethyl)-2-propanamine, DIPA
allylamine	[107-11-9]	C_3H_7N	57.10	monoallylamine, 3-aminopropene
diallylamine	[124-02-7]	$C_6H_{11}N$	97.16	
triallylamine	[102-70-5]	$C_9H_{15}N$	137.22	
n-butylamine	[109-73-9]	$C_4H_{11}N$	73.14	mono-n-butylamine, 1-aminobutane, MNBA
di-n-butylamine	[111-92-2]	$C_8H_{19}N$	129.24	N-butyl-1-butanamine, DNBA
tri-n-butylamine	[102-82-9]	$C_{12}H_{27}N$	185.35	TNBA
isobutylamine	[78-81-9]	$C_4H_{11}N$	73.14	monoisobutylamine, 1-amino-2-methylpropane, MIBA
diisobutylamine	[110-96-3]	$C_8H_{19}N$	129.24	2-methyl-N-(2-methylpropyl)-1-propanamine, DIBA
triisobutylamine	[1116-40-1]	$C_{12}H_{27}N$	185.35	TIBA
sec-butylamine	[13952-84-6]	$C_4H_{11}N$	73.14	2-aminobutane, 1-methylpropanamine
t-butylamine	[75-64-9]	$C_4H_{11}N$	73.14	2-aminoisobutane, 1,1-dimethylethanamine, trimethylaminomethane
ethyl-n-butylamine	[13360-63-9]	$C_6H_{15}N$	101.19	EBA
dimethyl-n-butylamine	[927-62-8]	$C_6H_{15}N$	101.19	DMBA
n-amylamine	[110-58-7]	$C_5H_{13}N$	87.16	
di-n-amylamine	[2050-92-2]	$C_{10}H_{23}N$	157.30	dipentylamine, dipentanamine
tri-n-amylamine	[621-77-2]	$C_{15}H_{33}N$	227.43	tripentylamine, tripentanamine

Thermodynamic data are available only for the lower alkylamines, mainly estimates based on a few experimental determinations (3,4). Many manufacturing processes appear to be limited by thermodynamic equilibria. The lack of accurate free energy data for these amines limits the application of thermodynamic considerations, in contrast to the situation in hydrocarbon technology.
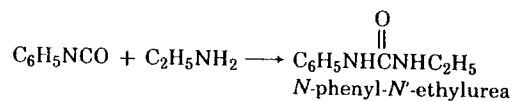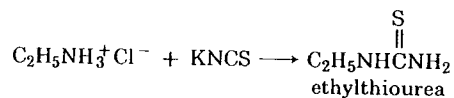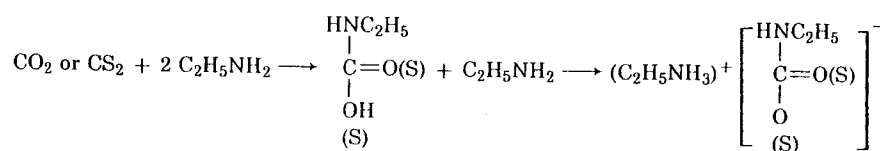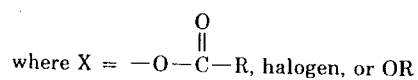
Table 2. Alkylamine Physical Properties[a]

Alkylamine	Mp, °C	Bp, °C	Vapor pressure at 20°C, kPa[b]	Density[c]	Refractive index[d]	Water solubility, g/100 g H2O	K_b 10^4
methylamine	−93.0	−6.3	288	0.67	1.351	108 (25°C)	4.26
dimethylamine	−93.0	6.9	170	0.656	1.347	163 (40°C)	6.03
trimethylamine	−117.0	2.9	191	0.633	1.3449	89 (30°C)	0.63
ethylamine	−81.0	16.6	116	0.683[e]	1.3663		5.62
diethylamine	−50.0	55.9	25.9	0.7062[e]	1.3823		1.29
triethylamine	−114.7	88.8	7.2	0.729[e]	1.401	5.5 (30°C)	5.75
n-propylamine	−83.0	47.8	33.9	0.718[e]	1.3879		2.51
di-n-propylamine	−40.0	109.3	2.8	0.7401[e]	1.4042		7.9
tri-n-propylamine	−93.5	151.0	0.3	0.7567	1.414		
isopropylamine	−95.2	32.4	63.7	0.689[e]	1.3742		4.27
diisopropylamine	−61.0	83.9	8	0.7178[e]	1.3924	sl sol	3.72
allylamine	−88.2	52.9		0.7627	1.42	5.6	0.53
diallylamine	−88.4	110.4		0.7874	1.44	0.25	0.13
triallylamine	−70.0	149.5		0.80	1.45		0.018
n-butylamine	−50.0	77.8	9.6	0.74	1.4031		4.07
di-n-butylamine	−61.9	159.6	0.3	0.76	1.4177	0.47	5.12
tri-n-butylamine	<−70	214.0		0.78[e]	1.4297	sl sol	
isobutylamine	−85.5	68.5	13.3	0.736[e]	1.409	sl sol	
diisobutylamine	−70.0	139.5	1.3	0.745	1.4252		
triisobutylamine	−21.8	191.5		0.7684	1.3932	sol	
sec-butylamine	−104.5	63.0	20.0	0.7246	1.375[g]		
t-butylamine	−72.7	44.5		0.69[f]	1.404		
ethyl-n-butylamine	−78.0	111.0	2.4	0.7398	1.397		
dimethyl-n-butylamine		95.0		0.7206			
n-amylamine	−55.0	104.5		0.7547	1.4118		
di-n-amylamine		202–203		0.7771	1.4272	sl sol	4.07
tri-n-amylamine		240–245		0.7907	1.43665	insol	

[a]Refs. 1, 2.
[b]To convert kPa to mm Hg, multiply by 7.5.
[c]d_4^{20} unless otherwise noted.
[d]n_D^{20} unless otherwise noted.
[e]d_{20}^{20}
[f]d_{25}^{25}
[g]n_D^{25}

Chemical Properties

The formation of salts with acids is the most characteristic reaction of amines. Since the amines are soluble in organic solvents and the salts are usually not soluble, acidic products can be conveniently separated by the reaction with an amine, the unshared electron pair on the amine nitrogen acting as proton acceptor. Amines are good nucleophiles; reactions of amines at the nitrogen atom have as a first step the formation of a bond with the unshared electron pair of nitrogen, eg, reactions with acid anhydrides, halides, and esters, with carbon dioxide or carbon disulfide, and with isocyanic or isothiocyanic acid derivatives.

$$C_6H_5\overset{O}{\overset{\|}{C}}X + (CH_3)_2NH \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}N(CH_3)_2 + HX$$

$$\text{where } X = -O-\overset{O}{\overset{\|}{C}}-R, \text{ halogen, or } OR$$

$$CO_2 \text{ or } CS_2 + 2\ C_2H_5NH_2 \longrightarrow \underset{\underset{(S)}{OH}}{\overset{\overset{HNC_2H_5}{|}}{C}}{=}O(S) + C_2H_5NH_2 \longrightarrow (C_2H_5NH_3)^+ \left[\underset{\underset{(S)}{O}}{\overset{\overset{HNC_2H_5}{|}}{C}}{=}O(S)\right]^-$$

$$C_2H_5NH_3^+ Cl^- + KNCS \longrightarrow C_2H_5NH\overset{S}{\overset{\|}{C}}NH_2$$
$$\text{ethylthiourea}$$

$$C_6H_5NCO + C_2H_5NH_2 \longrightarrow C_6H_5NH\overset{O}{\overset{\|}{C}}NHC_2H_5$$
$$N\text{-phenyl-}N'\text{-ethylurea}$$
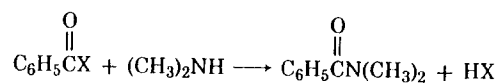
Oxidation by various means gives a wide variety of products. Tertiary aliphatic amines form N-oxides with hydrogen peroxide or peracids. Secondary or primary amines give amine oxide intermediates which rearrange to hydroxylamines. Since the hydroxylamines are easily oxidized to nitro compounds, mixtures are usually obtained (see AMINE OXIDES). The oxidation of amines by the oxides of nitrogen leads to various products, depending on the amine and the experimental conditions. Nitrous acid (HONO) can be used to determine whether an amine is primary, secondary, or tertiary. Primary amines evolve nitrogen; secondary amines give yellow liquids or solids (N-nitroso compounds); tertiary aliphatic amines react without evolution of gas and usually give a complex mixture of products. Since the N-nitrosamines have been classified as potential carcinogens, there is considerable concern about contamination of air with amines. Certain oxides of nitrogen, N_2O_3, N_2O_4, and NO plus air, react rapidly with amines to form nitrosamines under alkaline conditions (5).

Allylamines are somewhat unique in that both amine and olefin functionalities are available. This allows the allylamines to find uses in many areas where the simpler alkylamines are not suitable, eg, taking advantage of the double bond

to form polymeric ammonium salts used as flocculating agents (see ALLYL MONO-MERS AND POLYMERS).

Monobutylamines are easily soluble in water and hydrocarbons and can generally be steam distilled. These properties lead to uses in soaps for water and oil emulsions, and as corrosion inhibitors in steam boiler applications (see CORROSION AND CORROSION INHIBITORS; EMULSIONS). Morpholine is also exten-sively used as a corrosion inhibitor in steam boiler systems. In addition, it is widely used as an intermediate in the production of delayed-action rubber accel-erators.

Alkylamines are corrosive to copper, copper-containing alloys (brass), alu-minum, zinc, zinc alloy, and galvanized surfaces. Aqueous solutions of al-kylamines slowly etch glass as a consequence of the basic properties of the amines in water. Carbon or stainless steel vessels and piping have been used satisfacto-rily for handling alkylamines and, as noted above, some alkylamines can act as corrosion inhibitors in boiler applications.

Manufacture

Lower aliphatic amines can be prepared by a variety of methods, using many different types of raw materials. By far the largest commercial applications in-volve the reaction of alcohol with ammonia to form the corresponding amines. Other methods are employed depending on the particular amine desired, raw material availability, plant economics, and the ability to sell co-products. The following manufacturing methods are used commercially to produce the lower alkylamines. Table 5 gives plant and capacity information for these methods.

Method 1. Alcohol amination–acid catalyzed: high temperature amination of an alcohol over a solid acid catalyst.

Method 2. Alcohol amination–metal catalyzed: amination of an alcohol over a metal catalyst under reducing conditions.

Method 3. Reductive alkylation: reaction of an amine or ammonia and hydro-gen with an aldehyde or ketone over a hydrogenation catalyst.

Method 4. Ritter reaction: reaction of hydrogen cyanide with an olefin in an acidic medium to produce a primary amine.

Method 5. Nitrile reduction: reaction of a nitrile with hydrogen over a hydroge-nation catalyst.

Method 6. Olefin amination: reaction of an olefin with ammonia.

Method 7. Alkyl halide amination: reaction of ammonia or alkylamine with an alkyl halide.

Alcohol Amination.　There are many similarities in the process technolo-gies for Methods 1 and 2. In both, an alcohol reacts with ammonia over a fixed catalyst bed at elevated temperature. The reaction section consists of feed sys-tems, vaporizers, and/or preheaters which pass a liquid or gaseous feed mixture over the catalyst bed in the desired ratio, temperature, and pressure. Possible amination catalysts for each method are as follows.

Method 1: silica–alumina, silica, alumina, titania, tungstic oxides, phosphates, zeolites, and clays.

Method 2: cobalt, nickel, copper, and copper chromite.

Alcohol amination reactions are described by a network of two general types of reaction.

1. Sequential substitution reactions which transform alcohols into a family of primary, secondary, and tertiary amines.

$$ROH + NH_3 \longrightarrow RNH_2 + H_2O \qquad \text{primary amine}$$

$$ROH + RNH_2 \longrightarrow R_2NH + H_2O \qquad \text{secondary amine}$$

$$ROH + R_2NH \longrightarrow R_3N + H_2O \qquad \text{tertiary amine}$$
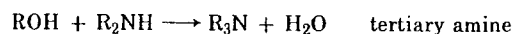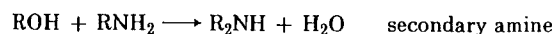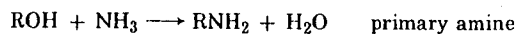
2. Reforming reactions which equilibrate the alkylamines.

$$2\,RNH_2 \rightleftharpoons R_2NH + NH_3$$

$$RNH_2 + R_2NH \rightleftharpoons R_3N + NH_3$$
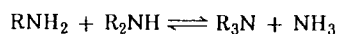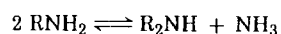
To manufacture the lower alkylamines by Method 1, ammonia and alcohol are passed continuously over a fixed bed containing the catalyst in a gas–solid heterogeneous reaction. The ammonia to alcohol mole ratio varies from 2:1 to 6:1 depending on the amine desired as shown in Figure 1. Operating conditions are maintained in the range from 300–500°C and 790–3550 kPa (100–500 psig) at a gas

Fig. 1.   Amine distribution general behavior. Converted alcohol to amine product as the ammonia to alcohol ratio increases.

hourly space velocity between 500–1500 vol/vol per hour. Yields are typically in excess of 90%.

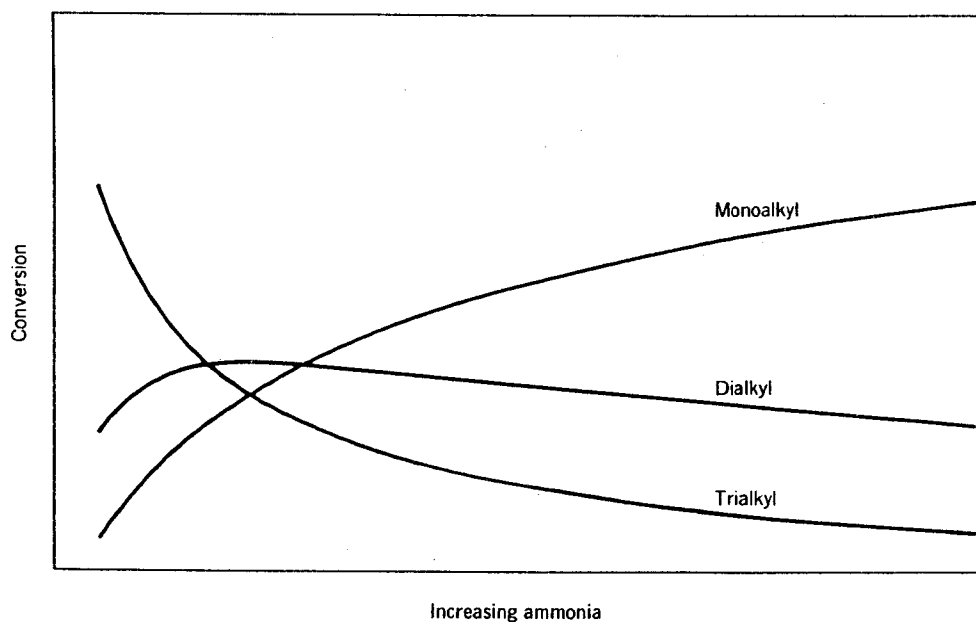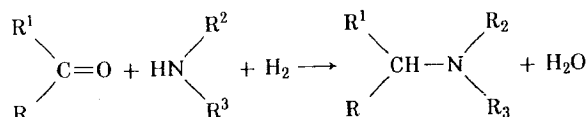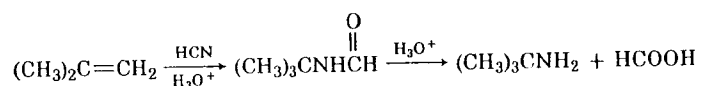In Method 2, hydrogen is also passed over the catalyst to prevent it from deactivating (6). The mole ratio of hydrogen is typically in the range of 1 to 2.5:1 with respect to the alcohol. Operating conditions are maintained in the range 130–250°C. As in Method 1, yields are usually in the 90% range.

Water is a by-product of the amination reactions in both methods. The mixture of ammonia, water, unconverted alcohol, and amines are continuously separated by distillation. Ammonia, unconverted alcohol, and any amines produced in excess of anticipated sales are recycled to the reactor section. A schematic depicting the typical process flows is presented as Figure 2. Note that the separation requirements vary from process to process depending on the by-products and product specifications.

Fig. 2.   Typical amination reactor and separation train.

Reforming of the amines produced in excess of anticipated sales is practiced commercially using both types of catalyst. Recent technological efforts have been directed at using zeolites to avoid an equilibrium product distribution. The zeolites can be used to conduct amination reactions via Method 1. The size of the zeolite pore openings to and from the catalytically active cages limits the production of the tertiary amine. Primary and secondary amines are produced using the zeolite, but the rate at which the tertiary amine is produced may be severely retarded. Studies on the formation of methylamines from methanol best illustrate this technology (7–10).

Reductive Alkylation (Method 3).   Ammonia or a primary or secondary amine, hydrogen, and an aldehyde or ketone form aliphatic amines when they react over a hydrogenation catalyst, eg, nickel, cobalt, copper chromite, platinum, or palladium. These reactions may be carried out at conditions similar to Method 2 and in similar equipment. Liquid-phase stirred-tank equipment operated either continuously or batch is also an option. A larger exothermic heat of

reaction is involved which limits fixed-bed applications to those with a large excess of ammonia, which acts as a heat sink, limiting the total bed temperature rise. Alternatively, a multistage reactor with interstage cooling or a multitubular reactor with cooling to remove the heat of reaction may be employed, but this increases the cost and operating complexity of the reactor. The heat removal problem is more readily controlled in stirred tank systems with cooling coils or systems which pump the reaction mass through external heat exchangers, eg, loop reactors. Typically these reactions take place at lower temperatures than alcohol amination, and reforming reactions compete less favorably with the reductive alkylation. Consequently, it is quite often possible to control the selectivity to a single product through the judicious choice of catalyst and of the mole ratio of the starting aldehyde or ketone to the amine or ammonia. Further it is possible to produce amines with mixed alkyl groups by this method. In the following, R_n = alkyl or H.

$$\begin{array}{c}R^1 \\ \diagdown \\ \diagup \\ R\end{array}C{=}O + HN\begin{array}{c}R^2 \\ \diagup \\ \diagdown \\ R^3\end{array} + H_2 \longrightarrow \begin{array}{c}R^1 \\ \diagdown \\ \diagup \\ R\end{array}CH{-}N\begin{array}{c}R_2 \\ \diagup \\ \diagdown \\ R_3\end{array} + H_2O$$

Operating conditions vary radically depending on the type of equipment selected but typically temperatures used are in the range of 50 to 180°C and pressures of 446 to 3550 kPa (50 to 500 psig) are sufficient (11).

Ritter Reaction (Method 4). A small but important class of amines are manufactured by the Ritter reaction. These are the amines in which the nitrogen atom is adjacent to a tertiary alkyl group. In the Ritter reaction a substituted olefin such as isobutylene reacts with hydrogen cyanide under acidic conditions (12). The resulting formamide is then hydrolyzed to the parent primary amine. Typically sulfuric acid is used in this transformation of an olefin to an amine. Stoichiometric quantities of sulfate salts are produced along with the desired amine.

$$(CH_3)_2C{=}CH_2 \xrightarrow[\text{H}_3\text{O}^+]{\text{HCN}} (CH_3)_3CNH\overset{\overset{\textstyle O}{\textstyle\|}}{C}H \xrightarrow{\text{H}_3\text{O}^+} (CH_3)_3CNH_2 + HCOOH$$

The only low molecular weight alkylamine produced by this method commercially is t-butylamine.

Nitrile Reduction (Method 5). The reduction of nitriles with hydrogen to simple alkylamines is another commercially practiced technology (13). As with Method 3, both continuous packed-bed reactor systems designed for removal of the heat of reaction or batch stirred tank or loop reactor systems may be used. Catalysts for this transformation are nickel, cobalt, platinum, palladium, and rhodium. Again the operating conditions vary widely, depending on the type of equipment; but temperatures and pressures are generally in the range, 50–150°C, and 446–73,900 kPa (50–2000 psig), respectively. Selectivity to primary amine is normally controlled by introducing ammonia as a diluent and nickel or cobalt as catalyst.

$$RC{\equiv}N \underset{cat}{\overset{H_2}{\rightleftharpoons}} RCH{=}NH \underset{cat}{\overset{H_2}{\rightleftharpoons}} RCH_2NH_2$$

$$(RCH_2)_3N \underset{(RCH_2)_2NH}{\overset{H_2,}{\rightleftharpoons}} RCH{=}NCH_2R \underset{cat}{\overset{H_2}{\rightleftharpoons}} (RCH_2)_2NH$$

Secondary and tertiary amines are preferentially produced when rhodium or palladium are chosen as catalyst. As in Method 3, reforming reactions do not normally compete with the hydrogenation reaction and high selectivities to the desired product are possible.

Olefin Amination (Method 6).   The most recent technology for the production of lower alkylamines is olefin amination (14). This is zeolite-catalyzed reaction of ammonia with an olefin, eg, isobutylene, and is practiced in a packed-bed reactor system in the vapor phase.

$$(CH_3)_2C{=}CH_2 + NH_3 \longrightarrow (CH_3)_3CNH_2$$

A number of zeolitic materials have been claimed to catalyze this reaction and reaction temperatures are on the order of 200–350°C with pressures as high as 18000 kPa (2600 psi) reported. This is a low conversion process and recycle of the unconverted starting materials is necessary to provide an economical process. Amination of ethylene to produce ethylamines catalyzed by ammonium iodide is reported, but not believed to be practiced commercially (15,16).

