ACETIC ACID, HALOGENATED DERIVATIVES

1. Introduction

The most important of the halogenated derivatives of acetic acid is chloroacetic acid. Fluorine, chlorine, bromine, and iodine derivatives are all known, as are mixed halogenated acids. For a discussion of the fluorine derivatives see FLUORINE COMPOUNDS, ORGANIC.

2. Chloroacetic Acid

2.1. Physical Properties. Pure chloroacetic acid [79-11-8] ($ClCH_2COOH$), mol wt 94.50, $C_2H_3ClO_2$, is a colorless, white deliquescent solid. It has been isolated in three crystal modifications: α, mp 63°C, β, mp 56.2°C, and γ, mp 52.5°C. Commercial chloroacetic acid consists of the α form. Physical properties are given in Table 1.

Chloroacetic acid forms azeotropes with a number of organic compounds. It can be recrystallized from chlorinated hydrocarbons such as trichloroethylene, perchloroethylene, and carbon tetrachloride. The freezing point of aqueous chloroacetic acid is shown in Figure 1.

Table 1. **Physical Properties of Chloroacetic Acid**

Property	Value
boiling point, °C	189.1
density, at 25°C, g/mL	1.4043
dielectric constant at 60°C	12.3
free energy of formation, at 100°C, ΔG_f, kJ/mol[a]	−368.7
heat capacity, J/(mol·k)[b] at 100°C	181.0
heat of formation, at 100°C, ΔH_f, kJ/mol[a]	−490.1
heat of sublimation, at 25°C, ΔH_s, kJ/mol[a]	88.1
vapor pressure, kPa[c]	
at 25°C	8.68×10^{-3}
at 100°C	3.24
viscosity, at 100°C, mPa·s (= cP)	1.29
refractive index at 55°C	1.435
surface tension, at 100°C, mN/m (= dyn/cm)	35.17
dissociation constant K_a	1.4×10^{-3}
solubility (g/100 g solvent)	
water	614
acetone	257
methylene chloride	51
benzene	26
carbon tetrachloride	2.75

[a] To convert kJ/mol to kcal/mol, divide by 4.184.
[b] To convert J/(mol·K) to cal/(mol·K), divide by 4.184.
[c] To convert kPa to mm Hg, multiply by 7.5.

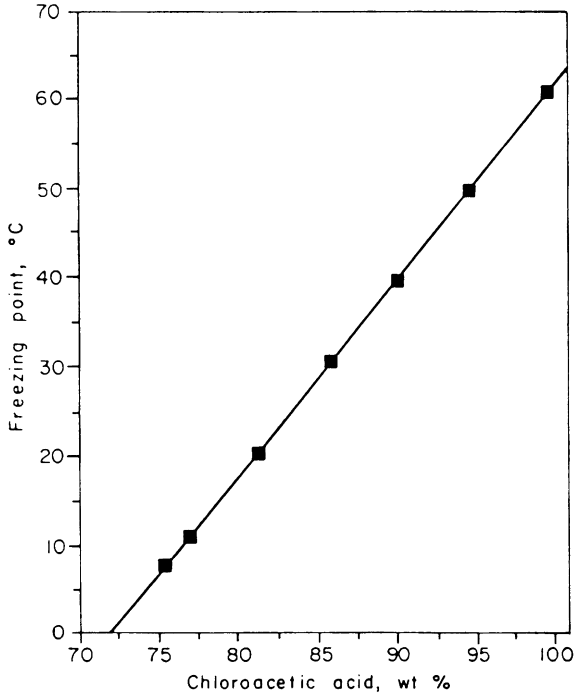

Fig. 1. The freezing point of monochloroacetic acid (MCAA)–water mixtures. For wt % acid >75%: fp(°C) = 2.17 × (wt % MCAA) − 156.5. Data courtesy of the Dow Chemical Company.

2.2. Chemical Properties. Chloroacetic acid has wide applications as an industrial chemical intermediate. Both the carboxylic acid group and the α-chlorine are very reactive. It readily forms esters and amides, and can undergo a variety of α-chlorine substitutions. Electron withdrawing effects of the α-chlorine give chloroacetic acid a higher dissociation constant than that of acetic acid.

