Kirk-Othmer Encyclopedia of Chemical Technology.

FORMAMIDE

Formamide [75-12-7] (methanamide), $HCONH_2$, is the first member of the primary amide series and is the only one liquid at room temperature. It is hygroscopic and has a faint odor of ammonia. Formamide is a colorless to pale yellowish liquid, freely miscible with water, lower alcohols and glycols, and lower esters and acetone. It is virtually immiscible in almost all aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, and ethers. By virtue of its high dielectric constant, close to that of water and unusual for an organic compound, formamide has a high solvent capacity for many heavy-metal salts (1) and for salts of alkali and alkaline-earth metals (2). It is an important solvent, in particular for resins and plasticizers. As a chemical intermediate, formamide is especially useful in the synthesis of heterocyclic compounds, pharmaceuticals, crop protection agents, pesticides, and for the manufacture of hydrocyanic acid [74-90-8].

Even though formamide was synthesized as early as 1863 by W. A. Hoffmann from ethyl formate [109-94-4] and ammonia, it only became accessible on a large scale, and thus industrially important, after development of high pressure production technology. In the 1990s, formamide is mainly manufactured either by direct synthesis from carbon monoxide and ammonia, or more importantly in a two-stage process by reaction of methyl formate (from carbon monoxide and methanol) with ammonia.

1. Properties

Tables 1 and 2 list the important physical properties of formamide. Formamide is more highly hydrogen bonded than water at temperatures below 80°C but the degree of molecular association decreases rapidly with increasing temperature. Because of its high dielectric constant, formamide is an excellent ionizing solvent for many inorganic salts and also for peptides, proteins (eg, keratin), polysaccharides (eg, cellulose [9004-34-6], starch [9005-25-8]), and resins.

Formamide decomposes thermally either to ammonia and carbon monoxide or to hydrocyanic acid and water. Temperatures around 100°C are critical for formamide, in order to maintain the quality required. The lowest temperature range at which appreciable decomposition occurs is 180–190°C. Boiling formamide decomposes at atmospheric pressure at a rate of about 0.5%/min. In the absence of catalysts the reaction forming NH_3 and CO predominates, whereas hydrocyanic acid formation is favored in the presence of suitable catalysts, eg, aluminum oxides, with yields in excess of 90% at temperatures between 400 and 600°C.

Formamide is hydrolyzed very slowly at room temperature. The rate of hydrolysis increases rapidly in the presence of acids or bases and is further accelerated at elevated temperatures.

2. Reactions

As a result of its bifunctionality, formamide is a highly reactive intermediate that is useful in a wide variety of synthetic applications. The destructive distillation of formamide at atmospheric pressure gives rise to

Table 1. Physical Properties of Formamide

Property	Condition	Value	Reference
molecular formula		CH_3NO	
molecular weight		45.04	
melting point, °C		2.55	3
boiling point, °C	101.3 kPa[a]	210.5 (decomp.)	3
	2.4 kPa[a]	111–112	4
	1.5 kPa[a]	105–106	5
density, g/cm^3	20°C	1.1334	3
	25°C	1.1292	3
	50°C	1.1078	6
	80°C	1.0823	7
dielectric constant	20°C	109 ± 1.5	8
dipole moment, C·m[b]	30°C	1.12×10^{-29}	3
heat of combustion, kJ/mol[c]		−568.2	3
heat of vaporization, kJ/mol[c]		64.98	3
heat of fusion, kJ/mol[c]		6.694	7
standard heat of formation, kJ/mol[c]		−254.0	3
heat capacity, C_p, J/(K·mol)[c]	25°C	107.62	3
pK_a	20°C	−0.48	3
electrical conductivity, $S(=\Omega^{-1})$	25°C	2×10^{-7}	3
refractive index n_D^{15}	15°C	1.4491	(6, 9)
n_D^{20}	20°C	1.44754	3
n_D^{25}	25°C	1.44682	3
coefficient of expansion, cm^3/K		0.000775	3
specific heat, kJ/(kg·K)[c]	19°C	2.30	10
surface tension, mN/m(= dyn/cm)	20°C	58.35	3
	25°C	58.15	3
	50°C	55.72	10
dynamic viscosity, mPa·s(= cP)	15°C	4.320	
	20°C	3.764	3
	25°C	3.302	3
	30°C	2.926	
flash point, °C[d]		175	4
ignition temperature, °C[e]		>500	4
explosive limits in air, vol %		2.7–19	4
speed of sound, m/s	23°C	1661	11