Alkyl Halide Amination (Method 7).   The oldest technology for producing amines is the reaction of ammonia with an alkyl halide. This method is still of commercial importance for the manufacture of allylamines and select mixed alkylamines. Allylamines are not readily made by the other methods mentioned here primarily because either the double bond in the allylamine becomes saturated (methods involving hydrogen) or the severe reaction conditions result in cyclization or polymerization by-products (17). Alkyl halide amination occurs under very mild conditions, typically with the addition of aqueous alkali to neutralize the hydrogen halide coproduced by the reaction. As in the Ritter reaction, stoichiometric quantities of salt are produced. The resulting waste disposal problem detracts from the general utility and popularity of this and the Ritter reaction.

$$n\,RX + NH_3 + n\,NaOH \longrightarrow (R)_nNH_{(3\text{-}n)} + n\,NaX + n\,H_2O$$

Where the value of n denotes a 1°, 2°, or 3° amine.

Shipment and Handling

The methylamines and ethylamine have vapor pressures above atmospheric at ambient temperatures and are available in the pure form only in pressurized containers. These amines are also sold as aqueous solutions with vapor pressures below atmospheric for ease of handling. Diethylamine, triethylamine, and all of the higher mol wt amines are sold as the pure compounds.

Anhydrous methylamines and ethylamine are considered flammable gases. They are shipped under pressure (239–446 kPa, 20–50 psig) and are available in bulk tank trucks and railcars. Aqueous solutions of the methylamines and ethylamine are considered flammable liquids and are available in drums, bulk tank trucks, and railcars. Most of the other higher amines are considered flammable or combustible liquids. All the lower alkylamines are also considered toxic and have strong odors.

The Department of Transportation requires labelling of all shipments of amines commensurate with the associated hazards. Amine shipments are regulated by the Coast Guard, the DOT, and the International Air Transport Association. Aliphatic amines are stored satisfactorily in carbon steel and stainless steel, but are corrosive to copper, aluminum, zinc, and their alloys.

Health and Safety, Toxicology

Alkylamines are toxic. Both the liquids and vapors can cause severe irritations to mucous membranes, eyes, and skin. Protective butyl rubber gloves, aprons, chemical face shields, and self-contained breathing apparatus should be used by all personnel handling alkylamines. Amines are flammable and the lower mol wt alkylamines with high vapor pressures at ordinary temperatures have low flash points. Amines should be handled in well-ventilated areas only after eliminating potential sources of ignition.

Alkylamines should be stored away from oxidizing agents and acids because of incompatibility. Contact with these chemicals gives a rapid and exothermic reaction.

Threshold limit values (TLV) adopted by the ACGIH are guidelines for the control of health hazards. Table 3 shows the eight-hour TWA and the STEL TLV values for those lower alkylamines listed in the ACGIH guideline (18).

Table 3. ACGIH Threshold Limit Values

Alkylamine	TWA, ppm	STEL, ppm
methylamine	10	
dimethylamine	10	
trimethylamine	10	15
ethylamine	10	
diethylamine	10	25
isopropylamine	5	10
diisopropylamine[a]	5	
n-butylamine[a,b]	5	15
morpholine[a]	20	30

[a]Skin exposure should be avoided and must be considered when selecting protective equipment and clothing.
[b]The TLV listed is a ceiling limit and should never be exceeded.

Left margin fragments:

ases.
le in
thyl-
tank
le or
have

's of
egu-
ocia-
teel,

ns to
emi-
y all
l wt
flash
ting

ause
rmic

r the
TLV

Table 4. Products Manufactured Using Alkylamines

Chemical name	CAS Registry Number	Trade name/ common name	Use
From Monomethylamine			
3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione	[58-08-2]	Caffeine	stimulant, diuretic
3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione	[58-55-9]	Theophylline	antispasmodic
1-naphthyl-N-methylcarbamate	[63-25-2]	Sevin/carbaryl	insecticide
sodium N-methyldithiocarbamate	[137-42-8]	Vapam/metham	pesticide
ethyl 1-methyl-4-phenylpiperidine-4-carboxylate	[57-42-1]	Demerol	analgesic
p-N-methylaminophenol sulfate	[55-55-0]	Metol	photographic developer
2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate	[1563-66-2]	Furadan	systemic insecticide
N-methyl-2-pyrrolidone	[872-50-4]		solvent, paint stripper
monomethylammonium nitrate	[22113-87-7]		water gel explosive
2-methyl-2-(methylthio)-propanal O-[(methylamino)-carbonyl]oxime	[116-06-3]	Temik/aldicarb	insecticide
methyl-N-{[(methylamino)carbonyl]oxy}-ethanimidothioate	[16752-77-5]	Lannate/methomyl	insecticide
N,N-dimethyl-2-methylcarbamoyloxyimino-2-(methylthio)acetamide	[23135-22-0]	Vydate/oxamyl	insecticide
2,2-dimethylbenzo-1,3-dioxol-4-ol-N-methyl carbamate	[22781-23-3]	Ficam/bendiocarb	pesticide
N-[5(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N-dimethylurea	[34014-18-1]	Spike/tebuthiuron	herbicide
2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-3,5-dione	[20354-26-1]	Probe/metazole	herbicide
methyl isothiocyanate	[556-61-6]		fungicide/nematicide
2-methylaminoethanol	[109-83-1]		electrostatic automotive coatings, acid gas scrubbing

379

Table 4. *(Continued)*

Chemical name	CAS Registry Number	Trade name/ common name	Use
From Dimethylamine			
dimethyldithiocarbamate zinc salt	[137-30-4]	Ziram	fungicide, rubber processing
dimethyldithiocarbamate iron salt	[14484-64-1]	Ferbam	fungicide, rubber processing
bis(dimethylthiocarbamoyl) disulfide	[137-26-8]	Thiram	rubber accelerator
tetramethylthiuram monosulfide	[63797-03-5]	Monex, Thionex	rubber accelerator
1,1-dimethylhydrazine	[57-14-7]	UDMH	propellant
2-dimethylaminoethyl-*p*-butylaminobenzoate hydrochloride	[136-47-0]	Pantocaine	anesthetic
2-(benzhydryloxy)-*N,N*-dimethylethylamine-HCl	[147-24-0]	Benadryl	antihistaminic
dimethylformamide	[68-12-2]		solvent
dimethylacetamide	[127-19-5]		solvent
1,3,5-tris(dimethylaminomethyl)phenol	[90-72-2]	DMP-30, Amicore TMR30	urethane catalyst
stearyldimethylbenzylammonium chloride	[122-19-0]	Triton X-400	surfactant
lauryldimethylamine	[112-18-5]		surfactant
copolymers of dimethyldiallylammonium chloride and acrylates or acrylamides		DMDAC, DADMAC, DADM	water treatment
epichlorohydrin-dimethylamine based polymers		epi-DMA	water treatment
alkyl(C$_{10}$–C$_{18}$)dimethylamine oxides			nonionic detergent
alkyl(C$_{10}$–C$_{18}$)benzyldimethylammonium salts			germicides
3-(3,4-dichloropheny)-1,1-dimethylurea	[330-54-1]	Karmex/diuron	herbicide
3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazin-2,4-(1*H*,3*H*)dione	[51235-04-2]	Velpar/hexazinone	herbicide
2-dimethylaminoethyl methacrylate	[2867-47-2]		water treatment dispersant/ pH control for water-based coatings
3-dimethylaminopropylamine	[109-55-7]		surfactants, liquid soaps, water treatment
benzyldimethylamine	[108-83-3]		epoxy resin accelerator

...benzyldimethylamine	[105-03-1]		surfactants, liquid soaps, water treatment
benzyldimethylamine	[108-83-3]		epoxy resin accelerator

From Trimethylamine

trimethylamine	[75-50-3]		acid scavenger for nylon and benzyl ester production
			animal feed supplement
choline chloride	[67-48-1]		ion-exchange resin
cross-linked polystyrene functionalized with alkyltrimethylammonium groups	[53664-47-4]	Amberlyst, Dowex	
benzyltrimethylammonium hydroxide	[100-85-6]	Triton B	base catalyst, dye leveling agent, polyester gelling inhibitor

From Monoethylamine

2-chloro-4-ethylamino-6-isopropyl-amino-1,3,5-triazine	[1912-24-9]	Atrazine	herbicide
2-chloro-4-(1-cyano-1-methylethyl-amino)-6-ethylamino-1,3,5-triazine	[21725-46-2]	Bladex/cyanazine	herbicide
2-ethylamino-4-isopropylamino-6-methylthio-1,3,5-triazine	[834-12-8]	Evik/ametryn	herbicide
2-chloro-4,6-bis(ethylamino)-1,3,5-triazine	[122-34-9]	Princep/simazine	herbicide
2-t-butylamino-4-ethylamino-6-methylthio-1,3,5-triazine	[886-50-0]	Terbutryn	herbicide
2,4-bis(ethylamino)-6-methylthio-1,3,5-triazine	[1014-70-6]	Simetryn	herbicide
S-ethyl-N-ethyl-N-cyclohexyl thiocarbamate	[1134-23-2]	Cycloate	herbicide
N-ethyl-o,p-toluenesulfonamide	[8047-99-2]	Santicizer 8	plasticizer

From Diethylamine

2-diethylaminoethanol	[100-37-8]		corrosion inhibitor, water-based coatings
2-diethylaminoethyl methacrylate	[105-16-8]		adhesion promoter in acrylic coatings
N,N-diethyldithiocarbamate salts			
triethylamine salt	[2391-78-8]		
diethylamine salt	[1518-58-7]		
sodium salt	[148-18-5]		rubber accelerator
tetraethylthiuram disulfide	[97-77-8]		rubber accelerator
N,N-diethylhydroxylamine	[3710-84-7]		radical scavenger
N,N-diethyl-m-toluamide	[134-62-3]	DEET	insect repellent

Table 4. (*Continued*)

Chemical name	CAS Registry Number	Trade name/ common name	Use
From Triethylamine			
triethylamine	[121-44-8]		catalyst for foundry-mold resin curing, adhesives, extraction agent in drug synthesis, corrosion inhibitor in paint remover, HCl scavenger in herbicide synthesis
triethylammonium 2-(2,4,5-trichlorophenoxy)propionate	[57213-69-1]	Garlon 3A	herbicide
From Di-n-propylamine			
α,α,α,-trifluoro-2,6-dinitro-*N,N*-di-*n*-propyl-*p*-toluidine	[1582-09-8]	Treflan/trifluralin	herbicide
3,5-dinitro-*N,N*-di-*n*-propyl sulfanilamide	[19044-88-3]	Surflan	herbicide
S-ethyl di-*n*-propyl thiocarbamate	[759-94-4]	Eptam	herbicide
S-propyl dipropyl thiocarbamate	[1929-77-7]	Vernam/vernolate	herbicide
From Monoisopropylamine			
2-ethylamino-4-isopropylamino-6-methylthio-1,3,5-triazine	[834-12-8]	Evik/ametryn	herbicide
2-chloro-4,6-bis(isopropylamino)-1,3,5-triazine	[139-40-2]	Milogard/propazine	herbicide
2-methoxy-4,6-bis(isopropylamino)-1,3,5-triazine	[1610-18-0]	Pramitol/prometon	herbicide
2-ethylthio-4,6-bis(isopropylamino)-1,3,5-triazine	[4147-51-7]	Sancap/dipropetryn	herbicide
2-chloro-4-(ethylamino)-6-(isopropylamino)-1,3,5-triazine	[1912-24-9]	Atrazine	herbicide
N-(phosphonomethyl)-glycine isopropylamine salt	[38641-94-0]	Roundup/glyphosate	herbicide
ethyl 4-(methylthio)-*m*-tolyl isopropylphosphoramide	[22224-92-6]	Nemacur/fenamiphos	nematicide
isopropylammonium dodecylbenzenesulfonate	[26264-05-1]		dry-cleaning detergent
From Diisopropylamine			
S-(2,3-dichloroallyl)-*N,N*-diisopropylthiocarbamate	[2303-16-4]	Avadex/diallate	herbicide

382

From Diallylamine

copolymers of dimethyldiallylammonium chloride with acrylates or acrylamides	DMDAC, DADMAC, DADM		water treatment

From Mono-n-butylamine

di-*n*-butylthiourea	[32841-23-9]		rubber accelerator
sodium di-*n*-butylthiocarbamate	[66344-11-4]		rubber accelerator
tetra-*n*-butylthiuram disulfide	[1634-02-2]	Pentexne	rubber accelerator
zinc di-*n*-butyldithiocarbamate	[136-23-2]		rubber accelerator
methyl (*n*-butylcarbamoyl)-2-benzimidazole carbamate	[17804-35-2]	Benlate/benomy	fungicide

From Di-n-butylamine

di-*n*-butylamine	[111-92-2]		catalyst for polyphenylene ethers
2-(di-*n*-butylamino)ethanol	[102-81-8]		emulsifier

From Tri-n-butylamine

tri-*n*-butylamine	[102-82-9]		urethane catalyst

From Monoisobutylamine

S-ethyldiisobutyl thiocarbamate	[2008-41-5]	Sutan, Gennate, butylate	herbicide

From Mono-t-butylamine

N-*t*-butyl-2-benzothiazole sulfenamide	[95-31-8]	Santocure NS, Delac NS	rubber accelerator
2-*t*-butylamino-4-ethylamino-6-methyl-thio-1,3,5-triazine	[886-50-0]	Igran	herbicide
3-*t*-butyl-5-chloro-6-methyluracil	[5902-51-2]	Sinbar	herbicide

383

Table 5. Manufacturing Data for Aliphatic Amines

Company and plant location	Amine products	Capacity, t/yr	Method
	United States producers		
Air Products and Chemicals	methyl	68,200	1
	C_2–C_4 + morpholine	63,600	1,2,3
E. I. du Pont de Nemours & Co., Inc.	methyl	81,800	1
Hoechst Celanese	C_2–C_4	36,400[a]	2,5
Fine Chemicals Division	allyl and methylallyl	3,200	7
Alcolac	methyl	10,000	1
BASF	morpholine	4,500	2
Texaco	morpholine	12,000	2
Atochem North America/Elf Aquitaine	C_2–C_5	13,600	2
Sterling Chemicals	*t*-butyl	5,500	4
Total United States		*298,800*	
	Other American producers		
Chinook Chemicals	methyl	9,000	1
Celanese Mexicana	methyl	8,000	1
BASF Quimica da Bahia	methyl	10,000	1
Nordeste Quimica	C_2–C_4	12,000	1,2
Total U.S. and Americas		*320,700*	
	West European producers		
BASF	methyl	60,000	1
	C_2–C_5	62,000[a]	1,2
	t-butyl	6,000	6
UCB	methyl	28,000	1
Virchem	C_3–C_5	8,000[a]	2
ATOCHEM	C_2–C_4	25,000	1,2
Rhône-Poulenc Chimie	*n*-butyl	2,000	2
Bayer AG	C_2	8,000	1,2
Ruhrchemie	C_3–C_6	20,000	2
Akzo	methyl	30,000	1
Ertisa	methyl	12,000	1
Imperial Chemicals Industries	methyl	33,000	1
	C_2–C_4	12,000	1,2
Total Western Europe		*306,000*	
	Japanese producers		
Daicel Chemical Industries	C_2	10,000	1,2
	C_3	1,000	2
Koei Chemical	C_3–C_4	1,800	2,3
Mitsubishi Gas Chemical	methyl	22,000	1
	C_2	2,400	3
Nitto Chemical Industry	methyl	23,400	1
	t-butyl	1,500	4
Sumitomo Chemical	*t*-butyl	1,000	4
Total Japan		*63,100*	
Total		*689,800*	

[a]Includes cyclohexylamine, see cycloaliphatic amines.

Method

1
1,2,3
1
2,5
7
1
2
2
2
4

1
1
1
1,2

1
1,2
6
1
2
1,2
2
1,2
2
1
1
1
1,2

1,2
2
2,3
1
3
1
4
4

Economic Aspects, Specifications, and Uses

Table 4 gives information on significant uses and Table 5 provides manufacturing data on various alkylamines for 1988, from capacity announcements in *Chemical Week, Hydrocarbon Processing,* and *European Chemical News.* Table 6 gives general sales specifications and the U.S. list price (1991). More detailed product specifications are available from the various indicated manufacturers.

Table 6. Alkylamines Specifications and Economic Data

Compound	Assay, wt %	Other amines, wt %	Water, wt %	1991 U.S. price, $/kg
methylamine	99.5	0.3	0.1	1.04
dimethylamine	99.5	0.1	0.1	1.04
trimethylamine	99.5	0.2	0.1	1.04
ethylamine	99.5	0.4	0.1	2.58
diethylamine	99.0	0.7	0.3	2.67
triethylamine	99.5	0.4	0.1	2.76
n-propylamine	99.0	0.5	0.5	2.45
di-*n*-propylamine	99.0	0.9	0.2	2.69
tri-*n*-propylamine	98.0	0.6	0.3	3.59
isopropylamine	99.0	0.7	0.3	2.16
diisopropylamine	99.5	0.3	0.2	2.95
n-butylamine	99.5		0.1	2.76
di-*n*-butylamine	99.0	0.3	0.2	2.89
tri-*n*-butylamine	98.0	0.6	0.3	3.48
diisobutylamine	98.0	1.3	0.2	2.78
ethyl-*n*-butylamine	98.5	1.5	0.2	4.39
morpholine	99.0		0.2	2.14

BIBLIOGRAPHY

"Methylamines" in *ECT* 1st ed., Vol. 9, pp. 62–67, by L. U. Spence and E. H. Riddle, Rohm & Haas Company; "Ethylamines" in Vol. 5, pp. 876–879, and "Propylamines" in Vol. 11, pp. 190–192, by R. H. Goshorn, Sharples Chemicals, Inc.; "Butylamines" in Vol. 2, pp. 680–683, and "Amylamines" in Vol. 1, pp. 849–851, by C. K. Hunt, Sharples Chemicals, Inc.; "Amines, Lower Alphatic" in *ECT* 2nd ed., Vol. 2, pp. 116–127; "Amines, Lower Aliphatic" in *ECT* 3rd ed., Vol. 2, pp. 272–283, by A. Schweizer, R. Fowlkes, J. McMakin, and T. Whyte, Air Products and Chemicals, Inc.

1. *Handbook of Chemistry and Physics,* 57th ed., CRC Press, Cleveland, Ohio, 1976, Sec. C.
2. R. T. Morrison and R. N. Boyd, *Organic Chemistry,* 3rd ed., Allyl and Bacon, Boston, Mass., 1973, pp. 729–730.
3. D. R. Stull, E. F. Westrum, and G. C. Sinke, *The Chemical Thermodynamics of Organic Compounds,* John Wiley & Sons, Inc., New York, 1969, pp. 457–467.
4. J. Pasek, P. Kondelik, and P. Richter, *Ind. Chem. Chem. Prod. Res. Dev.* **11,** 333 (1972).
5. B. C. Challis and S. A. Kyrtopoulos, *J. Chem. Soc. Chem. Commun.* **21,** 877–878, 1976.

6. A. Baiker and J. Kijenski, *Catal. Rev. Sci. Eng.* 27(4), 653–697 (1985).
7. M. Deeba, M. E. Ford, and T. A. Johnson, in D. W. Blackburn, ed., *Catalysis of Organic Reactions,* Marcel Dekker, New York, 1990, pp. 241–260.
8. R. Shannon and co-workers, *J. Catalysis* 113, 367–382 (1988).
9. U.S. Pat. 4,806,689 (Feb. 21, 1989), T. Gier and co-workers (to E. I. du Pont de Nemours & Co., Inc.).
10. U.S. Pat. 4,582,936 (Apr. 15, 1986), Y. Ashina, T. Fujita, M. Fukatsu, and J. Yagi (to Nitto Kagaku Kogyo Kabushiki Kaisha).
11. W. S. Emerson, in R. Adams, ed., *Organic Reactions,* Vol. 4, John Wiley & Sons, Inc., New York, 1948, p. 174.
12. L. I. Krimen and D. J. Cota, in W. G. Dauben, ed., *Organic Reactions,* Vol. 17, John Wiley & Sons, Inc., New York, 1969, p. 213.
13. J. Volf and J. Pasek, in L. Cerveny, ed. *Catalytic Hydrogenation,* Vol. 27, *Studies of Surface Science and Catalysis,* Elsevier, New York, 1986, pp. 105–144.
14. Gen. Offen. 3,326,579 (Jan. 31, 1985), V. Taglieber, and co-workers (to BASF A-G).
15. U.S. Pat. 4,827,031 (May 2, 1989), R. Clark, D. Gardner, and P. McElligott (to Pennwalt Corporation).
16. U.S. Pat. 4,483,757 (Nov. 20, 1984), D. Gardner and P. McElligott (Pennwalt Corporation).
17. W. E. Carroll and co-workers, *J. Mol. Catalysis* 44, 213–215 (1988).
18. *Threshold Limit Values for Chemical Substances in Workroom Air Adopted by ACGIH for 1989–1990,* American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 1976.

MICHAEL G. TURCOTTE
THOMAS A. JOHNSON
Air Products and Chemicals, Inc.

CYCLOALIPHATIC AMINES

Cycloaliphatic amines are comprised of a cyclic hydrocarbon structural component and an amine functional group external to that ring. Included in an extended cycloaliphatic amine definition are aminomethyl cycloaliphatics. Although some cycloaliphatic amine and diamine products have direct end use applications, their major function is as low cost organic intermediates sold as moderate volume specification products.

Physical Properties

For simple primary amines directly bonded to a cycloalkane by a single C—N bond to a secondary carbon the homologous series is given in Table 1. Up through C_8 each is a colorless liquid at room temperature. The ammoniacal or fishy odor and high degree of water solubility decrease with increased molecular weight and boiling point for these corrosive, hygroscopic mobile fluids.