The reaction of chloroacetic acid with alkaline cellulose yields carboxymethylcellulose which is used as a thickener and viscosity control agent (1) (see CELLULOSE ETHERS). Sodium chloroacetate reacts readily with phenols and cresols. 2,4,-Dichlorophenol and 4-chloro-2-cresol react with chloroacetic acid to give the herbicides 2,4-D and MCPA (2-methyl-4-chlorophenoxy acetic acid), respectively (2,3) (see HERBICIDES). Thioglycolic acid [68-11-1], $C_2H_4O_2S$, is prepared commercially by treating chloroacetic acid with sodium hydrosulfide. Sodium and ammonium salts of thioglycolic acid (qv) have been used for cold-waving human hair; the calcium salt is used as a depilating agent (see COSMETICS). Thioglycolic acid derivatives are also used as stabilizers in poly(vinyl chloride) (PVA) products.

Chloroacetic acid can be esterified and aminated to provide useful chemical intermediates. Amphoteric agents suitable as shampoos have been synthesized by reaction of sodium chloroacetate with fatty amines (4,5). Reactions with amines (6) such as ammonia, methylamine, and trimethylamine yield glycine [56-40-6], sarcosine [107-97-1], and carboxymethyltrimethylammonium chloride,respectively. Reaction with aniline forms *N*-phenylglycine [103-01-5], a starting point for the synthesis of indigo (7).

Reaction of chloroacetic acid with cyanide ion yields cyanoacetic acid [372-09-8], $C_3H_3NO_2$, (8) which is used in the formation of coumarin, malonic acid and esters, and barbiturates. Reaction of chloroacetic acid with hydroxide results in the formation of glycolic acid [79-14-1].

2.3. Manufacture. Most chloroacetic acid is produced by the chlorination of acetic acid using either a sulfur or phosphorus catalyst (9–12). The remainder is produced by the hydrolysis of trichloroethylene with sulfuric acid (13,14) or by reaction of chloroacetyl chloride with water.

A major disadvantage of the chlorination process is residual acetic acid and overchlorination to dichloroacetic acid. Although various inhibitors have been tried to reduce dichloroacetic acid formation, chloroacetic acid is usually purified by crystallization (15–17). Dichloroacetic acid can be selectively dechlorinated to chloroacetic acid with hydrogen and a catalyst such as palladium (18–20). Extractive distillation (21) and reaction with ketene (22) have also been suggested for removing dichloroacetic acid. Whereas the hydrolysis of trichloroethylene with sulfuric acid yields high purity chloroacetic acid, free of dichloracetic acid, it has the disadvantage of utilizing a relatively more expensive starting material and producing a sulfur containing waste stream.

Corrosive conditions of the chlorination process necessitate the use of glass-lined or lead-lined steel vessels in the manufacture of chloroacetic acid. Process piping and valves also are either glass-lined, or steel lined with a suitable polymer, eg, polytetrafluoroethylene (PTFE). Pumps, heat exchangers, and other process equipment can be fabricated from ceramic, graphite composite, tantalum, titanium, or certain high performance stainless steels. Chloroacetic acid can be stored as a molten liquid in glass-lined tanks for a short period of time, but

Table 2. **Producers of Chloroacetic Acid and Their Capacities**[a]

Producer	Capacity $\times 10^3$ t ($\times 10^6$ lb)
Dow, Midland, Mich.	22.7 (50)
Hercules, Hopewell, VA.	11.3 (25)
Niacet, Niagara Falls, N. Y.	9 (20)
Total	*43* (*95*)

[a] Ref. 23, as of Jan. 2001.

develops color on aging. For long-term storage, the solid, flaked form of the acid is held in a polyethylene-lined fiber drum. The drum is constructed so that no chloroacetic acid vapors contact the fiber or metallic portions. Stainless steels are acceptable for the shipment of 80% solutions of chloroacetic acid provided the temperature is maintained $< 50^{\circ}$C. However, long-term or continuous storage of the 80% solution results in significant pickup of iron from stainless steel.

2.4. Economic Aspects. U.S. producers of chloroacetic acid and their capacities are listed in Table 2. No new capacity is currently planned. Demand for chloroacetic acid in 1999 was 41.5×10^3 t (91.5×10^6 lb). Estimated demand for 2003 is 44.8×10^3 t (98.7×10^6 lb) (23).

Prices for the period 1994–1999 ranged from \$0.24/kg (\$0.53/lb) to \$0.34/kg (\$0.75 lb). Both prices are for high purity flake in bags, t.l., fob works. Current prices range from \$0.33/kg (\$0.73/lb) to \$0.34/kg (\$0.75/lb) (23).

2.5. Analytical and Test Methods. Gas or liquid chromatography (24) are commonly used to measure impurities such as acetic, dichloroacetic, and trichloroacetic acids. High purity 99 + % chloroacetic acid will contain < 0.5% of either acetic or dichloroacetic acid. Other impurities that may be present in small amounts are water and hydrochloric acid.