[a] To convert kPa to mm Hg, multiply by 7.5.
[b] To convert C·m to debye, divide by 3.336×10^{-30}.
[c] To convert J to cal, divide by 4.184.
[d] ASTM D92-85.
[e] ANSI/ASTM D2155-66.

the two principal decomposition products, ammonia and carbon monoxide, together with smaller amounts of hydrocyanic acid and water. In order to produce high yields of hydrocyanic acid, formamide can be dehydrated catalytically over aluminum oxides or silicates at temperatures exceeding 500°C (13–17). Although stable to hydrolysis at room temperature, formic acid and ammonia, as an ammonium salt, are formed at elevated temperatures. Treatment of formamide with acids and bases significantly accelerates the hydrolysis. In the past, the reaction of sulfuric acid with formamide served as the basis for the industrial-scale manufacture of formic acid, but this was replaced more recently by a new economic process based on methyl formate. In the presence of hydrogen halides, formamide reacts with alcohols to yield esters of formic acid. Thus ethyl formate is obtained from formamide, hydrochloric acid, and ethanol. In the absence of Lewis acids, which catalyze the esterification of formamide, reaction does not commence until the temperature exceeds 160°C (18). Fatty acid

Table 2. Vapor Pressure of Formamide atVarious Temperatures[a]

Temperature, °C	Vapor pressure, kPa[b]
20	0.008
55.1	0.10
65.6	0.20
72.1	0.30
80.9	0.50
93.7	1.00
101.7	1.51
116.4	3.00
125.6	4.50
136.2	7.00
145.3	10.05

[a] Ref. 12.

[b] To convert kPa to mm Hg, multiply by 7.5.

amides are formed in the photochemical addition reaction of formamide with olefins (19). Straight-chain acid amides have been obtained from formamide and α-olefins in the presence of peroxides (20). Formamide is useful as a formylating agent for primary and secondary amines.

Aqueous solutions of formamide react with formaldehyde [50-00-0] in neutral or alkaline media to yield the dimethylol derivative, *N,N*-bis(hydroxymethyl) formamide [6921-98-8] (21), which in solution is in equilibrium with the monomethylol derivative [13052-19-2] and formaldehyde. With benzaldehyde in the presence of pyridine, formamide condenses to yield benzylidene bisformamide [14328-12-2]. Similar reactions occur with ketones, which, however, require more drastic reaction conditions. Formamide is a valuable reagent in the synthesis of heterocyclic compounds. Synthetic routes to various types of compounds like imidazoles, oxazoles, pyrimidines, triazines, xanthines, and even complex purine alkaloids, eg, theophylline [58-55-9], theobromine [83-67-0], and caffeine [58-08-2], have been devised (22).

3. Manufacture and Processing

Early in the twentieth century, the first attempts to manufacture formamide directly from ammonia and carbon monoxide under high temperature and pressure encountered difficult technical problems and low yields (23). Only the introduction of alkali alkoxides in alcoholic solution, ie, the presence of alcoholate as a catalyst, led to the development of satisfactory large-scale formamide processes (24).

$$\mathrm{CO + NH_3 \xrightarrow{ROM/ROH} HCONH_2}$$

However, BASF developed a two-step process (25). After methyl formate [107-31-3] became available in satisfactory yields at high pressure and low temperatures, its conversion to formamide by reaction with ammonia gave a product of improved quality and yield in comparison with the earlier direct synthesis.

$$\mathrm{CO + CH_3OH \longrightarrow HCOOCH_3}$$

$$\mathrm{HCOOCH_3 + NH_3 \longrightarrow HCONH_2 + CH_3OH}$$

3.1. Direct Synthesis

The direct synthesis of formamide from ammonia and carbon monoxide requires pressures between 0.8 and 1.7 MPa and temperatures between 75–80°C (26). Stainless steel is used as construction material, since both starting materials and products are corrosive and would lead to iron contamination if brought into contact with it. Various attempts to replace the alcoholate catalyst with improved systems have failed (27). It is essential that pure feed gases be used in the process. If the carbon monoxide source is low grade product (eg, off-gases from furnaces or reforming operations) the raw gas has to be purified, because impurities such as water, carbon dioxide, or hydrogen sulfide may lead to undesired side reactions or may cause catalyst poisoning. In particular, sodium formate [141-53-7] in the presence of water can cause severe problems by forming insoluble precipitates. If ammonia is employed in excess, it first has to be taken off overhead in a distillation step and recycled. In a second column, methanol is recovered at the top and formamide is taken off at the bottom. The additional product purification steps are required for catalyst recovery and salt removal, and also for overhead distillation of formamide.