6. A. Baiker and J. Kijenski, *Catal. Rev. Sci. Eng.* **27**(4), 653–697 (1985).
7. M. Deeba, M. E. Ford, and T. A. Johnson, in D. W. Blackburn, ed., *Catalysis of Organic Reactions,* Marcel Dekker, New York, 1990, pp. 241–260.
8. R. Shannon and co-workers, *J. Catalysis* **113**, 367–382 (1988).
9. U.S. Pat. 4,806,689 (Feb. 21, 1989), T. Gier and co-workers (to E. I. du Pont de Nemours & Co., Inc.).
10. U.S. Pat. 4,582,936 (Apr. 15, 1986), Y. Ashina, T. Fujita, M. Fukatsu, and J. Yagi (to Nitto Kagaku Kogyo Kabushiki Kaisha).
11. W. S. Emerson, in R. Adams, ed., *Organic Reactions,* Vol. 4, John Wiley & Sons, Inc., New York, 1948, p. 174.
12. L. I. Krimen and D. J. Cota, in W. G. Dauben, ed., *Organic Reactions,* Vol. 17, John Wiley & Sons, Inc., New York, 1969, p. 213.
13. J. Volf and J. Pasek, in L. Cerveny, ed. *Catalytic Hydrogenation,* Vol. 27, *Studies of Surface Science and Catalysis,* Elsevier, New York, 1986, pp. 105–144.
14. Gen. Offen. 3,326,579 (Jan. 31, 1985), V. Taglieber, and co-workers (to BASF A-G).
15. U.S. Pat. 4,827,031 (May 2, 1989), R. Clark, D. Gardner, and P. McElligott (to Pennwalt Corporation).
16. U.S. Pat. 4,483,757 (Nov. 20, 1984), D. Gardner and P. McElligott (Pennwalt Corporation).
17. W. E. Carroll and co-workers, *J. Mol. Catalysis* **44**, 213–215 (1988).
18. *Threshold Limit Values for Chemical Substances in Workroom Air Adopted by ACGIH for 1989–1990,* American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 1976.

MICHAEL G. TURCOTTE
THOMAS A. JOHNSON
Air Products and Chemicals, Inc.

CYCLOALIPHATIC AMINES

Cycloaliphatic amines are comprised of a cyclic hydrocarbon structural component and an amine functional group external to that ring. Included in an extended cycloaliphatic amine definition are aminomethyl cycloaliphatics. Although some cycloaliphatic amine and diamine products have direct end use applications, their major function is as low cost organic intermediates sold as moderate volume specification products.

Physical Properties

For simple primary amines directly bonded to a cycloalkane by a single C—N bond to a secondary carbon the homologous series is given in Table 1. Up through C8 each is a colorless liquid at room temperature. The ammoniacal or fishy odor and high degree of water solubility decrease with increased molecular weight and boiling point for these corrosive, hygroscopic mobile fluids.

racemic mixture of optical isomers is specified; ultimate identification by CAS Registry Number is listed for the (+) and (−) enantiomers of trans-2-methylcyclohexylamine. The 1,4-isomer has a plane of symmetry and hence no chiral centers and no stereoisomers. The methylcyclohexylamine geometric isomers have different physical properties and are interconvertible by dehydrogenation–hydrogenation through the imine.
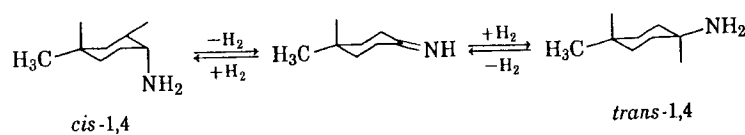
Table 3 lists cycloaliphatic diamines. Specific registry numbers are assigned to the optical isomers of trans-1,2-cyclohexanediamine; the cis isomer is achiral at ambient temperatures because of rapid interconversion of ring conformers. Com-

Table 3. Properties of Cycloaliphatic Diamines

Diamine	CAS Registry Number	Molecular formula	Boiling point[a], °C	Flash point, °C
cis,trans-1,2-cyclohexanediamine	[694-83-7]	$C_6H_{14}N_2$	183	75
cis-1,2-cyclohexanediamine	[1436-59-5]	$C_6H_{14}N_2$	182	72
(±)trans-1,2-cyclohexanediamine	[1121-22-8]	$C_6H_{14}N_2$		
(+)trans-1,2-cyclohexanediamine	[21436-03-3]	$C_6H_{14}N_2$		
(−)trans-1,2-cyclohexanediamine	[20439-47-8]	$C_6H_{14}N_2$		
cis,trans-1,3-cyclohexanediamine	[3385-21-5]	$C_6H_{14}N_2$		91
cis-1,3-cyclohexanediamine	[26772-34-9]	$C_6H_{14}N_2$	198	
trans-1,3-cyclohexanediamine	[26883-70-5]	$C_6H_{14}N_2$	203	
methylcyclohexanediamine	[28282-16-0]	$C_7H_{16}N_2$	99 (1.66)	83
cis,trans-1,3-cyclohexanediamine,2-methyl	[13897-56-8]			
cis,trans-1,3-cyclohexanediamine,4-methyl	[13897-55-7]			
cis,trans-1,4-cyclohexanediamine	[1436-59-5]	$C_6H_{14}N_2$	181	80
cis-1,4-cyclohexanediamine	[15827-56-2]	$C_6H_{14}N_2$		
trans-1,4-cyclohexanediamine	[2615-25-0]	$C_6H_{14}N_2$	197	71
cis,trans-1,8-menthanediamine	[80-52-4]	$C_{10}H_{22}N_2$	210	102
cis,trans-1,3-di(aminomethyl)cyclohexane	[2579-20-6]	$C_8H_{18}N_2$		106
cis-1,3-di(aminomethyl)cyclohexane	[10304-00-8]		114 (1.07)	
trans-1,3-di(aminomethyl)cyclohexane	[10339-97-6]		117 (1.33)	
cis,trans-1,4-di(aminomethyl)cyclohexane	[2549-93-1]	$C_8H_{18}N_2$	245	107
cis-1,4-di(aminomethyl)cyclohexane	[10029-09-9]	$C_8H_{18}N_2$		
trans-1,4-di(aminomethyl)cyclohexane	[10029-07-9]			
cis,trans-isophoronediamine	[2855-13-2]	$C_{10}H_{22}N_2$	252	112
methylenedi(cyclohexylamine)	[1761-71-3]	$C_{13}H_{26}N_2$	162 (2.40)	>110
isopropylidenedi(cyclohexylamine)	[3377-24-0]	$C_{15}H_{30}N_2$	182 (1.32)	>110
3,3'-dimethylmethylene-di(cyclohexylamine)	[6864-37-5]	$C_{15}H_{30}N_2$	160 (0.27)	174
cis,trans-tricyclodecanediamine[b]	[68889-71-4]	$C_{12}H_{22}N_2$	~314	165

[a]At 101.3 kPa unless otherwise indicated by the value (in kPa) in parentheses. To convert kPa to mm Hg, multiply by 7.5.

[b](4,7-Methano-1H-indene-dimethaneamine, octahydro).

property dependence on diamine structure is greater in the linear amorphous thermoplastic polyamides and elastomeric polyureas than in the highly cross-linked thermoset epoxies (2–4).

Manufacture and Processing

Cycloaliphatic amine synthesis routes may be described as distinct synthetic methods, though practice often combines, or hybridizes, the steps that occur: amination of cycloalkanols, reductive amination of cyclic ketones, ring reduction of cycloalkenylamines, nitrile addition to alicyclic carbocations, reduction of cyanocycloalkanes to aminomethylcycloalkanes, and reduction of nitro-cycloalkanes or cyclic ketoximes.

Secondary alcohols are aminated to secondary amines by dehydration catalysts or under H_2 pressure using metal dehydrogenation catalysts such as Ni or Co. The latter process becomes mechanistically equivalent to reductive alkylation of ammonia, though no hydrogen is consumed. Cyclohexylamine (CHA) is commercially produced from cyclohexanol [108-93-0] by reaction in the vapor phase with NH_3 and H_2. Controlled alkyl:ammonia, hydrogen ratios over metal dehydrogenation catalysts on solid supports at 160–200°C and 1350–2000 kPa (196–290 psi) at gas hourly space velocities of 1000–2500 vol/vol are analogous conditions to those of the preferred manufacturing process for other secondary aliphatic amines. Reduction of ammonia to cyclohexanol feed ratios in the fixed bed vapor phase process promotes dicyclohexylamine (DCHA) coproduction.

Reductive amination of cyclic ketones, or reductive alkylation of ammonia, is a general route to cycloaliphatic amines (5). Use of pressurized hydrogen and metal catalyst is the process technology of choice commercially; alternative (6) hydrogen sources include formic acid. Batch liquid-phase reaction technology predominates because cyclic ketone volatilization in the presence of ammonia leads to by-product-forming aldol condensations; higher molecular weight alicyclic ketones such as 2-adamantanone [700-58-3] are insufficently volatile. Short contact time (1–30 s), high temperature (to 275°C), and atmospheric vapor-phase reaction conditions for production of cyclohexylamine from mixtures of cyclohexanol and cyclohexanone [108-94-1] over heated copper chromite–nickel catalyst with an ammonia:alkyl ratio of 3.3:1 and hydrogen:alkyl ratio of 6.5:1 have, however, been claimed (8).

Aniline [62-53-3] ring reduction produces cyclohexylamine. Alternative historical synthetic routes and early (1905–1931) metal-catalyzed hydrogen additions under hydrogen pressure have been well reviewed (9). Increased efficiencies compared to those with Ni and Co catalysts are available from the more precious elements of the same subgroup, Ru and Rh. Batch reaction giving >90% selectivity to CHA with <5% DCHA may use 1–3% of supported precious metal catalyst and neat substrate. Representative reaction conditions are 100–150°C with 1400–3500 kPa (200–500 psi) H_2 requiring 4–20 hours. Subsequent distillation may be batch or continuous. CHA fractionation from trace reaction by-product lights, then from recoverable DCHA and distillate heavies is done under reduced pressure. CHA has been made directly from phenol at low H_2 plus NH_3 pressure using rhodium catalyst in batch reactions (10) and in the vapor phase over nickel (11). Reaction selectivity to CHA is but 56% with 37% DCHA in the latter case.

Methylenedianiline (4) (MDA) [*101-77-9*] hydrogenation to methylenedi(cyclohexylamine) generates first the *cis*-(6) and *trans*-(7) isomers of half-reduced 4-(*p*-aminobenzyl)-cyclohexylamine (5) [*28480-77-5*], a differentially reactive diamine offered in developmental quantities by Air Products and Chemicals.
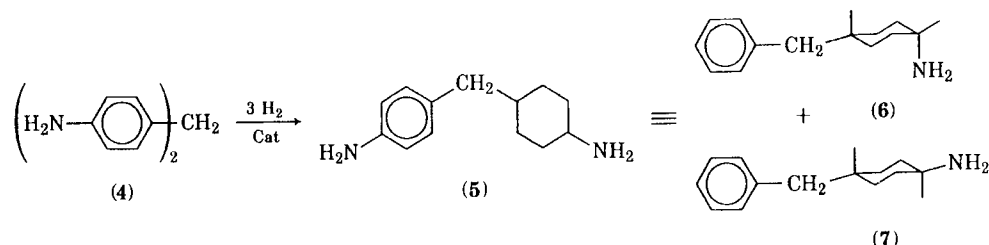
Addition of H_2 to the aromatic ring occurs cis, yielding a kinetic product subject to isomerization to the more thermodynamically stable trans isomer. Subsequent hydrogen addition to the remaining aromatic ring then produces the three fully reduced isomers (1–3). Catalyst systems were first optimized for efficient maximum trans isomer production (21–23). Batch reaction conditions using Ru on alumina catalyst for obtaining the thermodynamic mixture of product isomers were 200°C and 28–35 MPa (4000–5000 psi). Improved yields, including isomerization to a 50/40/10 mixture of (1,2,3), are enhanced by Ru alkali moderation (13,24,25).

Conditions cited for Rh on alumina hydrogenation of MDA are much less severe, 117°C and 760 kPA (110 psi) (26). With 550 kPa (80 psi) ammonia partial pressure present in the hydrogenation of twice-distilled MDA employing 2-propanol solvent at 121°C and 1.3 MPa (190 psi) total pressure, the supported Rh catalyst could be extensively reused (27). Medium pressure (3.9 MPa = 566 psi) and temperature (80°C) hydrogenation using iridium yields low *trans/trans* isomer MDCHA (28). Improved selectivity to alicyclic diamine from MDA has been claimed (29) for alumina-supported iridium and rhodium by introducing the tertiary amines 1,4-diazabicyclo[2.2.2]octane [*280-57-9*] and quinuclidine [*100-76-5*].

Direct production of select MDCHA isomer mixtures has been accomplished using ruthenium dioxide (30), ruthenium on alumina (31), alkali-moderated ruthenium (32) and rhodium (33). Specific isomer mixtures are commercially available from an improved 5–7 MPa (700–1000 psi) medium pressure process tolerant of oligomer-containing MDA feeds (34). Dimethylenetri(cyclohexylamine) (8) [*25131-42-4*] is a coproduct.

(8)
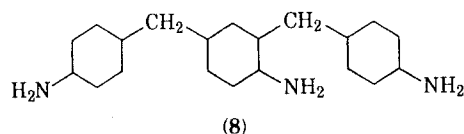
Continuous solvent-free hydrogenation of MDA over alkaline-earth-supported metals at 240°C and 25 MPa (3600 psi) has been described (35) as well as a similar

(13)
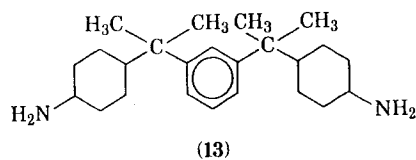
Cycloaliphatics capable of tertiary carbocation formation are candidates for nucleophilic addition of nitriles. HCN in strong sulfuric acid transforms 1-methyl-1-cyclohexanol to 1-methyl-1-cyclohexylamine through the formamide (47). The terpenes pinene (14) [2437-95-8] and limonene [5989-27-5] (15) each undergo a double addition of HCN to provide, after hydrolysis, the cycloaliphatic diamine 1,8-menthanediamine (16) (48).

(14)   (15)   (16)
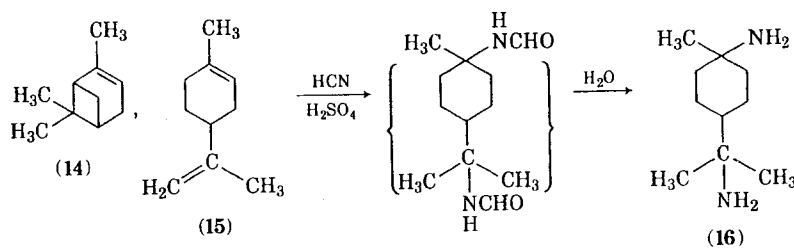
1-Adamantylamine is prepared from the corresponding alcohol or bromide by bridgehead cation generation in the presence of acetonitrile (49). Selective hydrolysis of the resultant acetamide to the rigid cycloaliphatic amine by acid or base is difficult.

Acetone's cyclic trimer, isophorone (17) [78-59-1], has reacted directly with ammonia (Ra Ni, 120°C), methylamine, (Pt/C, 100°C) and dimethylamine (Pd/C, 95°C) at 2400–3450 kPa H_2 pressure to form 3,3,5-trimethylcyclohexylamines (18), where R_1, R_2 = H, alkyl (50). The double bond is hydrogenated simultaneously with the imine:

(17)   (18)   cis
                                      (22)
(19)   (20)   (21)   ≡   +
                                      trans
                                      (23)
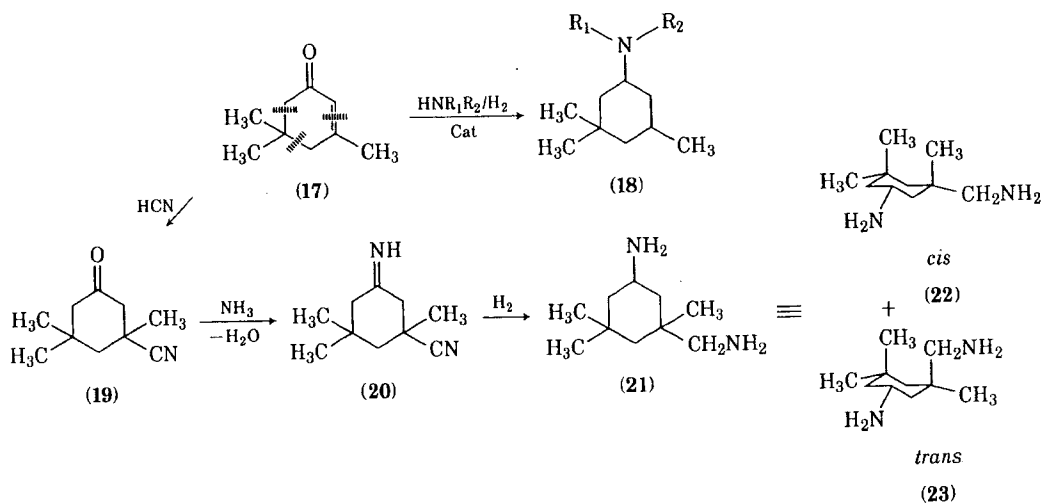
Production and Shipment

Larger volume cycloaliphatic amines and diamines, their worldwide major manufacturers and approximate January 1990 prices are shown in Table 4. Shipment of these liquid products is by nitrogen-blanketed tank truck or tank car. Drum shipments are usually in carbon steel, DOT-17E.

Table 4. Commercial Cycloaliphatic Amines

Amine	Volume, 10^3 t/yr	Price, $/kg	Manufacturers
cyclohexylamine	20	2.90	Air Products, BASF, Bayer, Hoechst, ICI, Kanto Denka, New Japan
isophoronediamine	18	5.40	Hüls
methylenedi(cyclohexylamine)	10	6.80	Air Products, BASF, Hüls, New Japan
3,3'-dimethylmethylene-di(cyclohexylamine)	3	8.90	BASF
dicyclohexylamine	2	3.75	Air Products, BASF, Hoechst
dimethylcyclohexylamine	2	4.85	Air Products, BASF, ICI
1,2-cyclohexanediamine	1	3.65	Du Pont/Milliken

Economic Aspects

Cycloaliphatic amine production economics are dominated by raw material charges and process equipment capital costs. Acetone (isophorone), adiponitrile, aniline, and MDA are all large-volume specification organic intermediates bordering on commodity chemicals. They are each cost-effective precursors.

Reductive alkylations and aminations require pressure-rated reaction vessels and fully contained and blanketed support equipment. Nitrile hydrogenations are similar in their requirements. Arylamine hydrogenations have historically required very high pressure vessel materials of construction. A nominal breakpoint of 8 MPa (~1200 psi) requires yet heavier wall construction and correspondingly more expensive hydrogen pressurization. Heat transfer must be adequate, for the heat of reaction in arylamine ring reduction is ~50 kJ/mol (12 kcal/mol) (59). Solvents employed to maintain catalyst activity and improve heat-transfer efficiency reduce effective hydrogen partial pressures and require fractionation from product and recycle to prove cost-effective.

Production of cyclohexylamine reflects this balance of raw material versus operating cost structure. When aniline cost and availablity are reasonable, the preferred route is aniline ring reduction; alternatively the cyclohexanol amination route is chosen.

Rhodium was about three times the price of gold through 1988–1989 until skyrocketing to $74/g (~$2300/troy oz) in early 1990. Thus precious metal catalyst costs require an absolute minimum level of use and maximum number of catalyst

Health and Safety Factors (Toxicology)

Cycloaliphatic amines and diamines are extreme lung, skin, and eye irritants. MSD sheets universally carry severe personal protective equipment use warnings due to the risk of irreversible eye damage. These compounds are generally not mutagenic in the Ames test, and are highly (50–500 mg/kg) to moderately (500–5000 mg/kg) toxic as graded by the Hodge–Sterner scale by acute animal testing (66) (Table 5).

Table 5. Acute Toxicity of Cycloaliphatic Amines

Cycloaliphatic amine	Rat oral LD_{50}, mg/kg
cyclohexylamine	360
dicyclohexylamine	370
N-methylcyclohexylamine	400
dimethylcyclohexylamine	348
N-ethylcyclohexylamine	590
cis,trans-1,3-cyclohexanediamine	390
methyl-1,3-cyclohexanediamine	1060
4-methyl-1,3-cyclohexanediamine	1410[a]
1,3-diaminomethylcyclohexane	880
1,4-diaminomethylcyclohexane	530
1,8-menthanediamine	700
1-adamantylamine	900
methylenedi(cyclohexylamine)	450
3,3′-dimethylmethylenedi(cyclohexylamine)	550
tricyclodecanediamine	502

[a]Ref. 67.

Use of dry chemical, alcohol foam, or carbon dioxide is recommended for cycloaliphatic amine fire fighting. Water spray is recommended only to flush spills away to prevent exposures. In the aquatic environment, cyclohexylamine has a high (420 mg/L) toxicity threshold for bacteria (*Pseudomonas putida*) (68), and is considered biodegradable, that is, mineralizable to CO_2 and H_2O, by acclimatized bacteria.