2.6. Health and Safety Aspects. Chloroacetic acid is extremely corrosive and will cause serious chemical burns. It also is readily absorbed through the skin in toxic amounts. Contamination of 5–10% of the skin area is usually fatal (25). The symptoms are often delayed for several hours. Single exposure to accidental spillage on the skin has caused human fatalities. The toxic mechanism appears to be blocking of metabolic cycles. Chloroacetic acid is 30–40 times more toxic than acetic, dichloroacetic, or trichloroacetic acid (26). When handling chloroacetic acid and its derivatives, rubber gloves, boots, and protective clothing must be worn. In case of skin exposure, the area should immediately be washed with large amounts of water and medical help should be obtained at once. Oral LD_{50} for chloroacetic acid is 76 mg/kg in rats (27).

2.7. Uses. Major industrial uses for chloroacetic acid are in the manufacture of thioglycolic acid (29%), cellulose ethers (mainly carboxymethylcellulose,CMC) (24%) and herbicides (18%). Other industrial uses (29%) include manufacture of glycine, amphoteric surfactants, cyanoacetic acid, phenoxyacetic acid, and chloroacetic acid esters (23).

3. Sodium Chloroacetate

Sodium chloroacetate [3926-62-3], mol wt 116.5, $C_2H_2ClO_2Na$, is produced by reaction of chloroacetic acid with sodium hydroxide or sodium carbonate. In

many applications, chloroacetic acid or the sodium salt can be used interchangeably. As an industrial intermediate, sodium chloroacetate may be purchased or formed *in situ* from free acid. The sodium salt is quite stable in dry solid form, but is hydrolyzed to glycolic acid in aqueous solutions. The hydrolysis rate is a function of pH and temperature (28).

4. Dichloroacetic Acid

Dichloroacetic acid [79-43-6] ($Cl_2CHCOOH$), mol wt 128.94, $C_2H_2Cl_2O_2$, is a reactive intermediate in organic synthesis. Physical properties are mp 13.9°C, bp 194°C, density 1.5634 g/mL, and refractive index 1.4658, both at 20°C. The liquid is totally miscible in water, ethyl alcohol, and ether. Dichloroacetic acid ($K_a = 5.14 \times 10^{-2}$) is a stronger acid than chloroacetic acid. Most chemical reactions are similar to those of chloroacetic acid, although both chlorine atoms are susceptible to reaction. An example is the reaction with phenol to form diphenoxyacetic acid (29). Dichloroacetic acid is much more stable to hydrolysis than chloroacetic acid.

Dichloroacetic acid is produced in the laboratory by the reaction of chloral hydrate [302-17-0] with sodium cyanide (30). It has been manufactured by the chlorination of acetic and chloroacetic acids (31), reduction of trichloroacetic acid (32), hydrolysis of pentachloroethane [76-01-7] (33), and hydrolysis of dichloroacetyl chloride. Due to similar boiling points, the separation of dichloroacetic acid from chloroacetic acid is not practical by conventional distillation. However, this separation has been accomplished by the addition of azeotrope-forming hydrocarbons such as bromobenzene (34) or by distillation of the methyl or ethyl ester.

Dichloroacetic acid is used in the synthesis of chloramphenicol [56-75-7] and allantoin [97-59-6]. Dichloroacetic acid has virucidal and fungicidal activity. It was found to be active against several staphylococci (35). The oral toxicity is low: the LD_{50} in rats is 4.48 g/kg. It can, however, cause caustic burns of the skin and eyes and the vapors are very irritating and injurious (27).

5. Trichloroacetic Acid

Trichloroacetic acid [76-03-9] (Cl_3CCOOH), mol wt 163.39, $C_2HCl_3O_2$, forms white deliquescent crystals and has a characteristic odor. Physical properties are given in Table 3.

Trichloroacetic acid ($K_a = 0.2159$) is as strong an acid as hydrochloric acid. Esters and amides are readily formed. Trichloroacetic acid undergoes decarboxylation when heated with caustic or amines to yield chloroform. The decomposition of trichloroacetic acid in acetone with a variety of aliphatic and aromatic amines has been studied (36). As with dichloroacetic acid, trichloroacetic acid can be converted to chloroacetic acid by the action of hydrogen and palladium on carbon (17).