3.2. Two-Step Process

The significant advantage of the two-step process is that it only requires commercial-grade methyl formate and ammonia. Thus the crude product leaving the reactor comprises, in addition to excess starting materials, only low boiling substances, which are easily separated off by distillation. The formamide obtained is of sufficient purity to meet all quality requirements without recourse to the costly overhead distillation that is necessary after the direct synthesis from carbon monoxide and ammonia.

In the BASF process (28), methyl formate is continuously fed into a reactor equipped with a circulation pump and an external heat exchanger. The ammonia, which is introduced through a nozzle, reacts to form formamide and methanol, releasing heat that is removed by an external heat exchanger. The typical reaction pressure is 0.2–0.3 MPa and the temperature is about 50–60°C. The processing is designed to serve the purposes of recovering methanol in high purity, so that it can be recycled into the methyl formate synthesis and, secondly, of producing formamide that meets the certified specifications. The off-gas leaving the reactor is scrubbed with water to remove excess ammonia, methanol, and methyl formate. The bulk of the released methanol in the liquid phase leaving the reactor is separated from formamide in a column overhead. The crude methanol is purified in a distillation system, whereby low boiling methyl formate and ammonia are separated. In order to complete the removal of low boiling by-products from the crude formamide, it has to undergo a vacuum distillation. The formamide so obtained is of $>99.5\%$ purity.

In addition to the processes mentioned above, there are also ongoing efforts to synthesize formamide directly from carbon dioxide [124-38-9], hydrogen [1333-74-0], and ammonia [7664-41-7] (29–32). Catalysts that have been proposed are Group VIII transition-metal coordination compounds. Under moderate reaction conditions, ie, 100–180°C, 1–10 MPa (10–100 bar), turnovers of up to 1000 mole formamide per mole catalyst have been achieved. However, since expensive noble metal catalysts are needed, further work is required prior to the technical realization of an industrial process for formamide synthesis based on carbon dioxide.

4. Shipment

Formamide is a registered substance, eg, in TSCA (75-12-7), EINECS (200-842-0), and MITI (2-681), and can, therefore, be produced in and imported into the United States, EEC, and Japan in compliance with the abovementioned acts.

In unalloyed steel containers formamide discolors slowly during shipment and storage. Both copper and brass are also subject to corrosion, particularly in the presence of water. Lead is less readily attacked. Aluminum

Table 3. Specifications of Formamide

Quality	Value[a]	Method of determination
formamide assay	99.5[b]	by difference
methanol content	0.1%	by photometry or gc
ammonium formate content	0.1%	by titration
water content	0.1%	DIN 51777, ASTM E203-75
iron content	0.0001%	by photometry

[a] Value is maximum unless otherwise stated.
[b] Value given is minimum.

and stainless steel are resistant to attack by formamide and should be used for shipping and storage containers where the color of the product is important or when metallic impurities must be minimized. Formamide attacks natural rubber but not neoprene. As a result of the solvent action of formamide, most protective paints and finishes are unsatisfactory when in contact with formamide. Therefore, formamide is best shipped in containers made of stainless steel or in drums made of, or coated with, polyethylene. Formamide supplied by BASF is packed in Lupolen drums (230 kg) or Lupolen canisters (60 kg) both in continental Europe and overseas.

5. Economic Aspects

The estimated capacity of formamide was approximately 100,000 t/yr worldwide in 1990. In 1993, there are only three significant producers; BASF in Germany is the leading manufacturer. Smaller quantities of formamide are produced in the former Czechoslovakia (Sokolov) and Japan (Nitto) by direct synthesis from carbon monoxide and ammonia. Most of the formamide produced is utilized directly by the manufacturers. The market price for formamide (ca 1993) is about $2.00/kg.

6. Specifications, Standards, and Quality Control

The quality of formamide supplied by BASF is certified as having a minimum assay of 99.5%. The principal impurities in the material are ammonium formate, methanol, water, and traces of iron. The quality of formamide supplied by BASF is certified to meet the specifications given in Table 3.

Direct determination of the formamide content by gc methods proves to be inaccurate because of its tendency to decompose at elevated temperatures. This also limits the accuracy of the classical Kjehldahl determination. The purity of formamide is, therefore, more reliably determined by analysis of its impurities and substraction of the combined contents from 100%.

For the purpose of quantitative analysis, formamide can be hydrolyzed under basic conditions to alkali formate and ammonia that can be determined by conventional methods.