Uses

Cyclohexylamine is miscible with water, with which it forms an azeotrope (55.8% H_2O) at 96.4°C, making it especially suitable for low pressure steam systems in which it acts as a protective film-former in addition to being a neutralizing amine. Nearly two-thirds of 1989 U.S. production of 5000–6000 t/yr cyclohexylamine serviced this application (69). Carbon dioxide corrosion is inhibited by deposition of nonwettable film on metal (70). In high pressure systems CHA is chemically more stable than morpholine [110-91-8] (71). A primary amine, CHA does not directly generate nitrosamine upon nitrite exposure as does morpholine. CHA is used for corrosion inhibitor radiator alcohol solutions, also in paper- and metal-coating industries for moisture and oxidation protection.

Use of 1,3-cycloaliphatic diamines as organic intermediates appears limited because of cis isomer endocyclization reactions. Ring hydrogenation of the low cost 80/20 2,4-/2,6-toluenediamine isomer mixture results in 4 geometric isomers of 4-methyl-1,3-cyclohexanediamine, 3 isomers of 2-methyl-1,3-cyclohexanediamine; the overall sum of methyl cis-1,3-diamine is ~50%. Phosgenation of the free-base or dicarbamate of hydrogenated TDA to produce methylcyclohexanediisocyanate results in low yields (81,82), possibly because of endocyclic urea formation. Diequatorial 1,3-cyclohexanediamine (35) is conformationally labile, and in the alternative 1,3-diaxial diamine conformation (36) allows facile condensation to urea (37). Phosgenation of the methylcyclohexanediamine dihydrochloride, however, is efficient, giving ~90% yields of methylcyclohexanediisocyanate in 4–14 hours at 125–185°C and, depending on solvent, pressure to 1 MPa (145 psi) (83).
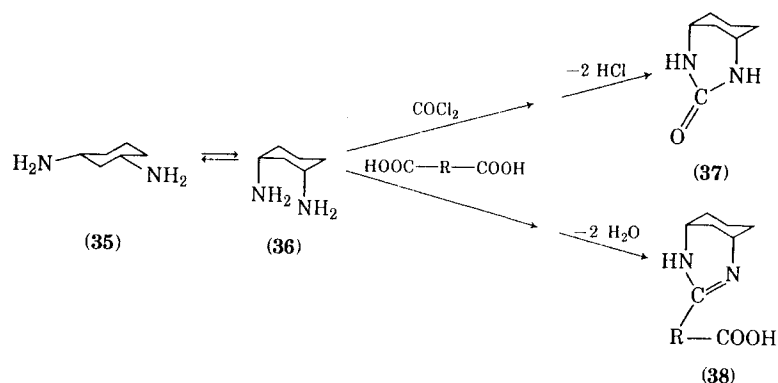
Use of 1,3 cycloaliphatic diamines in polyamides may be similarly limited by internal amide dehydration of the conformationally labile cis isomers to form a tetrahydropyrimidine (38) rather than high molecular weight polyamide. 1,3-Cyclohexanediamine is, however, a component of Spandex polyureas; Du Pont uses the hydrogenation product of m-phenylenediamine [108-45-2] (24) captively to produce Lycra (see FIBERS, ELASTOMERIC).

1,8-Menthanediamine has been effectively reacted to form polyamides (84) and is sold in metric tons per year volume as a premium (~$13/kg) epoxy curative (85) by Rohm and Haas. 1-Adamantylamine hydrochloride [665-66-7] is a prophylactic against type A viral infections sold by Du Pont under the trade name Symmetrel.

Derivatives

Before a 1/1/70 FDA ban (rescission proposed in early 1990), cyclamate noncaloric sweeteners were the major derivatives driving cyclohexylamine production. The cyclohexylsulfamic acid sodium salt (39) [139-05-9] and more thermally stable calcium (40) [139-06-1] salts were prepared from high purity cyclohexylamine by, among other routes, a reaction cycle with sulfamic acid.

(45)   (46)   (47)
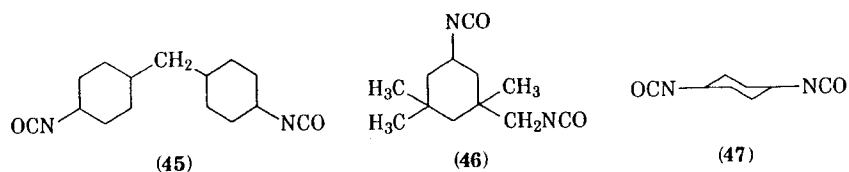
A representative agrochemical application of cycloaliphatic amines is the reaction of the commercial 30/70 cis/trans isomer mixture of 2-methylcyclohexylamine with phenylisocyanate to give the crabgrass and weed control agent Siduron (1-(2-methylcyclohexyl)-3-phenylurea (48) [1982-49-6] (91). The preplant herbicide Cycloate used for sugar beets, vegetable beets, and spinach, (S-ethyl-N-ethyl-N-cyclohexylthiocarbamate (49) [1134-23-2], incorporates N-ethylcyclohexylamine. The herbicide Hexazinone (3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4-dione (50) [51235-04-2]) is prepared from cyclohexylisocyanate [3173-53-3] (92).

(48)   (49)   (50)
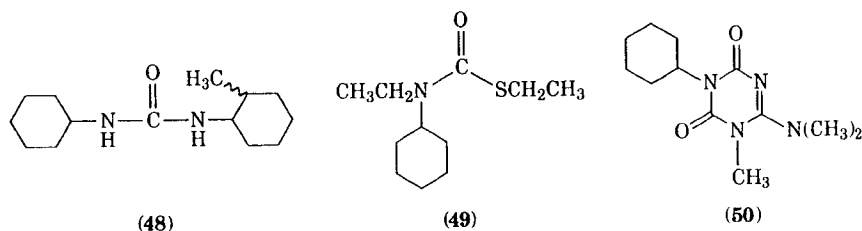
BIBLIOGRAPHY

"Amines" in ECT 1st ed., Vol. 1, pp. 702–717, by E. F. Landau, Celanese Corporation of America; "Amines, Survey" in ECT 2nd ed., Vol. 2, pp. 99–116, by Richard L. Bent, Eastman Kodak Company; "Amines, Cyclic" in ECT 3rd ed, Vol. 2, pp. 295–308, by Kenneth Mjos, Jefferson Chemical Company.

1. A. E. Barkdoll, H. W. Gray, and W. Kirk, J. Am. Chem. Soc. 73, 741–746 (1951).
2. T. F. Mika and R. S. Bauer, in C. A. May, ed., Epoxy Resins Chemistry and Technology, 2nd ed., Marcel Dekker, New York, 1988, pp. 465–550.
3. H. Lee and K. Neville, in Handbook of Epoxy Resins, McGraw-Hill, 1967, (1982 reissue), Chapt. 7.
4. EPON Resin Structural Reference Manual, Shell Chemical Company.
5. W. S. Emerson, in R. Adams, ed., Organic Reactions, Vol. 4, John Wiley & Sons, Inc., New York, 1948, Chapt. 3, pp. 174–255.
6. J. March, Advanced Organic Chemistry, Reactions, Mechanisms and Structure, 3rd ed., John Wiley & Sons, Inc., New York, 1985.
7. U.S. Pat. 3,532,748 (Oct. 6, 1970), G. W. Smith (to E. I. du Pont de Nemours & Co.).
8. U.S. Pat. 3,551,487 (Dec. 29, 1970), B. R. Bluestein, J. M. Solomon, and L. B. Nelson (to Witco).
9. T. S. Carswell and H. L. Morrill, Ind. Eng Chem. 29, 1247–1251 (1937).
10. U.S. Pat. 3,364,261 (Jan. 16, 1968), F. H. Van Munster (to Abbott).
11. Jpn. Kokai 85 239,444 (Nov. 28, 1985), H. Matsumoto, K. Hiraska, M. Hasiguchi, and H. Arimatsu (to Honshu).

52. U.S. Pat. 3,270,044 (Aug. 30, 1966), K. Schmitt, J. Disteldorf, W. Hubel, and K. Rindtorff (to Hibernia-Chemie Gesellschaft).
53. U.S. Pat. 4,299,775 (Nov. 10, 1981), B. Dubreux (to PCUK).
54. U.S. Pat. 4,429,157 (Jan. 31, 1984), J. Disteldorf, W. Hubel, and L. Broschinski.
55. L. Born, D. Wendisch, H. Reiff, and D. Dieterich, *Angew. Makrol. Chem.* **171**, 213–231 (1989).
56. U.S. Pat. 4,070,399, (Jan. 24, 1978), W. A. Butte (to Suntech).
57. U.S. Pat. 3,334,149 (Aug. 1, 1967), G. A. Akin, H. J. Lewis, and T. F. Reid (to Eastman Kodak).
58. Fr. Pat. 1575505, (May 21, 1962), V. L. R. Brown, J. G. Smith and T. E. Stanin (to Eastman Kodak).
59. D. V. Sokol'skii, A. E. Temirbulatova, and A. Ualikhanova, *Zh. Prik. Khim.* **56**, 1610–1614 (1983).
60. U.S. Pat. 3,450,759 (June 17, 1969), J. M. Cross, C. D. Campbell, and S. H. Metzger (to Mobay).
61. J. G. Theivagt, P. F. Helgren, and D. R. Luebke, "Cyclohexylamine," *Encyclopedia of Industrial Chemical Analysis,* Vol. 11, John Wiley & Sons, Inc., New York, 1971, pp. 209–219.
62. F. R. Prince and E. M. Pearce, *Macromolecules,* **4**, 347–350 (1971).
63. M. L. Moore, in R. Adams, ed., *Organic Reactions,* Vol. 5, John Wiley & Sons, Inc., New York, 1949, Chapt. 7, pp. 301–330.
64. M. W. Scroggins, L. Skurcenski, and D. S. Weinberg, *J. Chrom. Sci.* **10**, 678–681 (1972).
65. M. W. Scroggins, *J. Chrom. Sci.* **13**, 146–148 (1975).
66. T. J. Haley in N. L. Sax, ed., *Dangerous Properties of Industrial Materials,* 6th ed., sect. 1, Van Nostrand-Reinhold, New York, 1984.
67. Reference 66, p. 887 (misprinted as 1410 μg/kg).
68. K. Verschueren, ed., *Handbook of Environmental Data on Organic Chemicals,* 2nd ed., Van Nostrand-Reinhold, New York, 1983.
69. M. McCoy, *Chemical Marketing Reporter* (Aug. 28, 1989).
70. H. L. Kahler and J. K. Brown, *Combustion,* 55–58 (1954).
71. B. Tuck and E. M. Osborn, *Chem. Ind.,* 326–331 (1960).
72. U.S. Pat. 4,473,666 (Sept. 25, 1984), F. A. Casati, D. S. Raden, and F. W. Arbir (to Abbott).
73. U.S. Pat. 4,286,086 (Aug. 25, 1981), V. Mark (to General Electric).
74. U.S. Pat. 4,794,158 (Dec. 27, 1988), M. Hasuo, H. Urabe, M. Kawai, and T. Ohsako (to Mitsubishi Kasei).
75. U.S. Pat. 3,703,595 (Nov. 21, 1972), G. Falkenstein and co-workers (to BASF).
76. U.S. Pat. 4,525,571 (June 25, 1985), C. Burba and H. Franz (to Schering AG).
77. U.S. Pat. 3,629,181 (Dec. 21, 1971), A. Heer, W. Schneider, and B. Dreher (to CIBA Limited).
78. Can. Pat. 892,636 (Feb. 8, 1972), J. M. Cross and R. V. Norton (to Mobay).
79. U.S. Pat. 2,817,644 (Dec. 24, 1957), E. C. Shokal and H. A. Newey (to Shell).
80. U.S. Pat. 4,849,544 (July 18, 1989), S. A. Culley, K. A. Keblys, and C. J. Nalepa (to Ethyl).
81. U.S. Pat. 3,351,650 (Nov. 7, 1967), J. M. Cross, S. H. Metzger, and C. D. Campbell (to Mobay).
82. U.S. Pat. 3,419,612 (Dec. 31, 1968), J. M. Cross, S. H. Metzger, and C. D. Campbell (to Mobay).
83. U.S. Pat. 3,651,118 (Mar. 21, 1972), M. Cenker and P. T. Kan (to Mobay).
84. D. L. Trumbo, *J. Poly. Sci., part A, Poly. Chem.* **26**, 1859–2862 (1988).
85. A. Sabra, J. P. Pascault, and G. Seytre, *J. Appl. Polym. Sci.* **32**, 5147–5160 (1986).
86. H. G. Khorana, *Chem. Ind.* 1087–1088 (1955).
87. C. A. Byrne, D. P. Mack, and J. M. Sloan, *Rubber Chem. Tech.* **58**, 985–996 (1985).

, poultry, sauces, soups.

- 21CFR 182. GRAS when
ot in excess of the amount
d to accomplish the intended
CFR 318.7, 381.147. Suffi-

cology Program.

E: Moderately toxic by in-
Mildly toxic by ingestion and
xperimental teratogen. Human
by ingestion and intravenous
e, hallucinations and distorted
che, dyspnea, nausea or vom-
al reproductive effects. When
position it emits toxic fumes
).

and CODEN

5 g/kg (MGN):TER   EXPEAM

g/kg (14D pre-21D post):REP

104 mg/kg (17D preg):TER

50 mg/kg:PUL   NEJMAG

13 mg/kg:CNS,GIT   HYSAAV

g/kg   FRPPAO 27,19,72

CAS: 2163-80-6

M METHYLARSONATE

Ja   mw: 161.96

0 ◇ ARSONATE LIQUID ◇ ASAZOL
JATE 6 ◇ DAL-E-RAD ◇ HERB-ALL
RGE ◇ MESAMATE ◇ MESAMATE CON-
HYLARSENIC ACID, SODIUM SALT
IOSODIUM ACID METHANEARSONATE
CID METHARSONATE ◇ MONOSODIUM
TE ◇ MONOSODIUM METHANEAR-
MA ◇ NCI-C60071 ◇ PHYBAN
SODIUM ACID METHANEARSONATE
NEARSONATE ◇ TARGET MSMA
WEED 108 ◇ WEED-E-RAD ◇ WEED-

):

icide.
Animal feed, cottonseed hulls.
DA - 21CFR 561.280. Limitation
As₂O₃ in cottonseed hulls when
al feed.

Arsenic and its compounds are on the Commu-
nity Right-To-Know List. EPA Genetic Toxicol-
ogy Program.

OSHA PEL: TWA 0.5 mg(As)/m³   ACGIH
TLV: TWA 0.2 mg(As)/m³

SAFETY PROFILE: Poison by unspecified
route. Moderately toxic by ingestion. A skin
and eye irritant. When heated to decomposition
it emits toxic fumes of As and Na_2O.

TOXICITY DATA and CODEN

skn-rbt 54 mg open MLD   CIGET* -,-,77
eye-rbt 34 mg MLD   CIGET* -,-,77
orl-rat LD50:700 mg/kg   FMCHA2 -,C163,83

MRN260
MORANTEL TARTRATE
CAS: 26155-31-7

mf: $C_{12}H_{16}N_2S \cdot C_4H_6O_6$ mw: 370.46

SYNS: BANMINTH II ◇ MORANTREL TARTRATE

USE IN FOOD:

Purpose: Animal drug.

Where Used: Beef, milk.

Regulations: FDA - 21CFR 556.425. Limitation
of 0.70 ppm of N-methyl-1,3-propanediamine
in liver of cattle. Limitation of 0.4 ppm in milk.
21CFR 558.360.

SAFETY PROFILE: When heated to decompo-
sition it emits acrid smoke and irritating fumes.

TOXICITY DATA and CODEN

orl-rat LD50:926 mg/kg   AUVJA2 46,297,70

MRP750
MORPHOLINE
CAS: 110-91-8

DOT: 2054/1760
mf: C_4H_9NO mw: 87.14

PROP: Colorless, hygroscopic oil; amine odor.
Bp: 128.9°, fp: -7.5°, flash p: 100°F (OC),
autoign temp: 590°F, vap press: 10 mm @ 23°,
vap d: 3.00, mp: -4.9°, d: 1.007 @ 20°/4°.
Volatile with steam; misc with H_2O evolving
some heat; misc with acetone, benzene, ether,
castor oil, methanol, ethanol, ethylene, glycol,
linseed oil, turpentine, pine oil. Immiscible with
concentrated NaOH solns.

SYNS: DIETHYLENEIMIDE OXIDE ◇ DIETHYLENE
IMIDOXIDE ◇ DIETHYLENE OXIMIDE ◇ DIETHYLENIMIDE
OXIDE ◇ MORPHOLINE, AQUEOUS MIXTURE (DOT)
◇ 1-OXA-4-AZACYCLOHEXANE ◇ TETRAHYDRO-p-
ISOXAZINE ◇ TETRAHYDRO-1,4-ISOXAZINE ◇ TETRA-
HYDRO-1,4-OXAZINE ◇ TETRAHYDRO-2H-1,4-OXAZINE

USE IN FOOD:

Purpose: Boiler water additive, protective coat-
ing.

Where Used: Fruits (fresh), vegetables (fresh).

Regulations: FDA - 21CFR 172.235. Limited
use as one of the salts of fatty acids meeting
the requirements of 21CFR 172.860. FDA -
21CFR 173.310. Limitation of 10 ppm in steam
and excluding use of such steam in contact with
milk and milk products.

EPA Genetic Toxicology Program.

OSHA PEL: TWA 20 ppm (skin); STEL 30
ppm (skin)   ACGIH TLV: TWA 20 ppm;
STEL 30 ppm (skin)   DFG MAK: 20 ppm (70
mg/m³)   DOT Classification: Flammable Liq-
uid; Label: Flammable Liquid; Corrosive Mate-
rial; Label: Corrosive, aqueous solution.

SAFETY PROFILE: Moderately toxic by inges-
tion, inhalation, skin contact, intraperitoneal
and possibly other routes. An experimental neo-
plastigen. Mutagenic data. A corrosive irritant
to skin, eyes, and mucous membranes. Can
cause kidney damage. Flammable liquid. A very
dangerous fire hazard when exposed to flame,
heat, or oxidizers; can react with oxidizing mate-
rials. To fight fire, use alcohol foam, CO_2, dry
chemical. Mixtures with nitromethane are ex-
plosive. May ignite spontaneously in contact
with cellulose nitrate of high surface area. When
heated to decomposition it emits highly toxic
fumes of NO_x.

TOXICITY DATA and CODEN

skn-rbt 995 mg/24H SEV   BIOFX* 10-4/70
eye-rbt 2 mg SEV   AJOPAA 29,1363,46
otr-mus:lym 1 µL/L   ENMUDM 4,390,82
orl-mus TDLo:2560 mg/kg/Y-C:NEO   GISAAA
   44(8),15,79
orl-rat LD50:1050 mg/kg   UCDS** 4/21/67
ihl-rat LC50:8000 ppm/8H   NPIRI* 1,85,74

MRW775
MYCLOBUTANIL

SYN: α-BUTYL-α(4-CHLOROPHENYL)-1H-1,2,4-TRI-
AZOLE-1-PROPANENITRILE

USE IN FOOD:

Purpose: Fungicide.

Where Used: Raisins.

Regulations: FDA - 21CFR 193.477. Limitation
of 5 ppm in raisins. (Expires 2/28/1988)

Coosselin, Smith, Hodge

The vapor is also irritating to
ct, and various laboratory ani-
acutely to 104 ppm exhibited
· distress, lethargy and mild de-
in liver and kidneys (Treon et
y Treon, 1962). The OSHA air
; 3 ppm. In consumer products,
is usually present as a neutral
many acids, and as such, the
cation is believed to lack sig-
lthough no published evidence

tion in rat livers and causes a
ygen uptake and respiratory quo-
ssue. The chief clinical toxicity
bly moderate skin irritation and
ritation, perhaps with corrosive
nd esophagus. The presumptive
tancy is the high alkalinity of
water. A 0.1N aqueous solution
vhich suggests that it is a stron
iethanolamine but weaker than
ie. As a neutral salt, cationic di-
probably innocuous, but the pos-
jury after ingestion needs to be

973.

ie, TEA

fect in animals has been ascribed
(systemic alkalosis), but as with
(above), functional signs of tran-
have been described in animals
doses. Gross pathology has been
astrointestinal tract in fatal oral
ts and guinea pigs. Percutaneous
oid, but the compound is less irri-
d mucous membranes than most

the possibility of effects on liver
t be excluded (see Triethanolamine
the index for information about
ing sodium salt or look under the
d.

sis. In contrast the amine salts (e.g
are relatively benign.

69 Tris(hydroxymethyl)aminomethane 69

2-Amino-2-hydroxymethyl-1,3-propanediol, Tris, Tromethamine

Toxicity Rating: 3. A commercial emulsifier. Aqueous solutions are alkaline and consequently irritating. Even after neutralization, large oral doses in laboratory animals cause weakness, collapse, and coma (without convulsions). Injections of high doses in animals produce hypoglycemia, but concurrent administration of glucose does not prevent death. Solutions have been infused intravenously in human patients to correct acidosis and to promote diuresis. Doses of up to 76 grams (!) in one hour have caused hypoglycemia, but doses of 20 gm. produced no adverse effects.

Ref.: Brinkman et al., 1960; Commercial Solvents Corp., 1954; Roberts and Linn, 1961.

70 2-Amino-2-methyl-1-propanol 70

Toxicity Rating: 3. An emulsifier used in small amounts in polishes (floor, auto, shoe, etc.). Aminohydroxy compounds react with higher fatty acids to form soaps possessing good emulsifying powers. The oral toxicity of these compounds is low in rabbits and presumably in man. Prolonged skin exposure may cause irritation due to the alkalinity of the free material, but in most commercial formulas this alkalinity is neutralized. Allergic dermatitis is not described.

Ref.: Commercial Solvents Corp., 1954.