Trichloroacetic acid is manufactured in the United States by the exhaustive chlorination of acetic acid (37). The patent literature suggests two alternative

Table 3. **Physical Properties of Trichloroacetic Acid**

Property	Value
melting point, °C	59
boiling point, °C	197.5
density, at 64°C, g/mL	1.6218
refractive index at 61°C	1.4603
heat of combustion, kJ/g[a]	3.05
solubility, at 25°C, g/100 g solvent	
water	1306
methanol	2143
ethyl ether	617
acetone	850
benzene	201
o-xylene	110

[a] To convert kJ/g to kcal/g, divide by 4.184.

methods of synthesis: hydrogen peroxide oxidation of chloral (38) and hydrolytic oxidation of tetrachloroethene (39).

Sodium trichloroacetate [650-51-1], $C_2Cl_3O_2Na$, is used as a herbicide for various grasses and cattails (2). The free acid has been used as an astringent, antiseptic, and polymerization catalyst. The esters have antimicrobial activity. The oral toxicity of sodium trichloroacetate is quite low (LD_{50} rats, 5.0 g/kg). Although very corrosive to skin, trichloroacetic acid does not have the skin absorption toxicity found with chloroacetic acid (27).

6. Chloroacetyl Chloride

Chloroacetyl chloride [79-04-9] ($ClCH_2COCl$) is the corresponding acid chloride of chloroacetic acid (see ACETYL CHLORIDE). Physical properties include mol wt 112.94, $C_2H_2Cl_2O$, mp −21.8°C, bp 106°C, vapor pressure 3.3 kPa (25 mm Hg) at 25°C, 12 kPa (90 mm Hg) at 50°C, and density 1.4202 g/mL and refractive index 1.4530, both at 20°C. Chloroacetyl chloride has a sharp, pungent, irritating odor. It is miscible with acetone and benzene and is initially insoluble in water. A slow reaction at the water–chloroactyl chloride interface, however, produces chloroacetic acid. When sufficient acid is formed to solubilize the two phases, a violent reaction forming chloroacetic acid and HCl occurs.

Since chloroacetyl chloride can react with water in the skin or eyes to form chloroacetic acid, its toxicity parallels that of the parent acid. Chloroacetyl chloride can be absorbed through the skin in lethal amounts. The oral LD_{50} for rats is between 120 and 250 mg/kg. Inhalation of 4 ppm causes respiratory distress. A TLV of 0.05 ppm is recommended (27, 40).

Chloroacetyl chloride is manufactured by reaction of chloroacetic acid with chlorinating agents such as phosphorus oxychloride, phosphorus trichloride, sulfuryl chloride, or phosgene (41–43). Various catalysts have been used to promote the reaction. Chloroacetyl chloride is also produced by chlorination of acetyl chloride (44–46), the oxidation of 1,1-dichloroethene (47, 48), and the addition

of chlorine to ketene (49, 50). Dichloroacetyl and trichloroacetyl chloride are produced by oxidation of trichloroethylene or tetrachloroethylene, respectively.

Much of the chloroacetyl chloride produced is used captively as a reactive intermediate. It is useful in many acylation reactions and in the production of adrenalin [51-43-4], diazepam [439-15-5], chloroacetophenone [532-27-4], chloroacetate esters, and chloroacetic anhydride [541-88-8]. A major use is in the production of chloroacetamide herbicides (3) such as alachlor [15972-60-8].

7. Chloroacetate Esters

Two chloroacetate esters of industrial importance are methyl chloroacetate [96-34-4], $C_3H_5ClO_2$, and ethyl chloroacetate [105-39-5], $C_4H_7ClO_2$. Their properties are given in Table 4.

Both esters have a sweet pungent odor and present a vapor inhalation hazard. They are rapidly absorbed through the skin and hydrolyzed to chloroacetic acid. The oral LD_{50} for ethyl chloroacetate is between 50 mg/kg (51).

Chloroacetate esters are usually made by removing water from a mixture of chloroacetic acid and the corresponding alcohol. Reaction of alcohol with chloroacetyl chloride is an anhydrous process that liberates HCl. Chloroacetic acid will react with olefins in the presence of a catalyst to yield chloroacetate esters. Dichloroacetic and trichloroacetic acid esters are also known. These esters are useful in synthesis. They are more reactive than the parent acids. Ethyl chloroacetate can be converted to sodium fluoroacetate by reaction with potassium fluoride (see FLUORINE COMPOUNDS, ORGANIC). Both methyl and ethyl chloroacetate are used as agricultural and pharmaceutical intermediates, specialty solvents, flavors, and fragrances. Methyl chloroacetate and β-ionone undergo a Darzens reaction to form an intermediate in the synthesis of Vitamin A. Reaction of methyl chloroacetate with ammonia produces chloroacetamide [79-07-2], C_2H_4ClNO (52).