Methanol can be converted to a dye after oxidation to formaldehyde and subsequent reaction with chromatropic acid [148-25-4]. The dye formed can be determined photometrically. However, gc methods are more convenient. Ammonium formate [540-69-2] is converted thermally to formic acid and ammonia. The latter is trapped by formaldehyde, which makes it possible to titrate the residual acid by conventional methods. The water content can be determined by standard Karl Fischer titration. In order to determine iron, it has to be reduced to the iron(II) form and converted to its bipyridyl complex. This compound is red and can be determined photometrically. Contamination with iron and impurities with polymeric hydrocyanic acid are mainly responsible for the color number of the merchandized formamide (<20 APHA). Hydrocyanic acid is detected by converting it to a blue dye that is analyzed and determined photometrically.

For purposes of product identification and quality control it is useful not only to employ the abovementioned analytical methods but also to measure physical constants such as the density, refractive index, melting point, and pH value of the material.

7. Storage

The shelf life is unlimited in sealed containers. The product is neither explosive nor spontaneously flammable in air. Pure formamide is slightly hygroscopic, but stable to hydrolysis at room temperature. It is stable to the effects of light and air below ca 100°C. However, the product is combustible and should accordingly be stored with adequate precautions. The product is not included in Annex I (List of Dangerous Substances) of EEC Directive 76/907/EEC (including the latest amendment), but on the basis of the present data and in connection with the "EEC Guide to Labelling" it is a dangerous substance and should be labeled as follows: "Hazard symbol: Xn. R-phrase: 47. S-phrase: 53" (EEC Directive 91/325/EEC). To prevent contact with formamide, an approved organic vapor respirator, a face shield, goggles, coveralls, and other protective clothing should be worn as necessary. Spilled material must be disposed of in accordance with local, state, and federal regulations.

8. Health and Safety

Formamide exhibits no particular acute toxicity with oral, dermal, and other applications in rats and other species. LD_{50} values are in the range of 2.7–17 g/kg. The acute inhalation hazard is also low. In the rabbit skin test it is not irritating, but it is mildly irritating to guinea pigs. In the rabbit eye the substance caused slight to strong irritation. Formamide is not a sensitizer in guinea pigs.

Oral applications of 1500 mg/kg/d for two weeks caused death of rats. Repeated oral applications (4 wks) of 30 μL/kg to rats caused no toxic symptoms, 100 μL/kg resulted in minor toxic effects, and 300 μL/kg induced impairment of several organs and lethality. Repeated oral applications ($26\times$) of 0.1 mL/kg caused no toxic symptoms in cats or rabbits. Inhalation of 1500 ppm (2 wks) were without effects, whereas in a similar study with comparable concentrations, toxicity was observed. Exposure of 3 ppm (4 mo) to rats induced some organ toxicity. Repeated dermal applications of 3000 mg/kg in rats (3 mo) caused increased mortality, 300 and 1000 mg/kg caused only changes in blood, whereas 100 mg/kg were without effects.

In several mutagenicity tests formamide did not demonstrate a genotoxic potential. In a further study chromosome damage in rats was described but not clearly verified. Formamide produced adverse effects on the offspring after oral and dermal applications in different species. Formamide had no influence on the fertility of male rats after inhalation. TLV (1993–1994) is 10 ppm (18 mg/m^3) (33). Precautions that should be observed when handling formamide include avoidance of prolonged inhalation of vapors or contact of the liquid with skin or eyes. When handling the chemical its tetratogenic property has to be taken into account (34).

Small quantities of spilled formamide can be washed away with plenty of water. Larger amounts should be absorbed appropriately or pumped into containers for proper disposal by incineration or biological degradation in a sewage water treatment plant.

9. Uses

Formamide has a wide variety of applications and has become an important intermediate in the chemical industry where it is used for producing heterocyclic compounds, pharmaceuticals, crop protection agents, fungicides, and pesticides and has gained importance as a solvent. It is hydrolyzed to formic acid by sulfuric acid. With twice the stoichiometric proportion of sulfuric acid, ammonium hydrogen sulfate is obtained (35), which as a saturated solution itself is able to hydrolyze formamide (36), thus allowing the process to be carried out in two consecutive steps (37). For environmental reasons the production of formic acid based on formamide is declining. In the formamide vacuum process, anhydrous hydrocyanic acid is produced by passing a mixture of formamide and a small proportion of air at reduced pressure through a heated tube or over a catalyst (38).

The good solvent properties of formamide have been exploited widely in the manufacture and processing of plastics. Formamide has been recommended for removing coatings of wire enamel from copper conductors (39). It can also be used in the spinning of acrylonitrile copolymers (40). It is employed in the antistatic finishing of plastics or formation of conductive coatings on plastic particles (41). If acrolein and α-substituted acroleins are polymerized in the presence of formamide, clear resin solutions are obtained that can be used for fabricating films. The resins can also be cured by storing (42).

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