71 2-Amino-2-methyl-1,3-propanediol 71

Toxicity Rating: 3. An emulsifier used in small amounts in polishes, cleaners, cosmetic creams, etc. Aminohydroxy compounds react with higher fatty acids to form soaps possessing good emulsifying powers. The oral toxicity of these compounds is low in rabbits and presumably in man. Prolonged skin exposure may cause irritation due to the alkalinity of the free material, but in most commercial formulas this alkalinity is neutralized. Allergic dermatitis is not described.

Ref.: Commercial Solvents Corp., 1954.

72 Morpholine 72

Tetrahydro-1,4-oxazine, Diethyleneimide oxide

Toxicity Rating: 4. A secondary amine used as a corrosion inhibitor, as an antioxidant, and in the form of salts as an emulsifying agent. Strongly alkaline. Liquid and vapor are irritating to skin and mucous membranes. In rats pulmonary edema, liver necrosis, and renal tubular degeneration, but only at vapor concentrations which are intensely irritating. Moderately high percutaneous toxicity in rabbits. On the skin the liquid may produce necrosis.

Ref.: Amer. Petroleum Institute, 1948e.

Peroxides and peroxy-acids (inorganic and organic)

73 Hydrogen Peroxide 73

Official aqueous solutions are 3% with respect to H_2O_2. Said to have a low toxicity. No primary systemic effects when ingested because it is decomposed in the bowel before absorption. Decomposition may release large volumes of oxygen (10 times the volume of solution). Large doses presumably produce esophagitis and gastritis. Cases of rupture of the colon, proctitis and ulcerative colitis have been reported following hydrogen peroxide enemas. Powders and tablets that generate hydrogen peroxide, such as $KHSO_5$, have caused oral and esophageal burns when ingested.

Ref.: Abramson, 1978; Sheehan and Brynjolfsson, 1960.

74 Sodium Peroxide 74

Said to have a low toxicity. No primary systemic effects when ingested because it is decomposed in the bowel before absorption. Decomposition may release large volumes of oxygen (10 times the volume of the solution). Large doses presumably produce gastritis and esophagitis. Cases of rupture of the colon, proctitis and ulcerative colitis have been reported following hydrogen peroxide enemas.

Ref.: Sheehan and Brynjolfsson, 1960.

75 Methyl Ethyl Ketone Peroxide (and Hydroperoxides) 75

Available as a 60% solution in dimethyl phthalate (Lupersol DDM) to serve as a catalyst for polymerizing plastics. The mixture has a toxicity rating of 4 in mice (administered by mouth after diluting

Proctor & Hughes

1478

Hygiene and Toxicology. ed. 2, pp. 2218–2222. New York: Interscience, 1963.

5. A.C.G.I.H.: Monomethyl hydrazine. Documentation of the TLVs for Substances in Workroom Air. ed. 3, pp. 174–175. Cincinnati, 1976.

6. Adams, R. D.: The convulsive state and idiopathic epilepsy. *In* Thorn, G. W. *et al.* (eds.): Harrison's Principles of Internal Medicine. ed. 8, pp. 127–135. New York: McGraw-Hill, 1977.

MORPHOLINE

C_4H_9NO 1977 TLV 20 ppm

Synonyms: Diethylene oxide; diethylene imidoxide; diethylene oximide; *p*-isoxazine, tetrahydro; 1–oxa–4–azacyclohexane; 2H–1, 4–oxazine; tetrahydro–2H–1, 4–oxazine

Physical Form: Mobile hygroscopic liquid

Uses: Solvent for resins, waxes, casein, dyes; morpholine compounds used as corrosion inhibitors, insecticides, antiseptics

Exposure: Inhalation; skin absorption

Toxicology: Morpholine vapor is an irritant of the mucous membranes.

In industry, some instances of skin and respiratory tract irritation have been observed, but no chronic effects have been reported.[1] A human exposure to 12,000 ppm for 1.5 minutes in a laboratory produced nose irritation and cough; mouth pipetting of the liquid caused a severe sore throat and reddened mucous membranes.[2] Workers exposed for several hours to low vapor concentrations complained of foggy vision with rings around lights, the result of corneal edema which cleared within three to four hours after cessation of exposure.[3] The liquid is a severe skin irritant.[1]

Repeated daily exposure of rats to 18,000 ppm was lethal to some animals; those dying during the third to fifth days of exposure had damage to lungs, liver, and kidneys.[2] The liquid dropped in the eye of a rabbit caused moderate injury, with ulceration of the conjunctiva and corneal clouding.[3]

The TLV was set at a level to prevent irritation and harmful effects on the eyes and vision.[2]

Diagnosis: Signs and symptoms include visual aberrations; nose irritation; cough; respiratory irritation; severe eye and skin irritation from liquid splashes; skin irritation from repeated or prolonged overexposure.

Differential Diagnosis: Differentiate from other causes of conjunctivitis and mucous membrane irritation, such as viral infection of the upper respiratory tract and allergies.

Special Tests: If severe exposure is suspected, diagnostic studies should include electrocardiogram, sputum gram stain and culture, and differential white blood cell count. If pulmonary edema occurs, there should be analysis of arterial blood gas.

Treatment: Institute appropriate procedures, such as removal from exposure, immediate flushing of eyes with water, and washing of skin with soap and water. If dermatitis occurs, see section in Chapter 5 on Treatment of Contact Dermatitis. If exposure is severe, hospitalization and observation for 72 hours for delayed onset of severe pulmonary edema are advisable. Refer to Therapeutic Maneuvers in Treatment of Respiratory Irritants, Chapter 6.

Medical Control: Preplacement questionnaire with emphasis on detecting a history of chronic respiratory, liver, kidney, eye, or skin disease. Such persons may be at increased risk from exposure.

References

1. Sutton, W. L.: Heterocyclic and miscellaneous nitrogen compounds. *In* Fassett, D. W., and Irish, D. D. (eds.): Toxicology. vol. 2. *In* Patty, F. A. (ed.): Industrial Hygiene and Toxicology. ed. 2, pp. 2202–2204. New York: Interscience, 1963.

2. A.C.G.I.H.: Morpholine. Documentation of the TLVs for Substances in Workroom Air. ed. 3, pp. 175–176. Cincinnati, 1976.

3. Grant, W. M.; Toxicology of the Eye. ed. 2, pp. 722–723. Springfield: Charles C Thomas, 1974.

NALED

$(CH_3O)_2P(O)OHCBrCBrCl_2$
1977 TLV 3 mg/m³

Synonyms: DIBROM; 1,2–dibromo–2,2–dichloroethyl dimethyl phosphate; RE 4355

Physical Form: Light straw-co with slightly pungent odor

Uses: Acaricide; insecticide

Exposure: Inhalation; skin abs gestion

Toxicology: Naled is an antich gent.

Signs and symptoms of overe caused by the inactivation of cholinesterase, which results in ation of acetylcholine in the nerv skeletal and smooth muscles, an glands.[1-3] The sequence of the of systemic effects varies with entry. The onset of signs and s usually prompt, but it may be de to 12 hours. After inhalation of t piratory and ocular effects are appear, often within a few minu posure. Respiratory effects incl in the chest due to bronchocon excessive bronchial secretion spasms and excessive salivation the respiratory distress; cyano occur. Ocular effects include mi of distant vision (due to spasm dation), tearing, rhinorrhea, headache.

After ingestion of the liquid, nal effects, such as anorexia, n ing, abdominal cramps, and dia within 15 minutes to two hour absorption of the liquid, locali and muscular fasciculations in t area usually occur within 15 mi hours; skin absorption is somew higher ambient temperatures an by the presence of dermatitis.

With severe intoxication, acetylcholine at the neuromusc of skeletal muscle causes weak aggravated by exertion, involu ings, fasciculations, and eventu The most serious consequence the respiratory muscles. Effec tral nervous system include glid ion, ataxia, slurred speech, c respiration, convulsions, com reflexes. The blood pressure n levels and cardiac irregularit complete heart block, may oc symptomatic recovery usually one week; increased susceptib fects of anticholinesterase age
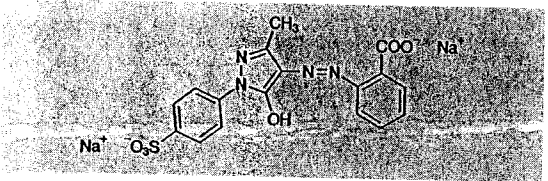
Ashford

Morpholine

Production:
- Broenner's acid + salicylic acid (diazotisation/azo coupling)

Uses: dye (wool)
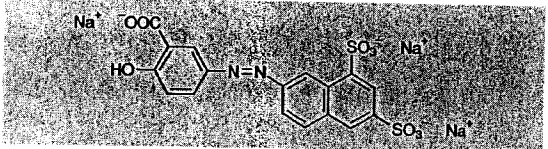
Mordant Yellow 8
18821 (CI)

$C_{17}H_{12}N_4Na_2O_6S_1$. M: 446.35.

Production:
- anthranilic acid + 1-(4′-sulphophenyl)-3-methyl-pyrazolone (diazotisation/azo coupling)

Uses: dye (wool, silk, leather)
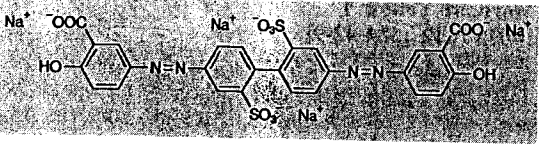
Mordant Yellow 20
14110 (CI)

$C_{17}H_9N_2Na_3O_9S_2$. M: 518.36.

Production:
- amino-G acid + salicylic acid (diazotisation/azo coupling)

Uses:
dye (wool, leather)

Mordant Yellow 26
22880 (CI)

$C_{26}H_{14}N_4Na_4O_{12}S_2$. M: 730.51.

Production:
- benzidine-2,2′-disulphonic acid + salicylic acid (diazotisation/azo coupling)

Uses:
dye (wool, silk, polyamide, cotton, leather)

moroxydine
[3731-59-7]
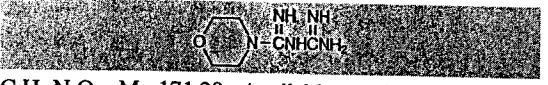
$C_6H_{13}N_5O_1$. M: 171.20. Available as the free base or hydrochloride.

Production:
- morpholine + dicyandiamide (nitrile addition)

Uses: antiviral drug

morphine
[57-27-2]
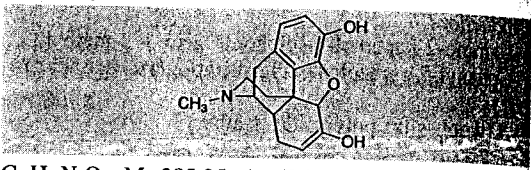
$C_{17}H_{19}N_1O_3$. M: 285.35. Available commercially as the free base monohydrate, acetate trihydrate, tartrate tetrahydrate, various phosphate and other derivatives.

Production:
- opium (extraction; coproduced with codeine/thebaine)

Derivatives: codeine; hydromorphone; normorphine

Uses: analgesic drug

morpholine
[110-91-8]
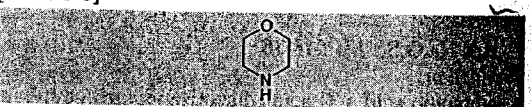
$C_4H_9N_1O_1$. M: 87.12. Colourless liquid with an amine-like odour. BP: 127–130°C. FP: -5°C. d: 1.00 kg/l (20°C). Soluble in water.

Production:
- diethylene glycol + ammonia (amine formation)
- diethanolamine (dehydration)

Derivatives: N-(3-aminopropyl)morpholine; bis(2-morpholinoethyl)ether; N-cetyl ethylmorpholinium ethosulphate; dextromoramide; 4,4′-dithiodimorpholine; Fluorescent Brightener 103; Fluorescent Brightener DM; 4-(2-hydroxyethyl)morpholine; molsidomine; moroxydine; 2-morpholinobenzothiazylsulphenamide; 2-morpholinodithiobenzothiazole; morpholinomethylnitropropane adduct; N-oxydiethylenedithiocarbamyl-N′-oxydiethylenesulphenamide; timolol

Uses: corrosion inhibitor (boilers, steam distribution systems); solubiliser (water-based printing inks); solvent

2-morpholinobenzothiazylsulphenamide
benzothiazyl-2-(oxydiethylene)sulphenamide; MBS; 2-(morpholinothio)benzothiazole
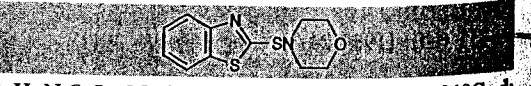
$C_{11}H_{12}N_2O_1S_2$. M: 252.36. Brown flakes. MP: 81°C. d: 1.34 kg/l. Insoluble in water. Soluble in oxygenated and aromatic solvents.

Production:
- 2-mercaptobenzothiazole + morpholine (oxidative coupling)

Uses: vulcanisation accelerator

Carbon Dioxide but Not Bicarbonate Inhibits N-Nitrosation of Secondary Amines. Evidence for Amine Carbamates as Protecting Entities

Michael Kirsch,[†] Hans-Gert Korth,[‡] Reiner Sustmann,[‡] and Herbert de Groot*,[†]

*Institut für Physiologische Chemie, Universitätsklinikum Essen, Hufelandstrasse 55,
D-45122 Essen, and Institut für Organische Chemie, Universität-GH Essen, Universitätsstrasse 5,
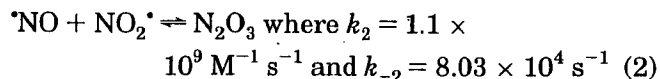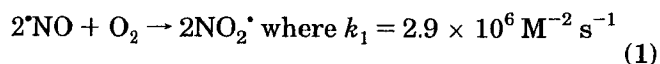D-45117 Essen, Germany*

Hydrogen carbonate (bicarbonate, HCO_3^-) has been proposed to accelerate the decomposition of N_2O_3 because N-nitrosation of morpholine via a nitric oxide/oxygen mixture ($\cdot NO/O_2$) was inhibited by the addition of HCO_3^- at pH 8.9 [Caulfield, J. L., Singh, S. P., Wishnok, J. S., Deen, W. M., and Tannenbaum, S. R. (1996) *J. Biol. Chem.* **271**, 25859−25863]. In the study presented here, it is shown that carbon dioxide (CO_2) is responsible for this kind of protective effect because of formation of amine carbamates, whereas an inhibitory function of HCO_3^- is excluded. N-Nitrosation of morpholine (1−10 mM) at pH 7.4−7.5 by the $\cdot NO$-donor compounds PAPA NONOate and MAMA NONOate (0.5 mM each) was not affected by the presence of large amounts of HCO_3^- (up to 100 mM) in aerated aqueous solution. Similar results were obtained by replacing the $\cdot NO$-donor compounds with authentic $\cdot NO$ (900 μM). In agreement with data from the study cited above, $\cdot NO/O_2$-mediated formation of N-nitrosomorpholine (NO-Mor) was indeed inhibited by about 45% in the presence of 50 mM HCO_3^- at pH 8.9. However, 500 MHz ^{13}C NMR analysis with ^{13}C-enriched bicarbonate revealed that significant amounts of morpholine carbamate are formed from reaction of equilibrated CO_2 with morpholine (1−100 mM) at pH 8.9, but only to a minor extent at pH 7.5. The protective effect of morpholine carbamate formation is explained by a significantly reduced charge density at nitrogen. This view is supported by the results of density functional theory/natural population analysis, i.e., quantumchemical calculations for morpholine and morpholine carbamate. In agreement with its lower pK_a, another secondary amine, piperazine, had already produced significant amounts of piperazine carbamate at pH 7.4 as shown by ^{13}C NMR spectrometry. Consequently, and in contrast to morpholine, N-nitrosation of piperazine (2 mM) by both $\cdot NO/O_2$ (PAPA NONOate, 0.5 mM) and the $\cdot NO/O_2^-\cdot$-releasing compound SIN-1 (1 mM) was inhibited by about 66% in the presence of 200 mM HCO_3^-.

Introduction

A variety of cells generate nitric oxide ($\cdot NO$) from L-arginine by a family of NADPH-dependent enzymes, the NO synthases. Among other functions, $\cdot NO$ is an important physiological mediator in smooth muscle relaxation, neurotransmission, and blood pressure regulation (*1*). Although in most biological systems the basal level of $\cdot NO$ lies in the nanomolar range, it can efficiently react with superoxide radicals ($O_2^-\cdot$) in a diffusion-controlled process [$k(\cdot NO + O_2^-\cdot) = 3.9-19 \times 10^9 \, M^{-1} \, s^{-1}$ (*2−4*)] to form the cytotoxic species peroxynitrite ($ONOO^-/ONOOH$) (*5*, *6*). At nanomolar concentrations, the rate of reaction of $\cdot NO$ with physiological concentrations of oxygen is too slow to be of great importance for the formation of the more toxic, higher nitrogen oxides, namely, $NO_2\cdot$, N_2O_3, and N_2O_4 [reactions 1−3 (*9−11*)]. However, under pathological conditions, the local $\cdot NO$ concentrations may increase to levels in the range of

$4-30 \, \mu M$ (*7*, *8*), thus additionally allowing the formation of, preferably, dinitrogen trioxide (N_2O_3) to proceed.

$$2\cdot NO + O_2 \rightarrow 2NO_2\cdot \quad \text{where } k_1 = 2.9 \times 10^6 \, M^{-2} \, s^{-1} \tag{1}$$

$$\cdot NO + NO_2\cdot \rightleftharpoons N_2O_3 \quad \text{where } k_2 = 1.1 \times 10^9 \, M^{-1} \, s^{-1} \text{ and } k_{-2} = 8.03 \times 10^4 \, s^{-1} \tag{2}$$

$$2NO_2\cdot \rightleftharpoons N_2O_4 \quad \text{where } 2k_3 = 9 \times 10^8 \, M^{-1} \, s^{-1} \text{ and } k_{-3} = 1.38 \times 10^4 \, s^{-1} \tag{3}$$
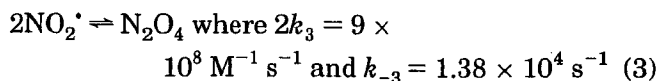
N_2O_3 is a very strong nitrosating species which effectively S-nitrosates sulfhydryl groups (*12*). The pathophysiological significance of N_2O_3 derives from its properties to generate mutagenic diazopeptides at terminal primary amino groups (*13*), to form carcinogenic N-nitrosoamines in the presence of secondary amines (*14*), and to deaminate the primary aromatic amines of DNA bases (*15*, *16*).

The aliphatic secondary amine morpholine has been used previously to study the nitrosative effects of $\cdot NO/O_2$ and, thus, of N_2O_3 at physiological pH (*17*, *18*). The major advantage of this model compound is that only one, stable, and easily detectable product, namely, N-nitroso-

* To whom correspondence should be addressed: Institut für Physiologische Chemie, Universitätsklinikum Essen, Hufelandstrasse 55, D-45122 Essen, Germany. Telephone: +201/723-4101. Fax: +201/723-5943. E-mail: h.de.groot@uni-essen.de.
† Universitätsklinikum Essen.
‡ Universität-GH Essen.

morpholine (NO-Mor),[1] is formed, in contrast to primary amines and thiols, which form a variety of products. Interestingly, at pH 7.4, chloride and phosphate react with N_2O_3 to yield presumably the intermediates nitrosyl chloride and nitrosyl phosphate (17). The inhibitory effect of these physiological anions toward N_2O_3-mediated formation of NO-Mor has been explained by the assumption that in aqueous solution nitrosyl chloride and nitrosyl phosphate are hydrolyzed faster than they react with amines (17). On the basis of experiments performed at pH 8.9, it has recently been postulated that the hydrogen carbonate (bicarbonate) anion (HCO_3^-) acts in a similar manner (19). As shown here, however, we found that HCO_3^- is unable to protect morpholine against the attack of N_2O_3 at a physiological pH. On the other hand, CO_2 prevented $\cdot NO/O_2$-induced nitrosation of morpholine at pH 8.9 and also of other amines at pH 7.4. This protective effect of CO_2 is related to the formation of amine carbamates, which are well-known protecting groups for primary and secondary amines in, for example, peptide synthesis (20). It is suggested that the formation of amine carbamates in vivo is a further possibility for preventing N-nitrosation of amines by both $\cdot NO/O_2$ and $\cdot NO/O_2^-\cdot$.

Experimental Procedures

Caution: *N-Nitrosomorpholine, N-nitrosodimethylamine, and N-mononitrosopiperazine are potentially carcinogenic and mutagenic compounds. SIN-1, MAMA NONOate, PAPA NONOate, and solutions of authentic $\cdot NO$ are hazardous chemicals. These chemicals yield nitrosoamines from morpholine and piperazine. Generally, care should be exercised in handling of these compounds.*

Materials. N-Nitrosomorpholine, N-nitrosodimethylamine, Chelex 100, sodium acetate, acetic acid, sodium nitrite, morpholine, and piperazine were obtained from Aldrich-Sigma (Deisenhofen, Germany). Sodium [^{13}C]bicarbonate (99% ^{13}C) was purchased from Cambridge Isotope Laboratories (Andover, MA). MAMA NONOate and PAPA NONOate were from Situs (Düsseldorf, Germany). SIN-1 and its decomposition product, SIN-1C, were generously provided by K. Schönafinger (Hoechst Marion Roussel, Frankfurt/Main, Germany). Nitric oxide 2.0, nitrogen 5.0, and a commercially available mixture of oxygen 5.0 and nitrogen 5.0 (20.5% O_2/79.5% N_2, "synthetic air") were obtained from Messer-Griessheim (Oberhausen, Germany). All other chemicals were of the highest purity commercially available. The program Chemical Kinetics Simulator 1.01 was kindly donated by International Business Machines Corp. (http.//www.almaden.ibm.com/st/msim/).