8. Bromoacetic Acid

Bromoacetic acid [79-08-3] ($BrCH_2COOH$), mol wt 138.96, $C_2H_3BrO_2$, occurs as hexagonal or rhomboidal hygroscopic crystals, mp 49°C, bp 208°C, d^{50} 1.9335,

Table 4. **Physical Properties of Chloroacetate Esters**

Property	Methyl ester	Ethyl ester
molecular weight	108.52	122.55
melting point, °C	−32.1	−26
boiling point, °C	129.8	143.3
density, at 20°C, g/mL	1.2337	1.159
flash point, °C	57	66
vapor pressure, kPa[a]		
at 25°C	0.96	0.61
at 50°C	4.3	2.6
structural formula	$ClCH_2COOCH_3$	$ClCH_2COOC_2H_5$

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

n^{50}_{D} 1.4804. It is soluble in water, methanol, and ethyl ether. Bromoacetic acid undergoes many of the same reactions as chloroacetic acid under milder conditions, but is not often used because of its greater cost. Bromoacetic acid must be protected from air and moisture, since it is readily hydrolyzed to glycolic acid. The simple derivatives such as the acid chloride, amides, and esters are well known. Esters of bromoacetic acid are the reagents of choice in the Reformatsky reaction, which is used to prepare β-hydroxy acids or α,β-unsaturated acids. Similar reactions with chloroacetate esters proceed slowly or not at all (53).

Bromoacetic acid can be prepared by the bromination of acetic acid in the presence of acetic anhydride and a trace of pyridine (54), by the Hell-Volhard-Zelinsky bromination catalyzed by phosphorus, and by direct bromination of acetic acid at high temperatures or with hydrogen chloride as catalyst. Other methods of preparation include treatment of chloroacetic acid with hydrobromic acid at elevated temperatures (55), oxidation of ethylene bromide with fuming nitric acid, hydrolysis of dibromovinyl ether, and air oxidation of bromoacetylene in ethanol.

9. Dibromoacetic Acid

Dibromoacetic acid [631-64-1] ($Br_2CHCOOH$), mol wt 217.8, $C_2H_2Br_2O_2$, mp 48°C, bp 232–234°C (decomposition), is soluble in water and ethyl alcohol. It is prepared by adding bromine to boiling acetic acid, or by oxidizing tribromoethene [598-16-3] with peracetic acid.

10. Tribromoacetic Acid

Tribromoacetic acid [75-96-7] (Br_3CCOOH), mol wt 296.74, $C_2HBr_3O_2$, mp 135°C, bp 245°C (decomposition), is soluble in water, ethyl alcohol, and diethyl ether. This acid is relatively unstable to hydrolytic conditions and can be decomposed to bromoform in boiling water. Tribromoacetic acid can be prepared by the oxidation of bromal [115-17-3] or perbromoethene [79-28-7] with fuming nitric acid and by treating an aqueous solution of malonic acid with bromine.

11. Iodoacetic Acid

Iodoacetic acid [64-69-7] (ICH_2COOH), mol wt 185.95, $C_2H_3IO_2$, is commercially available. The colorless, white crystals (mp 83°C) are unstable upon heating. It has a K_a of 7.1×10^{-4}. Iodoacetic acid is soluble in hot water and alcohol, and slightly soluble in ethyl ether. Iodoacetic acid can be reduced with hydroiodic acid at 85°C to give acetic acid and iodine (56). Iodoacetic acid cannot be prepared by the direct iodination of acetic acid (57), but has been prepared by iodination of acetic anhydride in the presence of sulfuric or nitric acid (58). Iodoacetic acid can also be prepared by reaction of chloroacetic or bromoacetic acid with sodium or potassium iodide (59).

12. Diiodoacetic Acid

Diiodoacetic acid [598-89-0] ($I_2CHCOOH$), mol wt 311.85, $C_2H_2I_2O_2$, mp 110°C, occurs as white needles and is soluble in water, ethyl alcohol, and benzene. It has been prepared by heating diiodomaleic acid with water (60) and by treating malonic acid with iodic acid in a boiling water solution (61).

13. Triiodoacetic Acid

Triiodoacetic acid [594-68-3] (I_3CCOOH), mol wt 437.74, $C_2HO_2I_3$, mp 150°C (decomposition), is soluble in water, ethyl alcohol, and ethyl ether. It has been prepared by heating iodic acid and malonic acid in boiling water (62). Solutions of triiodoacetic acid are unstable as evidenced by the formation of iodine. Triiodoacetic acid decomposes when heated above room temperature to give iodine, iodoform, and carbon dioxide. The sodium and lead salts have been prepared.

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