Solutions. Care was taken to exclude possible contamination by either bicarbonate or carbon dioxide and transition metals. Doubly distilled water was bubbled (2 L/min) with synthetic air at room temperature for 20 min. With this water, potassium phosphate buffer (50 mM) with various additives, namely, HCO_3^-, morpholine, and piperazine, was prepared freshly each day. The heavy metal scavenger resin Chelex 100 (0.3 g) was added to 10 mL of these solutions and incubated under gentle shaking for 18 h in the dark. After low-speed centrifugation for 5 min, the solutions were carefully decanted from the resin. Since the pH increased during the resin treatment by about 0.25 unit and because anions can influence the nitrosating activity of $\cdot NO/O_2$, the pH of all solutions had to be readjusted at 37 °C

by mixing two resin-treated solutions with different pH values. Aqueous $\cdot NO$ solutions were prepared in gastight bottles (2(mL) which were fitted with a septum. Oxygen purging of wate (15 mL) was accomplished by bubbling with N_2 (50 mL/min) fo 20 min at room temperature. Subsequently, a purified $\cdot NO$ ga stream (50 mL/min) was bubbled for 15 min through thes solutions. As checked with a fluorescent nitric oxide cheletropi trap (21), the solutions contained 1.8 mM $\cdot NO$. A stock solutior of N-mononitrosopiperazine (NO-Pip) was prepared by nitrit (10 mM)-induced nitrosation of piperazine (11 mM) at pH 4.9 in 80 mM acetate buffer. The absorbance of a piperazine-fre aliquot was read at 249 nm, and the reaction was started b adding piperazine. After incubation for 24 h at room tempera ture in the dark, the concentration of NO-Pip was detected b reading the absorbance at 249 nm ($\Delta\epsilon_{249} = 4530 \pm 9$ M^{-1} cm$^-$ (22). The reaction was stopped by adding 100 mM K_3PO_4 (1: v/v), and the stock solution containing 4.45 mM NO-Pip wa stored at −79 °C. A stock solution of morpholine carbamate wa prepared by adding 300 mM morpholine N-formyl chloride to M NaOH under vigorous stirring at 4 °C. Solutions of MAML NONOate, PAPA NONOate (in 10 mM NaOH each), and SIN- (in 50 mM H_2KPO_4) were prepared as 100-fold stock solution at 4 °C and used within 15 min after preparation.

Experimental Conditions. MAMA NONOate and PAP NONOate were added to 1 mL of phosphate buffer, and th mixture was incubated in reaction tubes (volume of each tut being 2.1 mL, Eppendorf, Hamburg, Germany). The experimen in the absence of HCO_3^- were carried out in a glovebag (Rotl Karlsruhe, Germany) under synthetic air. After addition of th NONOate, the closed tubes were thermostated in a water bat at 37 °C. The experiments with SIN-1 were performed ε described previously (23). Anaerobic solutions of authentic $\cdot N$ (1.8 mM, 200 µL) were mixed with aerobic solutions of morph line (2 mM, 100 mM potassium phosphate buffer, pH 7.4−10.! 200 µL) by vortexing in reaction tubes (2.1 mL) in the absen and presence of 100 mM HCO_3^- under authentic air at roo temperature. After the solution had been vortexed, the final p. was instantaneously measured.

Determination of N-Nitrosomorpholine and N-Mon nitrosopiperazine. NO-Mor and NO-Pip were quantified t capillary zone electrophoresis on a Beckman P/ACE 50(apparatus under the following conditions. For NO-Mor, we us a fused silica capillary column (50 cm effective length, 75 µ: internal diameter), hydrodynamic injection for 5 s, a temper ture of 30 °C, a voltage of 20 kV, normal polarity, and U detection at 254 nm. As an electrolyte solution, a mixture of ζ mM sodium phosphate and 100 mM sodium dodecyl sulfate (p 6.45) was used. To each sample was added 1 mM N-nitrosod methylamine as an internal standard. The detection limit w found at 9 µM NO-Mor. For NO-Pip, we used a fused sili capillary (50 cm effective length, 75 µm internal diametei hydrodynamic injection for 10 s, a temperature of 30 °C, voltage of 20 kV, normal polarity, and UV detection at 254 nr As an electrolyte solution, a mixture of 20 mM sodium pho phate and 75 mM sodium dodecyl sulfate (pH 11) was used. each sample was added 250 µM N-nitrosomorpholine as ε internal standard. The detection limit was found at 12 µM N(Pip. It should be noted that a quantitative analysis of tl nitrosoamine concentration by capillary zone electrophoresis c be performed without any extraction procedures.

Quantification of MAMA NONOate and PAPA NO Oate. The $\cdot NO$-donor compounds MAMA NONOate and PAF NONOate were quantified by reading the absorbance at 250 ρ ($\epsilon_{250} = 7300$ M^{-1} cm^{-1}) and at 252 nm ($\epsilon_{250} = 8100$ M^{-1} cm respectively (24).
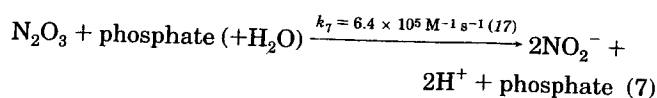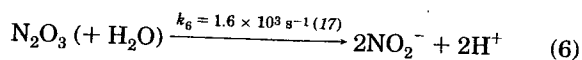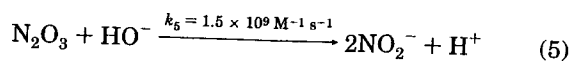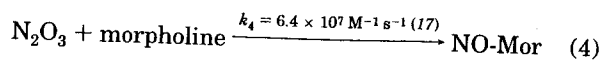
Quantification of Nitrite and Nitrate. NO_2^- and NO were quantified by the Griess method as described previou (25).

Identification of Morpholine Carbamate and Piper zine Carbamate. Morpholine carbamate and piperazine ca bamate were identified in 50 mM phosphate buffer soluti(

---

[1] Abbreviations: PAPA NONOate, (Z)-1-[N-(3-ammoniopropyl)-N-(n-propyl)amino]diazen-1-ium 1,2-diolate; MAMA NONOate, (Z)-1-(N-methyl-N-{6-[(N-methylammonio)hexyl]amino})diazen-1-ium 1,2-diolate; nitric oxide, nitrogen monoxide; SIN-1, 5-amino-3-(4-morpholinyl)-1,2,3-oxadiazolium; NO-Mor, N-nitrosomorpholine; NO-Pip, N-mononitrosopiperazine; DFT, density functional theory; NPA, natural population analysis; NBO, natural bond orbitals.

Protective Role of CO₂

Chem. Res. Toxicol., Vol. 13, No. 6, 2000 **453**

500 MHz ^{13}C NMR spectrometry on a Bruker AVANCE DRX500 instrument.

Kinetic Analysis. By far the most common computational methods of numerical simulations of chemical reactions used a deterministic approch, in which the time dependence of species concentrations is written as a set of coupled differential equations which are then integrated via an iterative process. The stochastic simulation method, which is used in the applied software package, simulates a reaction using probabilities derived from rate laws for each step in the mechanism. The stochastic simulation method approximates wrong yields when the employed number of molecules is too low, i.e., $n \leq 10^4 - 10^5$. The kinetic analysis of the experimental values was performed with both 2×10^9 molecules and the assumption of N_2O_3 acting as a nitrosating species using the following reaction rate constants:

$$N_2O_3 + \text{morpholine} \xrightarrow{k_4 = 6.4 \times 10^7 \text{ M}^{-1}\text{s}^{-1} \, (17)} \text{NO-Mor} \quad (4)$$

$$N_2O_3 + HO^- \xrightarrow{k_5 = 1.5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}} 2NO_2^- + H^+ \quad (5)$$

$$N_2O_3 (+ H_2O) \xrightarrow{k_6 = 1.6 \times 10^3 \text{ s}^{-1} \, (17)} 2NO_2^- + 2H^+ \quad (6)$$

$$N_2O_3 + \text{phosphate} (+H_2O) \xrightarrow{k_7 = 6.4 \times 10^5 \text{ M}^{-1}\text{s}^{-1} \, (17)} 2NO_2^- + 2H^+ + \text{phosphate} \quad (7)$$

$$N_2O_3 + HCO_3^- (+H_2O) \xrightarrow{k_8 = 1.49 \times 10^6 \text{ M}^{-1}\text{s}^{-1}} 2NO_2^- + 2H^+ + HCO_3^- \quad (8)$$

$$\text{morpholine} + H^+ \underset{k_{-9} = 588 \text{ s}^{-1}}{\overset{k_9 = 1 \times 10^{11} \text{ M}^{-1}\text{s}^{-1} \, (26)}{\rightleftharpoons}} \text{morpholinium ion} \quad (9)$$
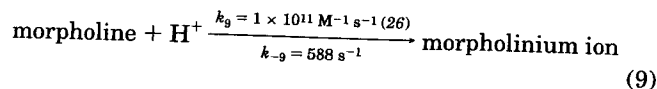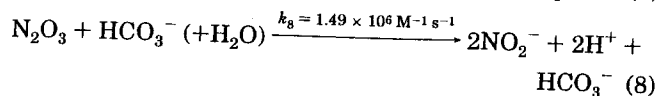
with k_5 and k_8 calculated from the data of Caulfield et al. (*19*) with a k_6 of 1.6×10^3 s^{-1} (*17*). For k_{-9}, the rate constant of deprotonation of the morpholinium ion was calculated from the pK_a value at 37 °C, i.e., 8.23 (*27*), and assuming a typical rate constant for protonation of amines in the range of 1×10^{11} M^{-1} s^{-1} (*26*).

Quantum Chemical Calculations. Density functional theory (DFT) calculations were carried out with the Gaussian 94 suite of programs (*28*). Geometries were fully optimized to stationary points using the B3LYP method on the 6-31G(d,p) basis set. Ground states were verified by frequency calculations on the same level of theory. Natural population analysis (NPA) was performed on the optimized geometries with the natural bond orbital (NBO) program (*29*) incorporated in Gaussian 94.

Statistical Analysis. Each data point represents the mean of four to eight experiments performed in duplicate. In some cases, an ANOVA was performed and the significance of differences was determined using a two-tailed Student's *t* test.

Results

To exclude possible artifacts due to an altered decomposition of PAPA NONOate [$t_{1/2} = 15$ min at 37 °C and pH 7.4 (*24*)], MAMA NONOate [$t_{1/2} = 1$ min at 37 °C and pH 7.4 (*24*)], and SIN-1 [$t_{1/2} = 40$ min at 37 °C and pH 7.4 (*30*)] in the presence of HCO$_3^-$ and/or at an alkaline pH, all experiments were performed as end point determinations.

Morpholine as a Target. In the absence of HCO$_3^-$, about 260 μM *N*-nitrosomorpholine (NO-Mor) was found from reaction of 0.5 mM PAPA NONOate with 10 mM morpholine at pH 7.5 and 37 °C after incubation for 4 h (Figure 1). The addition of HCO$_3^-$ in concentrations up to 100 mM did not alter this yield. In contrast to this observation, calculations of the "theoretical" yields of NO-Mor on the basis of reported reaction rate constants at
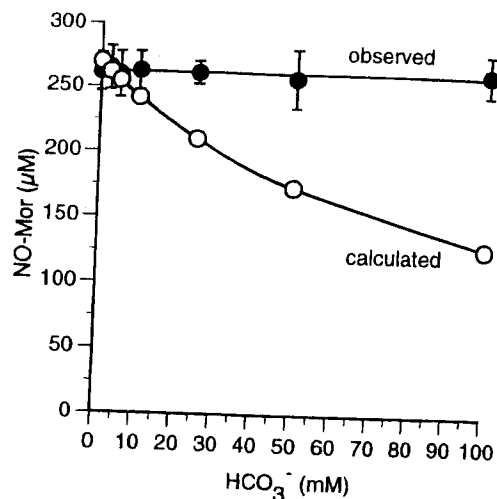

Figure 1. Influence of HCO$_3^-$ on PAPA NONOate-derived NO-Mor formation. PAPA NONOate (0.5 mM) was incubated for 4 h with 10 mM morpholine in 50 mM potassium phosphate buffer (pH 7.5, 37 °C) in the presence of various concentrations of HCO$_3^-$ (0−100 mM). NO-Mor was quantified by capillary zone electrophoresis. Each value represents the mean ± SD of four experiments performed in duplicate. A kinetic analysis was performed with known rate constants at 25 °C, with the reported "reaction rate constant of HCO$_3^-$ with N$_2$O$_3$" (*19*), with a rate constant of deprotonation of the morpholinium ion estimated from the pK_a at 37 °C, and with an initial concentration of 370 μM N$_2$O$_3$ as the nitrosating species. Since the unprotonated morpholine is the decisive target for N$_2$O$_3$, the equilibrated amounts of morpholine and morpholinium ion were first calculated in an additional kinetic simulation. As checked by control calculations, other equilibria, i.e., CO$_3^{2-}$/HCO$_3^-$/H$_2$CO$_3$/CO$_2$, did not affect the NO-Mor yield and were therefore neglected.
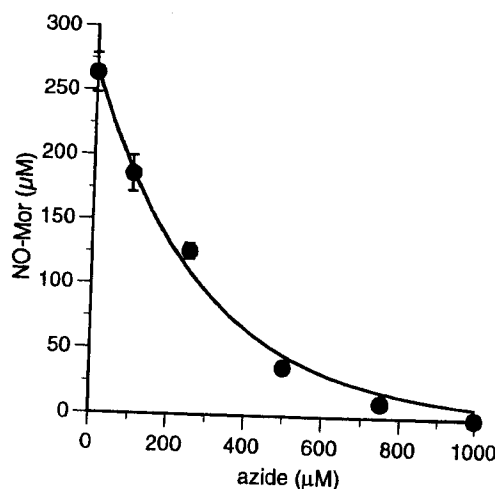

Figure 2. Influence of azide on PAPA NONOate-induced NO-Mor formation. PAPA NONOate (0.5 mM) was incubated for 4 h with 10 mM morpholine in 50 mM potassium phosphate buffer (pH 7.5, 37 °C) in the presence of various concentrations of azide (0−1 mM). NO-Mor was quantified by capillary zone electrophoresis. Each value represents the mean ± SD of three experiments performed in duplicate.

25 °C (under the assumption that only unprotonated morpholine will be attacked by ~370 μM N$_2$O$_3$; see below) predicted that HCO$_3^-$ should exert a protective effect. Hence, HCO$_3^-$ is not a scavenger for •NO/O$_2$.

Because one might speculate that PAPA NONOate may nitrosate morpholine via a transnitrosation reaction rather than via the •NO/O$_2$ pathway, the known N$_2$O$_3$/N$_2$O$_4$ scavenger azide (N$_3^-$) was applied to suppress formation of NO-Mor (Figure 2). Indeed, N$_3^-$ very strongly inhibited PAPA NONOate-driven production of NO-Mor, in line with the view that N$_2$O$_3$/N$_2$O$_4$ (most likely N$_2$O$_3$)
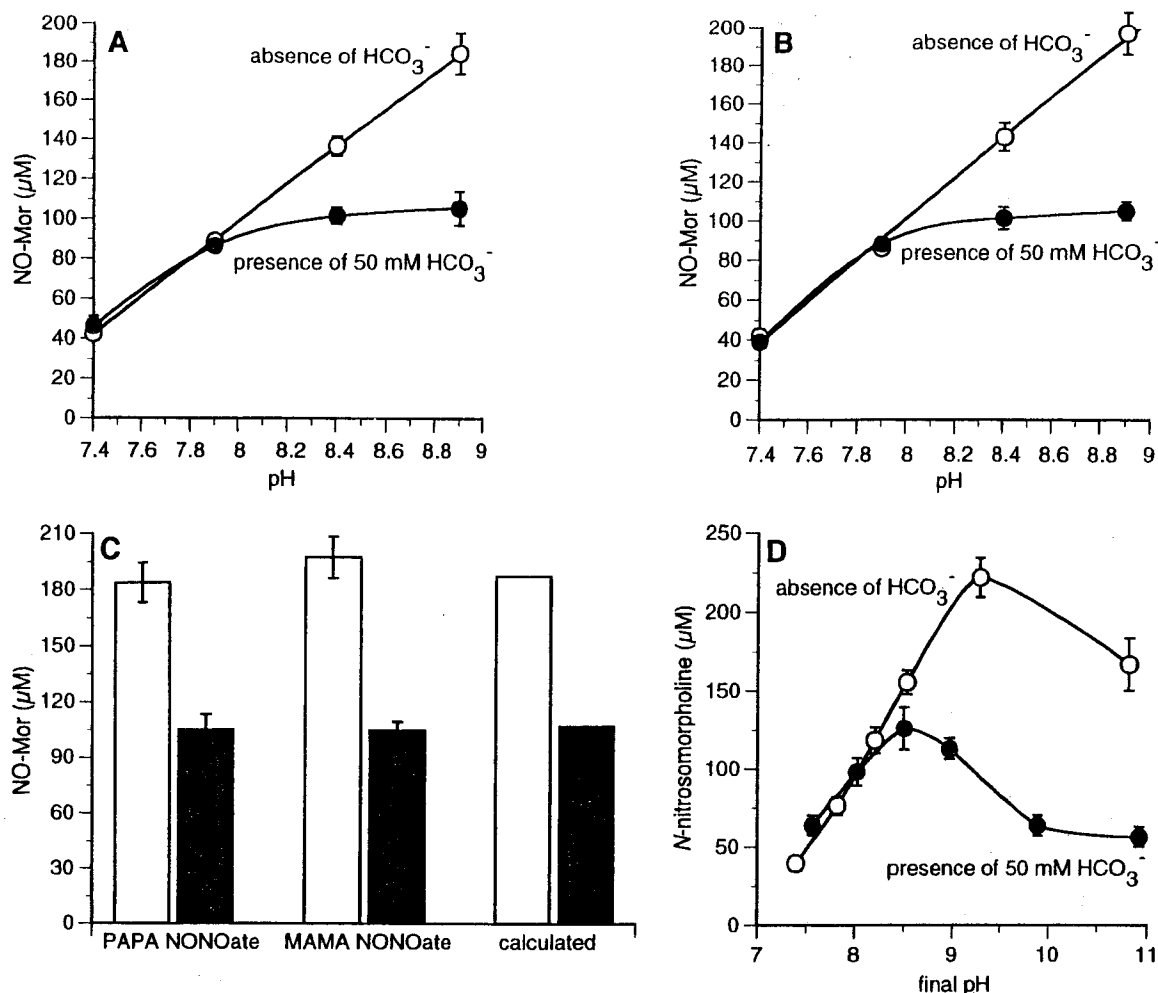
Figure 3. Influence of pH on formation of NO-Mor. NO-donor compounds (PAPA NONOate or MAMA NONOate, each at 0.5 mM were incubated with 1 mM morpholine in 50 mM potassium phosphate buffer (pH 7.4–8.9, 37 °C) in the absence and in the presenc of HCO_3^- (50 mM). Alternatively, anaerobic solutions of authentic ·NO (1.8 mM, 25 °C, 200 μL) were vortexed with aerobic solutior of 2 mM morpholine in 100 mM potassium phosphate buffer (pH 7.4–10.9, 25 °C, 200 μL) in the absence and presence of 100 ml HCO_3^-. NO-Mor was quantified by capillary zone electrophoresis. (A) PAPA NONOate was incubated for 8 days with 1 mM morpholin (B) MAMA NONOate was incubated for 60 h with 1 mM morpholine. (C) The results at pH 8.9 were compared with data from kinetic simulation which used the stated assumptions from Figure 1: (white bars) absence of HCO_3^- and (black bars) presence of 5 mM HCO_3^-. (D) Solutions of authentic ·NO (final concentration of 900 μM) were vortexed with morpholine (final concentration, 1 mM), and the amount of NO-Mor was instantaneously determined. Each value represents the mean ± SD of four experimen performed in duplicate.

is the attacking species. In pure phosphate buffer, 0.5 mM PAPA NONOate (and also 0.5 mM MAMA NON-Oate) did not produce any nitrate but yielded 740 ± 12 μM nitrite (NO_2^-), in agreement with the fact that ·NO decays in an oxygen-containing aqueous solution via hydrolysis of N_2O_3 (*31*). Thus, under aerobic conditions, PAPA NONOate (0.5 mM) acts as a source of N_2O_3 (370 μM).

Under the conditions applied by Caulfield et al. (*19*), the pH of the reaction mixture increased from 7.4 to 8.9. Therefore, the effect of pH on formation of NO-Mor from 1 mM morpholine and 0.5 mM PAPA NONOate in the absence and in the presence of 50 mM HCO_3^- was studied (Figure 3A). At pH 7.4, about 45 μM NO-Mor was formed, independent of the presence of HCO_3^-. This result is in excellent agreement with the experiments whose results are shown in Figure 1. With increasing pH, the extent of NO-Mor formation linearly increased in the absence of HCO_3^- to reach a concentration of about 185 μM at pH 8.9. In the presence of HCO_3^-, however, NO-Mor formation leveled off to about 100 μM at pH 8.4. Thus, only at pH ≥8, HCO_3^- is able to protect morpholine

against the attack by ·NO/O_2. Since the decompositio of PAPA NONOate at pH 8.9 is slow (~8 days fo complete decomposition), the experiments with 1 m morpholine and 0.5 mM NONOate were repeated wit MAMA NONOate as the NO donor (Figure 3B). Aft incubation for 60 h, similar results were found with th exception that the yield of NO-Mor at pH 8.9 in th absence of 50 mM HCO_3^- increased to ~195 μM. A kine analysis (Figure 3C) revealed that the effect at pH 8.9 virtual identical to that reported by Caulfield et al. (*19* Since one might argue that the NONOate compoun may release species other than ·NO at stronger alkalir pH values, additional experiments were employed (Figur 3D) with authentic ·NO (900 μM) and morpholine (1 mM in the absence and presence of HCO_3^- (50 mM) an various pH values (7.4–10.9). In the absence of HCO about 45 μM NO-Mor was found at pH 7.4. The yiel NO-Mor increased to about 225 μM on increasing the p to 9.9, in line with the experiments performed with t NONOates (Figure 3A,B). This behavior indicates tha only the unprotonated morpholine is a target for N (*17*). Further increases in the pH value result in lower
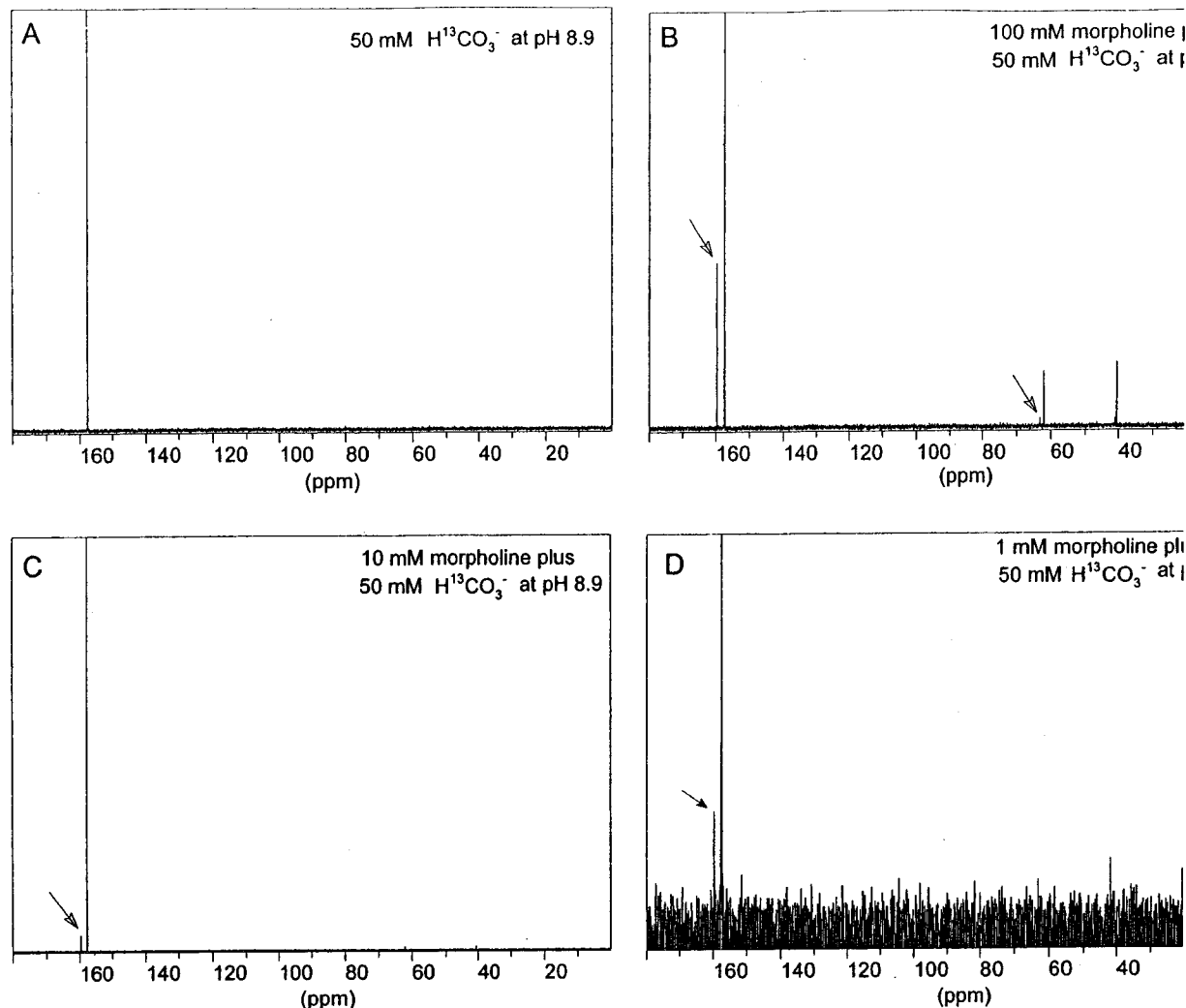
Figure 5. Formation of morpholine carbamate at pH 8.9. A 500 MHz ^{13}C NMR analysis was employed with potassium buffer solutions (pH 8.9, 25 °C) containing various morpholine concentrations (0–100 mM) in the presence of H^{13}CO$_3^-$ (5 50 mM H^{13}CO$_3^-$, (B) 100 mM morpholine and 50 mM H^{13}CO$_3^-$, (C) 10 mM morpholine and 50 mM H^{13}CO$_3^-$, and (D) 1 mM and 50 mM H^{13}CO$_3^-$. In panel D, the gain was increased 100-fold. The arrows indicate the resonances of morpholine c

absence of HCO$_3^-$, 136.6 ± 5.0 μM N-mononitrosopiperazine (NO-Pip) was formed on reaction of 0.5 mM PAPA NONOate with 1 mM piperazine after incubation for 4 h (Figure 6A). The addition of a physiological amount of HCO$_3^-$ (25 mM) inhibited PAPA NONOate-mediated formation of NO-Pip significantly (104.9 ± 4.2 μM). The possibility that the inhibition was due to a change in the ionic strength can be excluded because in the presence of 25 mM NaSCN, which does not affect the nitrosating activity of ·NO/O$_2$ under such conditions (17), 139.9 ± 6.2 μM NO-Pip was formed. For comparison, neither HCO$_3^-$ nor SCN$^-$ affected 0.5 mM PAPA NONOate-dependent formation of NO-Mor from 1 mM morpholine (Figure 6B). To determine whether a significant amount of piperazine carbamate was formed, solutions with different concentrations of piperazine were analyzed by ^{13}C NMR spectrometry in the presence of 25 mM H^{13}CO$_3^-$ (Figure 7A–D). A concentration of 1 mM appeared to be too low for piperazine to be detected by ^{13}C NMR under our conditions, and only the signals of ^{13}CO$_2$ (δ = 124.6 ppm) and HCO$_3^-$ (δ = 160.2 ppm) can be seen (Figure 7A). However, at a concentration of 2 mM, where piperazine at natural abundance is hardly detectable, formation of piperazine carbamate is already evident from its resonance at δ = 162.6 ppm (Figure 7B). Thus,

significant amounts of piperazine carbamates w formed under such conditions. The concen piperazine carbamate increases with increasi zine concentrations (Figure 7C), until at 100 the applied ^{13}CO$_2$ is completely converted (F To further demonstrate that formation of carbamate is responsible for the depleted yie Pip, additional experiments with piperazine (2 various concentrations of H^{13}CO$_3^-$ or HCO$_3^-$ formed at pH 7.4. As expected, the extent of of piperazine carbamate (δ = 162.6 ppm) incre increasing concentrations of H^{13}CO$_3^-$ (Figure the yield of NO-Pip should decrease with i concentrations of HCO$_3^-$. In the absence of HC 300 μM NO-Pip was found from reaction NONOate (0.5 mM) with piperazine (2 mM) aft tion for 4 h at 37 °C (Figure 8B). The yield decreased in an exponential manner with i concentrations of HCO$_3^-$; only ~115 μM N(detected at 200 mM HCO$_3^-$. Control experin formed with NaNO$_3$ as an additive revealed ations in the ionic strength cannot induce such in the yield of NO-Pip. Since the extent of for piperazine carbamate was approximately d increasing the HCO$_3^-$ concentration from 50 t
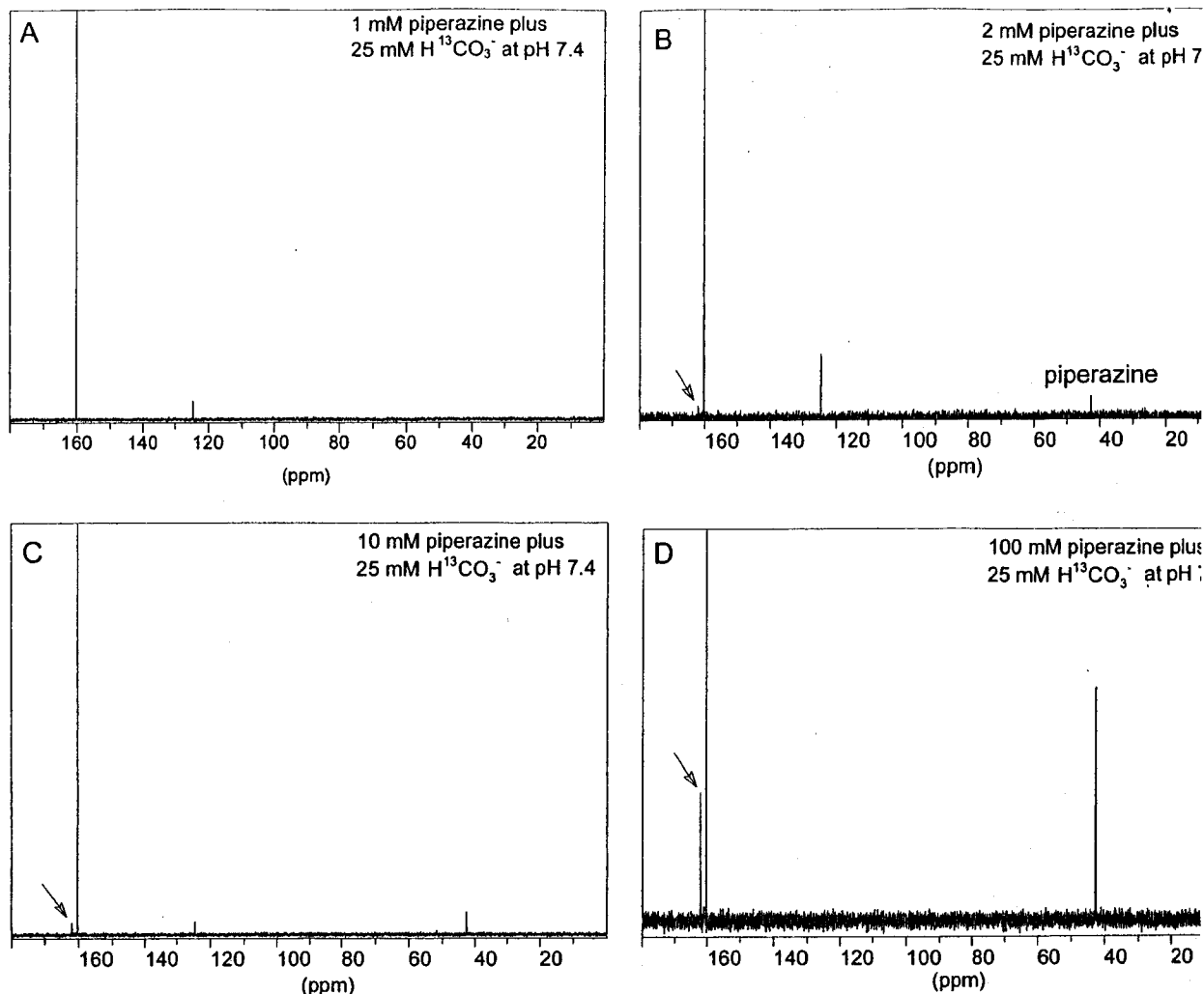
Figure 7. Formation of piperazine carbamate at pH 7.4. A 500 MHz ^{13}C NMR analysis was employed in 50 mM potassium ph buffer solutions (pH 7.4, 25 °C) containing various piperazine concentrations (1–100 mM) in the presence of $H^{13}CO_3^-$ (25 m gain was increased 100-fold: (A) 1 mM piperazine and 25 mM $H^{13}CO_3^-$, (B) 2 mM piperazine and 25 mM $H^{13}CO_3^-$ (here the was increased 4-fold), (C) 10 mM piperazine and 25 mM $H^{13}CO_3^-$, and (D) 100 mM piperazine and 25 mM $H^{13}CO_3^-$. The indicate the resonances of piperazine carbamate.

charge at nitrogen is reduced from −0.71 to −0.59 and −0.51 when replacing the amino hydrogen with COO^- and COOH, respectively. Thus, the nitrogen atom of morpholine carbamate and/or carbamic acid is a weaker nucleophile than the nitrogen atom of morpholine or, vice versa, is less susceptible to oxidative attack by N_2O_3. In line with this view, the oxidation potential ($E_{1/2}$) of dibutylamine increases from 0.87 to 1.52 V (*40, 41*) by forming the corresponding dibutylamine carbamate methyl ester. Such an increase in the oxidation potential should also strongly inhibit the capabilities of oxidants (e.g., the CO_3^- radical) to remove an electron of the lone pair at nitrogen. Thus, carbamate formation protects the amines against the non-radical-driven attack of N_2O_3 as well as a possible radical-driven one initiated by ·NO/ O_2^-.

The pK_a values of the primary (e.g., in amino acids) and secondary amines (e.g., in polyamines, proline, and its derivatives) common in living organisms lie in the range of 9–12. In general, these amines will be protected against a nitrosative attack because at pH 7.4 they are almost completely present in the protonated form. In acidic media similar to that of the stomach, nitrite is able to nitrosate secondary amines and to deaminate primary amines (*12, 42*). Under such conditions, nitrite may

generate two nitrosating species, namely, N_2O_3 a nitrous acidium ion ($H_2NO_2^+$). The latter entit equilibrium with NO^+ which is supposed to N-ni protonated amines directly (*12*). However, in a fe important cases, the pK_a value of the ammoniu falls to values below 8. This is true for the N-te amino acid of peptides and proteins and the α groups of hemoglobin (pK_a = 6.1–7.1) (*43*). T protection against nitrosation via the formation corresponding ammonium ion is less effective h the other hand, CO_2 can then inhibit nitrosation re via formation of amine carbamate. Previously, (*13*) has noted that "the reactivities of peptide te primary amino groups towards nitrosation sh similar to dialkylamines" (secondary amines). In ment with this view, the nitrosation of N-terminal in peptides leads to the corresponding N-nitros peptides (*44*). Accordingly, N-nitrosoproline ha found in urine after endogenous nitrosation in h (*45*), and there are indications of an extragastric p of N-nitrosation of proline (*46, 47*). In hemo formation of amine carbamates is evident (deox globin transports CO_2 into the alveoli) but ami bamates are also present in oxyhemoglobin and moglobin (*43, 48*). As the piperazinium ion ha

460 *Chem. Res. Toxicol., Vol. 13, No. 6, 2000*

Kirsch et al.

Pro

technical advice. This investigation would have been impossible without the skilled technical assistance of E. Heimeshoff and A. Wensing.

References

(1) Moncada, S., Palmer, R. M. J., and Higgs, E. A. (1991) Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacol. Rev.* **43**, 109−142.

(2) Huie, R. E., and Padmaja, S. (1993) The reaction of NO with superoxide. *Free Radical Res. Commun.* **18**, 195−199.

(3) Kobayashi, K., Miki, M., and Tagawa, A. (1995) Pulse-radiolysis study of the reaction of nitric oxide with superoxide. *J. Chem. Soc., Dalton Trans.*, 2885−2889.

(4) Kissner, R., Nauser, T., Bugnon, P., Lye, P. G., and Koppenol, W. H. (1997) Formation and properties of peroxynitrite by laser flash photolysis, high-pressure stopped-flow technique, and pulse radiolysis. *Chem. Res. Toxicol.* **10**, 1285−1292.

(5) Beckman, J. S., Beckman, T. W., Chen, J., Marshall, P. A., and Freeman, B. A. (1990) Apparent hydroxyl radical production by peroxynitrite: Implications for endothelial injury from nitric oxide and superoxide. *Proc. Natl. Acad. Sci. U.S.A.* **87**, 1620−1624.

(6) Ischiropoulos, H., Zhu, L., and Beckman, J. S. (1992) Peroxynitrite formation from macrophage-derived nitric oxide. *Arch. Biochem. Biophys.* **298**, 446−451.

(7) Hooper, D. C., Ohnishi, S. T., Kean, R., Numagami, Y., Dietzschold, B., and Koprowski, H. (1995) Local nitric oxide production in viral and autoimmune diseases of the central nervous system. *Proc. Natl. Acad. Sci. U.S.A.* **92**, 5312−5316.

(8) Malinski, T., Zhang, Z. G., and Chopp, M. (1995) Nitric oxide measured by a porphyrinic microsensor in rat brain after transient middle cerebral artery occlusion. *J. Cerebral Blood Flow Metab.* **13**, 355−358.

(9) Goldstein, S., and Czapski, G. (1995) Kinetics of nitric oxide autoxidation in aqueous solution in the absence and presence of various reductants. The nature of the oxidizing intermediates. *J. Am. Chem. Soc.* **117**, 12078−12084.

(10) Grätzel, M., Taniguchi, S., and Henglein, A. (1970) Pulsradiolytische Untersuchungen der NO-Oxydation und des Gleichgewichtes $N_2O_3 \leftrightarrow NO + NO_2$ in wäßriger Lösung. *Ber. Bunsen-Ges.* **74**, 488−492.

(11) Grätzel, M., Henglein, A., Lilie, J., and Beck, G. (1969) Pulsradiolytische Untersuchung einiger Elementarprozesse der Oxydation und Reduktion des Nitritions. *Ber. Bunsen-Ges.* **73**, 646−653.

(12) Williams, D. L. H. (1986) *Nitrosation*, Cambridge University Press, Cambridge, U.K.

(13) Challis, B. C. (1989) Chemistry and biology of nitrosated peptides. *Cancer Surv.* **8**, 363−384.

(14) Challis, B. C., and Kyrtopoulos, S. A. (1978) The chemistry of nitroso-compounds. Part 11. Nitrosation of amines by the two-phase interaction of amines with gaseous oxides of nitrogen. *J. Chem. Soc., Perkin Trans. 1*, 299−304.

(15) Nguyen, T., Brunson, D., Crespi, C. L., Penman, B. W., Wishnok, J. S., and Tannenbaum, S. R. (1992) DNA damage and mutation in human cells exposed to nitric oxide in vitro. *Proc. Natl. Acad. Sci. U.S.A.* **89**, 3030−3034.

(16) Wink, D. A., Kasprzak, K. S., Maragos, C. M., Elespuru, R. K., Misra, M., Dunams, T. M., Cebula, T. A., Koch, W. H., Andrews, A. W., Allen, J. S., and Keefer, L. K. (1991) DNA deaminating ability and genotoxicity of nitric oxide and its progenitors. *Science* **254**, 1001−1003.

(17) Lewis, R. S., Tannenbaum, S. R., and Deen, W. D. (1995) Kinetics of N-nitrosation in oxygenated nitric oxide solutions at physiological pH: role of nitrous anhydride and effects of phosphate and chloride. *J. Am. Chem. Soc.* **117**, 3933−3939.

(18) Lewis, R. S., Tamir, S., Tannenbaum, S. R., and Deen, W. M. (1995) Kinetic analysis of the fate of nitric oxide synthesized by macrophages in vitro. *J. Biol. Chem.* **270**, 29350−29355.

(19) Caulfield, J. L., Singh, S. P., Wishnok, J. S., Deen, W. M., and Tannenbaum, S. R. (1996) Bicarbonate inhibits N-nitrosation in oxygenated nitric oxide solutions. *J. Biol. Chem.* **271**, 25859−25863.

(20) Yadav, J. S., Reddy, G. S., Reddy, M. M., and Meshram, H. M. (1998) Zinc promoted simple and convenient synthesis of carbamates: an easy access for amino group protection. *Tetrahedron Lett.* **39**, 3259−3262.

(21) Meineke, P., Rauen, U., de Groot, H., Korth, H.-G., and Sustmann, R. (1999) Cheletropic traps for the fluorescence spectroscopic detection of nitric oxide (nitrogen monoxide) in biological systems. *Chem. Eur. J.* **5**, 1738−1747.

(22) Casado, J., Castro, A., Mosquera, M., Prieto, M. F. R., and Tato, J. V. (1984) Kinetic studies on the formation of N-nitroso compounds IX. Nitrosyl acetate as a nitrosating agent. *Monatsh. Chem.* **114**, 669−682.

(23) Kirsch, M., and de Groot, H. (1999) Reaction of peroxynitrite with reduced nicotinamide nucleotides, formation of hydrogen peroxide. *J. Biol. Chem.* **274**, 24664−24670.

(24) Keefer, L. K., Nims, R. W., Davies, K. M., and Wink, D. A. (1996) "NONOates" (1-substituted diazen-1-ium-1,2-diolates) as nitric oxide donors: convenient nitric oxide dosage forms. *Methods Enzymol.* **268**, 281−293.

(25) Ioannidis, I., and de Groot, H. (1993) Cytotoxicity of nitric oxide in Fu5 rat hepatoma cells: Evidence for co-operative action with hydrogen peroxide. *Biochem. J.* **296**, 341−345.

(26) Eigen, M. (1964) Proton transfer, acid−base catalysis, and enzymatic hydrolysis. Part I: elementary processes. *Angew. Chem., Int. Ed. Engl.* **3**, 1−19.

(27) Hetzer, H. B., Bates, R. G., and Robinson, R. A. (1966) Dissociation constant of morpholinium ion and related thermodynamic quantities from 0 to 50 °C. *J. Phys. Chem.* **70**, 2869−2872.

(28) Frisch, M. J., Trucks, G. W., Schlegel, H. B., Gill, P. M. W., Johnson, B. G., Robb, M. A., Cheeseman, J. R., Keith, T., Petersson, G. A., Montgomery, J. A., Raghavachari, K., Al-Laham, M. A., Zakrzewski, V. G., Ortiz, J. V., Foresman, J. B., Cioslowski, J., Stefanov, B. B., Nanayakkara, A., Challacombe, M., Peng, C. Y., Ayala, P. Y., Chen, W., Wong, M. W., Andres, J. L., Replogle, E. S., Gomperts, R., Martin, R. L., Fox, D. J., Binkley, J. S., Defrees, D. J., Baker, J., Stewart, J. P., Head-Gordon, M., Gonzalez, C., and Pople, J. A. (1995) *Gaussian 94*, revision E.2, Gaussian Inc., Pittsburgh, PA.

(29) Glendening, E. D., Reed, A. J., Carpenter, J. E., and Weinhold, F. (1995) *Gaussian 94*, NBO version 3.1, Gaussian Inc., Pittsburgh, PA.

(30) Lomonosova, L. L., Kirsch, M., Rauen, U., and de Groot, H. (1998) The critical role of Hepes in SIN-1 cytotoxicity, peroxynitrite versus hydrogen peroxide. *Free Radical Biol. Med.* **24**, 522−528.

(31) Ignarro, L. J., Fukuto, J. M., Griscavage, J. M., Rogers, N. E., and Byrns, R. E. (1993) Oxidation of nitric oxide in aqueous solution to nitrite but not nitrate: Comparison with enzymatically formed nitric oxide from L-arginine. *Proc. Natl. Acad. Sci. U.S.A.* **90**, 8103−8107.

(32) Crooks, J. E., and Donnellan, J. P. (1989) Kinetics and mechanism of the reaction between carbon dioxide and amines in aqueous solution. *J. Chem. Soc., Perkin Trans. 2*, 331−333.

(33) Caplow, M. (1968) Kinetics of carbamate formation and breakdown. *J. Am. Chem. Soc.* **90**, 6795−6803.

(34) Mayer, B., Pfeiffer, S., Schrammel, A., Koesling, D., Schmidt, K., and Brunner, F. (1998) A new pathway of nitric oxide/cyclic GMP signaling involving S-nitrosoglutathione. *J. Biol. Chem.* **273**, 3264−3270.

(35) Roughton, F. J. W. (1970) Some recent work on the interactions of oxygen, carbon dioxide and haemoglobin. *Biochem. J.* **117**, 801−812.

(36) Challis, B. C., and Kyrtopoulos, S. A. (1978) The chemistry of nitroso compounds. Part 12. The mechanism of nitrosation and nitration of aqueous piperidine by gaseous dinitrogen tetraoxide and dinitrogen trioxide in aqueous alkaline solutions. Evidence for the existence of molecular isomers of dinitrogen tetraoxide and dinitrogen trioxide. *J. Chem. Soc., Perkin Trans. 2*, 1296−1302.

(37) Wolfe, S. K., and Swinehart, H. J. (1975) Photochemistry of pentacyanonitrosylferrate(2-), Nitroprusside. *Inorg. Chem.* **14**, 1049−1053.

(38) Kirsch, M., Lomonosova, E. E., Korth, H.-G., Sustmann, R., and de Groot, H. (1998) Hydrogen peroxide formation by reaction of peroxynitrite with HEPES and related tertiary amines. Implications for a general mechanism. *J. Biol. Chem.* **273**, 12716−12724.

(39) Uppu, R. M., and Pryor, W. A. (1999) Nitrosation of 1,2-phenylenediamine by peroxynitrite/CO_2: Evidence for a free radical mechanism. *J. Am. Chem. Soc.* **121**, 9738−9739.

(40) Yoon, U. C., Mariano, P. S., Givens, R. S., and Atwater, B. W. (1994) Photoinduced electron-transfer chemistry of amines and related electron donors. In *Advances in Electron-Transfer Chemistry*, pp 117−205, JAI Press, London.

(41) Chow, Y. L., Dauen, W. C., Nelsen, S. F., and Rosenblatt, D. H. (1978) Nonaromatic aminium radicals. *Chem. Rev.* **78**, 243−273.

(42) Archer, M. C., Clark, S. D., Thilly, J. E., and Tannenbaum, S. R. (1971) Environmental nitroso compounds: Reaction of nitrite with creatine and creatinine. *Science* **174**, 1341−1343.

(43)

(44)

(45)

(46)

Left-margin fragments:
al.
ato,
oso
sh.

ith
ide.

96)
tric
ods

ide
ith

and
ew.

tion
nti-

W.,
T.,
am,
ski,
C.
gle,
S.,
M.,
E.2,

old,
itts-

998)
trite
528.
E.,
eous
ally
S.A.

ism
eous

eak-

K.,
GMP
273,

ions
01—

ry of
and
xide
ence
xide
96—

ry of
14,

and
on of
lica-
724.
1,2-
free

. W.
and
hem-

D. H.
-273.
S. R.
with

(43) Gros, G., Rollema, H. S., and Forster, R. E. (1981) The carbamate equilibrium of α- and ε-amino groups of human hemoglobin at 37 °C. *J. Biol. Chem.* **256**, 5471–5480.

(44) Kubacka, W., Libbey, L. M., and Scanlan, R. A. (1984) Formation and chemical characterization of some nitroso dipeptides N-terminal in proline. *J. Agric. Food Chem.* **32**, 401–404.

(45) Ohshima, H., and Bartsch, H. (1981) Quantitative estimation of endogenous nitrosation in human by monitoring *N*-nitrosoproline in the urine. *Cancer Res.* **41**, 3658–3662.

(46) Wagner, D. A., Shuker, D. E. G., Bilmazes, C., Obiedzinski, M. W., Baker, I., Young, V. R., and Tannenbaum, S. R. (1985) Effect of vitamins C and E on endogenous synthesis of N-nitrosamino acids in humans: precusor-product studies with [¹⁵N]nitrate. *Cancer Res.* **45**, 6519–6522.

(47) Licht, W. R., and Deen, W. D. (1988) Theoretical model for predicting rates of nitrosamine and nitrosamide formation in the human stomach. *Carcinogenesis* **9**, 2227–2237.

(48) Böning, D., Schünemann, H. J., Maassen, N., and Busse, M. W. (1993) Reduction of oxylabile CO₂ in human blood by lactate. *J. Appl. Physiol.* **74**, 710–714.

TX990138Z

Occupational Health Guideline for Morpholine

INTRODUCTION

This guideline is intended as a source of information for employees, employers, physicians, industrial hygienists, and other occupational health professionals who may have a need for such information. It does not attempt to present all data; rather, it presents pertinent information and data in summary form.

SUBSTANCE IDENTIFICATION

- Formula: C_4H_9ON
- Synonyms: Tetrahydro-1,4-oxazine; diethyleneimide oxide
- Appearance and odor: Colorless liquid with a weak, ammonia-like odor.

PERMISSIBLE EXPOSURE LIMIT (PEL)

The current OSHA standard for morpholine is 20 parts of morpholine per million parts of air (ppm) averaged over an eight-hour work shift. This may also be expressed as 70 milligrams of morpholine per cubic meter of air (mg/m^3).

HEALTH HAZARD INFORMATION

- Routes of exposure

Morpholine can affect the body if it is inhaled, comes in contact with the eyes or skin, or is swallowed. It may enter the body through the skin.
- Effects of overexposure

1. *Short-term Exposure:* Morpholine may cause irritation of the eyes, nose, throat, lungs, and skin.

2. *Long-term Exposure:* Repeated or prolonged overexposure to morpholine may cause skin irritation.

3. *Reporting Signs and Symptoms:* A physician should be contacted if anyone develops any signs or symptoms and suspects that they are caused by exposure to morpholine.

- Recommended medical surveillance

The following medical procedures should be made available to each employee who is exposed to morpholine at potentially hazardous levels:

1. *Initial Medical Screening:* Employees should be screened for history of certain medical conditions (listed below) which might place the employee at increased risk from morpholine exposure.

—Chronic respiratory disease: Morpholine causes respiratory irritation in animals. In persons with impaired pulmonary function, especially those with obstructive airway diseases, the breathing of morpholine might cause exacerbation of symptoms due to its irritant properties.

—Liver disease: Morpholine causes liver damage in animals. The importance of this organ in the biotransformation and detoxification of foreign substances should be considered before exposing persons with impaired liver function.

—Kidney disease: Morpholine causes kidney damage in animals. The importance of this organ in the elimination of toxic substances justifies special consideration in those with impaired renal function.

—Eye disease: Morpholine is an eye irritant and has caused corneal edema in workers. Persons with pre-existing eye disorders may be more susceptible to the effects of this agent.

—Skin disease: Morpholine is a primary skin irritant and induces hypersensitive responses. Persons with pre-existing skin disorders may be more susceptible to the effects of this agent.

2. *Periodic Medical Examination:* Any employee developing the above-listed conditions should be referred for further medical examination.

- Summary of toxicology

Morpholine vapor is an irritant to the skin, eyes, mucous membranes, and the respiratory tract. Hypersensitivity is common. Repeated daily exposure of rats to 18,000 ppm was lethal to some animals; those dying during the third to fifth days of exposure revealed damage to lungs, liver, and kidneys. A human exposure

---

These recommendations reflect good industrial hygiene and medical surveillance practices and their implementation will assist in achieving an effective occupational health program. However, they may not be sufficient to achieve compliance with all requirements of OSHA regulations.

to 12,000 ppm for 1-¼ minutes in a laboratory produced nose irritation and cough; mouth pipetting of the liquid caused a severe sore throat and reddened mucous membranes. The liquid dropped in the eye of a rabbit caused moderate injury with ulceration of the conjunctiva and corneal clouding. Workers exposed for several hours to low vapor concentrations complained of foggy vision with rings around lights, the result of corneal edema which cleared within 3 to 4 hours after cessation of exposure. The liquid is a severe skin irritant and may produce contact dermatitis. In industry, some instances of skin and respiratory tract irritation have been observed.

CHEMICAL AND PHYSICAL PROPERTIES

- Physical data
  1. Molecular weight: 87.1
  2. Boiling point (760 mm Hg): 128 C (263 F)
  3. Specific gravity (water = 1): 1.0
  4. Vapor density (air = 1 at boiling point of morpholine): 3.0
  5. Melting point: −4.8 C (23 F)
  6. Vapor pressure at 20 C (68 F): 7 mm Hg
  7. Solubility in water, g/100 g water at 20 C (68 F): Miscible in all proportions
  8. Evaporation rate (butyl acetate = 1): Less than 1
- Reactivity
  1. Conditions contributing to instability: Heat
  2. Incompatibilities: Contact of liquid morpholine with strong acids will cause violent spattering. Contact with strong oxidizers may cause fires and explosions.
  3. Hazardous decomposition products: Toxic gases and vapors (such as oxides of nitrogen and carbon monoxide) may be released in a fire involving morpholine.
  4. Special precautions: Liquid morpholine will attack some forms of plastics, rubber, and coatings.
- Flammability
  1. Flash point: 35 C (95 F) (closed cup)
  2. Autoignition temperature: 310 C (590 F)
  3. Flammable limits in air, % by volume: Lower: 1.8 (calculated); Upper: 11 (estimated)
  4. Extinguishant: Carbon dioxide, dry chemical, alcohol foam
- Warning properties
  1. Odor Threshold: Grant states that morpholine has a characteristic amine odor. No quantitative information is available concerning the odor threshold, however.
  2. Eye Irritation Level: Grant reports that lacrimation has been observed among experimental animals and among industrial workers who have been exposed to high vapor concentrations. "At low concentrations in air, morpholine has been listed with its N-ethyl and N-methyl derivatives among the amines which have been observed to cause transient edema of the cornea and temporary foggy vision with haloes around lights in workers exposed to the vapors for many hours, the

symptoms usually coming on after work and clearing spontaneously by the next day."

Patty also reports that morpholine irritates the mucous membranes.

No quantitative information is available, however, concerning the threshold of eye irritation.

3. Other Information: Both Patty and Grant note that morpholine is a respiratory tract irritant, but no quantitative information is available concerning the threshold of this irritation.

4. Evaluation of Warning Properties: Since no quantitative information relating warning properties to air concentrations is available, morpholine is treated as a substance with poor warning properties.

MONITORING AND MEASUREMENT PROCEDURES

- General
Measurements to determine employee exposure are best taken so that the average eight-hour exposure is based on a single eight-hour sample or on two four-hour samples. Several short-time interval samples (up to 30 minutes) may also be used to determine the average exposure level. Air samples should be taken in the employee's breathing zone (air that would most nearly represent that inhaled by the employee).

- Method
Sampling and analyses may be performed by collection of morpholine in an adsorption tube containing silica gel, followed by desorption with sulfuric acid, and gas chromatographic analysis. Also, detector tubes certified by NIOSH under 42 CFR Part 84 or other direct-reading devices calibrated to measure morpholine may be used. An analytical method for morpholine is in the NIOSH Manual of Analytical Methods, 2nd Ed., Vol. 3, 1977, available from the Government Printing Office, Washington, D.C. 20402 (GPO No. 017-033-00261-4).

RESPIRATORS

- Good industrial hygiene practices recommend that engineering controls be used to reduce environmental concentrations to the permissible exposure level. However, there are some exceptions where respirators may be used to control exposure. Respirators may be used when engineering and work practice controls are not technically feasible, when such controls are in the process of being installed, or when they fail and need to be supplemented. Respirators may also be used for operations which require entry into tanks or closed vessels, and in emergency situations. If the use of respirators is necessary, the only respirators permitted are those that have been approved by the Mine Safety and Health Administration (formerly Mining Enforcement and Safety Administration) or by the National Institute for Occupational Safety and Health.

- In addition to respirator selection, a complete respiratory protection program should be instituted which includes regular training, maintenance, inspection, cleaning, and evaluation.

PERSONAL PROTECTIVE EQUIPMENT

- Employees should be provided with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent any possibility of skin contact with liquid morpholine or solutions containing greater than 25% morpholine by weight and to prevent repeated or prolonged skin contact with solutions containing 25% or less of morpholine by weight.
- Clothing contaminated with morpholine should be placed in closed containers for storage until it can be discarded or until provision is made for the removal of morpholine from the clothing. If the clothing is to be laundered or otherwise cleaned to remove the morpholine, the person performing the operation should be informed of morpholine's hazardous properties.
- Where there is any possibility of exposure of an employee's body to liquid morpholine or solutions containing greater than 25% morpholine by weight, facilities for quick drenching of the body should be provided within the immediate work area for emergency use.
- Any clothing which becomes wet with liquid morpholine should be removed immediately and not reworn until the morpholine is removed from the clothing.
- Non-impervious clothing which becomes contaminated with morpholine should be removed promptly and not reworn until the morpholine is removed from the clothing.
- Employees should be provided with and required to use splash-proof safety goggles where there is any possibility of liquid morpholine or solutions containing morpholine contacting the eyes.
- Where there is any possibility that employees' eyes may be exposed to liquid morpholine or solutions containing greater than 15% morpholine by weight, an eye-wash fountain should be provided within the immediate work area for emergency use.

SANITATION

- Skin that becomes contaminated with morpholine should be promptly washed or showered to remove any morpholine.
- Employees who handle liquid morpholine or solutions containing morpholine should wash their hands thoroughly before eating, smoking, or using toilet facilities.

COMMON OPERATIONS AND CONTROLS

The following list includes some common operations in which exposure to morpholine may occur and control methods which may be effective in each case:

Operation	Controls
Use in manufacture of rubber chemicals for rubber accelerators, catalysts, plasticizers, curing agents, stabilizers of halogenated butyl rubber, and emulsifying agents	Process enclosure; local exhaust ventilation; general dilution ventilation; personal protective equipment
Use as a corrosion inhibitor in steam boiler systems, petroleum refining, sterilization autoclaves, and in natural gas processing; use in manufacture of optical brightening agents in bleaches and detergents	Process enclosure; local exhaust ventilation; general dilution ventilation; personal protective equipment
Use in compounding of waxes and polishes for commercial use as automobile waxes, rubless waxes and polishes, and water-resistant polishes	Process enclosure; local exhaust ventilation; general dilution ventilation; personal protective equipment
Use as a chemical intermediate for textile industry as lubricants, sizing emulsifiers, and softening agents; in pharmaceutical industry as bactericides, analgesics, anesthetics, anti-spasmotics, and anti-malarials; in chemical industry for alkyl morpholines, emulsifying agents, surface-active agents, cosmetics, and soap emulsifiers; in agriculture for protective coatings for fresh fruits and vegetables, pesticide emulsifiers, insecticides, fumigants, and herbicides	Process enclosure; local exhaust ventilation; general dilution ventilation; personal protective equipment
Use as a solvent for dyes, waxes, resins, and casein	Local exhaust ventilation; general dilution ventilation; personal protective equipment

EMERGENCY FIRST AID PROCEDURES

In the event of an emergency, institute first aid procedures and send for first aid or medical assistance.

• Eye Exposure

If liquid morpholine or solutions containing morpholine get into the eyes, wash eyes immediately with large amounts of water, lifting the lower and upper lids occasionally. Get medical attention immediately. Contact lenses should not be worn when working with this chemical.

• Skin Exposure

If liquid morpholine or solutions containing morpholine get on the skin, immediately flush the contaminated skin with water. If liquid morpholine or solutions containing morpholine soak through the clothing, remove the clothing immediately and flush the skin with water. If irritation persists after washing, get medical attention.

• Breathing

If a person breathes in large amounts of morpholine, move the exposed person to fresh air at once. If breathing has stopped, perform artificial respiration. Keep the affected person warm and at rest. Get medical attention as soon as possible.

• Swallowing

When morpholine has been swallowed, give the person large quantities of water immediately. After the water has been swallowed, try to get the person to vomit by having him touch the back of his throat with his finger. Do not make an unconscious person vomit. Get medical attention immediately.

• Rescue

Move the affected person from the hazardous exposure. If the exposed person has been overcome, notify someone else and put into effect the established emergency rescue procedures. Do not become a casualty. Understand the facility's emergency rescue procedures and know the locations of rescue equipment before the need arises.

SPILL, LEAK, AND DISPOSAL PROCEDURES

• Persons not wearing protective equipment and clothing should be restricted from areas of spills or leaks until cleanup has been completed.

• If morpholine is spilled or leaked, the following steps should be taken:

1. Remove all ignition sources.
2. Ventilate area of spill or leak.
3. For small quantities, absorb on paper towels. Evaporate in a safe place (such as a fume hood). Allow sufficient time for evaporating vapors to completely clear the hood ductwork. Burn the paper in a suitable location away from combustible materials. Large quantities can be collected and atomized in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device. Morpholine should not be allowed

to enter a confined space, such as a sewer, because of the possibility of an explosion.

• Waste disposal method:

Morpholine may be disposed of by atomizing in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device.

ADDITIONAL INFORMATION

To find additional information on morpholine, look up morpholine in the following documents:

• Medical Surveillance for Chemical Hazards

• Respiratory Protection for Chemical Hazards

• Personal Protection and Sanitation for Chemical Hazards

These documents are available through the NIOSH Division of Technical Services, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

REFERENCES

• American Conference of Governmental Industrial Hygienists: "Morpholine," *Documentation of the Threshold Limit Values for Substances in Workroom Air* (3rd ed., 2nd printing), Cincinnati, 1974.

• Gleason, M. N., Gosselin, R. E., Hodge, H. C., and Smith, R. P.: *Clinical Toxicology of Commercial Products* (3rd ed.), Williams and Wilkins, Baltimore, 1969. *1969.*

• Grant, W. M.: *Toxicology of the Eye* (2nd ed.), C. C. Thomas, Springfield, Illinois, 1974.

• International Labour Office: *Encyclopedia of Occupational Health and Safety*, McGraw-Hill, New York, 1971.

• Jefferson Chemical Company: *Material Safety Data Sheet – Morpholine.*

• Patty, F. A. (ed.): *Toxicology*, Vol. II of *Industrial Hygiene and Toxicology* (2nd ed. rev.), Interscience, New York, 1963.

• Sax, N. I.: *Dangerous Properties of Industrial Materials* (3rd ed.), Van Nostrand Reinhold, New York, 1968.

• Shea, T. E.: "The Acute and Sub-Acute Toxicity of Morpholine," *Journal of Industrial Hygiene and Toxicology*, 21:7, September 1939.

• Smyth, H. F., et al.: "Range-Finding Toxicity Data, List V," *Archives of Industrial Hygiene and Occupational Medicine*, 10:61, July 1954.

• Stecher, P. G. (ed.): *The Merck Index* (8th ed.), Merck Co., Inc., Rahway, New Jersey, 1968.

• *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, U.S. Public Health Service Publication No. 149, Original, Supplements 1 and 2, 1961-1967, 1968-1969, and 1970-1971.

• Union Carbide Corporation, Industrial Medicine and Toxicology Department: *Toxicology Studies – Morpholine*, New York, 1967.

RESPIRATORY PROTECTION FOR MORPHOLINE

Condition	Minimum Respiratory Protection* Required Above 20 ppm
Vapor Concentration	
1000 ppm or less	Any supplied-air respirator with a full facepiece, helmet, or hood. Any self-contained breathing apparatus with a full facepiece.
8000 ppm or less	A Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure mode or with a full facepiece, helmet, or hood operated in continuous-flow mode.
Greater than 8000 ppm or entry and escape from unknown concentrations	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode. A combination respirator which includes a Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure or continuous-flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode.
Fire Fighting	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.
Escape	Any gas mask providing protection against organic vapors. Any escape self-contained breathing apparatus.

*Only NIOSH-approved or MSHA-approved equipment should be used.