Kirk-Othmer Encyclopedia of Chemical Technology.

THIOGLYCOLIC ACID

Thioglycolic acid (2-mercaptoacetic acid [68-11-1]), $HSCH_2COOH$, molecular weight 92.11, is the first member of the mercaptocarboxylic acids series. It was prepared and identified in 1862 by Carius (1) and studied around 1900 (2). Thioglycolic acid was first developed commercially in the early 1940s in the field of cosmetology as an active material for cold wave permanents and depilatories (see Hair preparations). The advent of the PVC industry in the 1950s brought thioglycolic acid a significant application as a raw material in the manufacture of organotin stabilizers (see Heat stabilizers; Vinyl polymers). These stabilizers improved thermal stability and prevented discoloration during polymer processing. As large-scale commercial chemical production grew, thioglycolic acid began to be used more and more as a raw material in the manufacture of fine and specialty chemicals in the pharmaceutical and agricultural sectors.

1. Properties

Pure thioglycolic acid is a water-white liquid that freezes at $-16°C$ and distills under reduced pressure. Reported constants are bp at 3.9 kPa (29 mm Hg), 123°C, bp at 1.33 kPa (10 mm Hg), 96°C (3); d_4^{20}, 1.325 g/cm^3; viscosity at 20°C, $6.55 mPa{\cdot}s(= cP)$; refractive index n_D^{20}, 1.5030; heat of vaporization, 627.2 J/g (149.9 cal/g); heat of combustion, 1446 kJ/mol (345.6 kcal/mol); electrical conductivity at 20°C, $2 \times 10^6 (\Omega{\cdot}cm)^{-1}$; dielectric constant, $7.4 \times 10^{-30} C{\cdot}m$ (2.25 debye); dipole moment, $7.6 \times 10^{-30} C{\cdot}m$ (2.28 debye); flash point in closed cup, 132°C.

Both the carboxyl and the mercapto moieties of thioglycolic acid are acidic. Dissociation constants at 25°C are for pK_1, 3.6; pK_2, 10.5. Thioglycolic acid is miscible in water, ether, chloroform, dichloroethane and esters. It is weakly soluble in aliphatic hydrocarbons such as heptane, hexane. Solvents such as alcohols and ketones can also react with thioglycolic acid.

2. Reactions

Thioglycolic acid is altered by self-esterification. This alteration depends on temperature and concentration of aqueous solutions. Thioglycolic acid is almost stable at room temperature in 70 wt % aqueous solution. At room temperature, the loss in assay for pure product under correct storage conditions is about 1% of the initial value in a month. At a lower (5°C) temperature this figure is below 0.3% in a month; at higher temperatures the self-esterification increases. Under an air atmosphere oxidation to disulfide occurs. Many self-esterification products, called thioglycolides, have been detected by nmr. Examples are *S*-mercaptoacetylthioacetic acid [99-68-3], $HSCH_2COSCH_2COOH$, which represents more than 90% of thioglycolides, some polythioglycolides, $HS(CH_2COS)_xCH_2COOH$, cyclic thioglycolides such as 1,4-dithioglycolide [4835-42-6], and also solid ortho thioesters such as tetracarboxylmethylmercapto-1,4-dithiane [52959-43-0]. Formation of the last is promoted by acid species. The self-esterification products can be reversed in the presence of dilute acids or alkalies, and aged thioglycolic acid can be completely recovered by hydrolysis.

Thioglycolic acid undergoes reactions typical of carboxylic acids, forming salts, esters, amides, and reactions typical of mercaptans, and forming thioethers with olefins or halogenated compounds, disulfides by oxidation, and metal mercaptides by reaction with metal oxides or metal chlorides. Thioglycolic acid or its salts in aqueous solutions are rapidly oxidized by air or hydrogen peroxide to the disulfide, dithiodiglycolic acid [505-73-7], $HOOCCH_2SSCH_2COOH$. More vigorous oxidative conditions, eg, with dilute nitric acid, produce sulfoacetic acid [123-43-3], HO_3SCH_2COOH. Thioglycolic acid is a powerful reducing agent in neutral or alkaline solutions. One of the most widely used reactions of thioglycolic acid is the thiol disulfide interchange reaction, particularly with the disulfide bond of cystine [923-32-0] (**1**) in protein material, eg, wool and hair, to form the amino acid cysteine **(2)**. The rate at which equilibrium is established is a function of pH; it is low at pH <6 and rapid at pH 8–10.

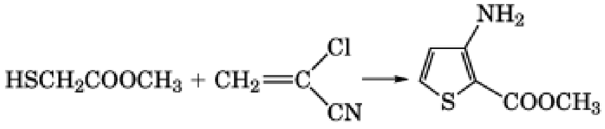
$$2\ HSCH_2COOH + HOOCCH(NH_2)CH_2SSCH_2CH(NH_2)COOH \rightleftarrows \qquad (1)$$

$$HOOCCH_2SSCH_2COOH + 2\ HOOCCH(NH_2)CH_2SH \qquad (1) \qquad\qquad (2)$$

Long-chain thioacetic acids are obtained by reaction of primary alkenes with thioglycolic acid, by using uv lamps or radical initiators. This is the case for dodecylthioacetic acid [13753-71-4], $C_{12}H_{24}SCH_2COOH$, prepared from dodecene, or carboxymethylthiosuccinic acid [99-68-3], $HOOCCH_2SCH(CH_2COOH)COOH$, prepared from maleic acid. Similar products have been described for the reaction of chloroacetic acid [79-11-8], $ClCH_2COOH$, and corresponding mercaptans.

Other products of commercial value, such as laurylthiopropionic acid [1462-52-8], $C_{12}H_{24}SCH_2CH_2COOH$, are produced starting from 3-mercaptopropionic acid [107-96-0], $HSCH_2CH_2COOH$, and unsaturated products. *S*-Alkylthiocarboxylic acids and their potassium salts have been described and evaluated as surfactants (qv). They provide excellent thermally stable behavior and good surface activity for their alkaline salts (4).

Because of its two active functions, thioglycolic acid is an ideal reagent for a variety of chemical reactions, including addition, elimination, and cyclization. The methyl [2365-48-2] and ethyl [623-51-8] esters of thioglycolic acid, $HSCH_2COOR$, have shown promise as raw materials in several fine chemicals. These block the carboxylic group, leaving the mercapto group free to react. In the presence of bases, the mercapto group becomes a strong nucleophile able to react with halogenated compounds by a substitution reaction. This property is applied to the manufacture of many valuable pharmaceutical and agrochemical intermediates, such as ethyl trifluoromethane thioglycolate [75-92-9], $F_3CSCH_2CO_2C_2H_5$. The methylene group of thioglycolic acid esters, having a particular position between a mercapto and an ester function, displays a significant ability to react. Under alkaline conditions, interesting routes are available to a variety of heterocyclic compounds, such as thiophene, thiazole and other N–S heterocyclic compounds. Methyl thioglycolate [2365-48-2], $HSCH_2COOCH_3$, can be used as the starting material to obtain methyl 3-amino-2-thiophenecarboxylate [22288-78-4] **(3)** by reaction with 2-chloroacrylonitrile [920-37-6]. Compound **(3)** is a key intermediate to drugs and agrochemicals (5).



(2)

(3)

Several kinds of products can be obtained by reaction of thioglycolic acid and its esters with aldehydes to form mercaptals, $RCH(SCH_2COOH)_2$, or with ketones to form thiolketals, $RR'C(SCH_2COOH)_2$. Reaction with

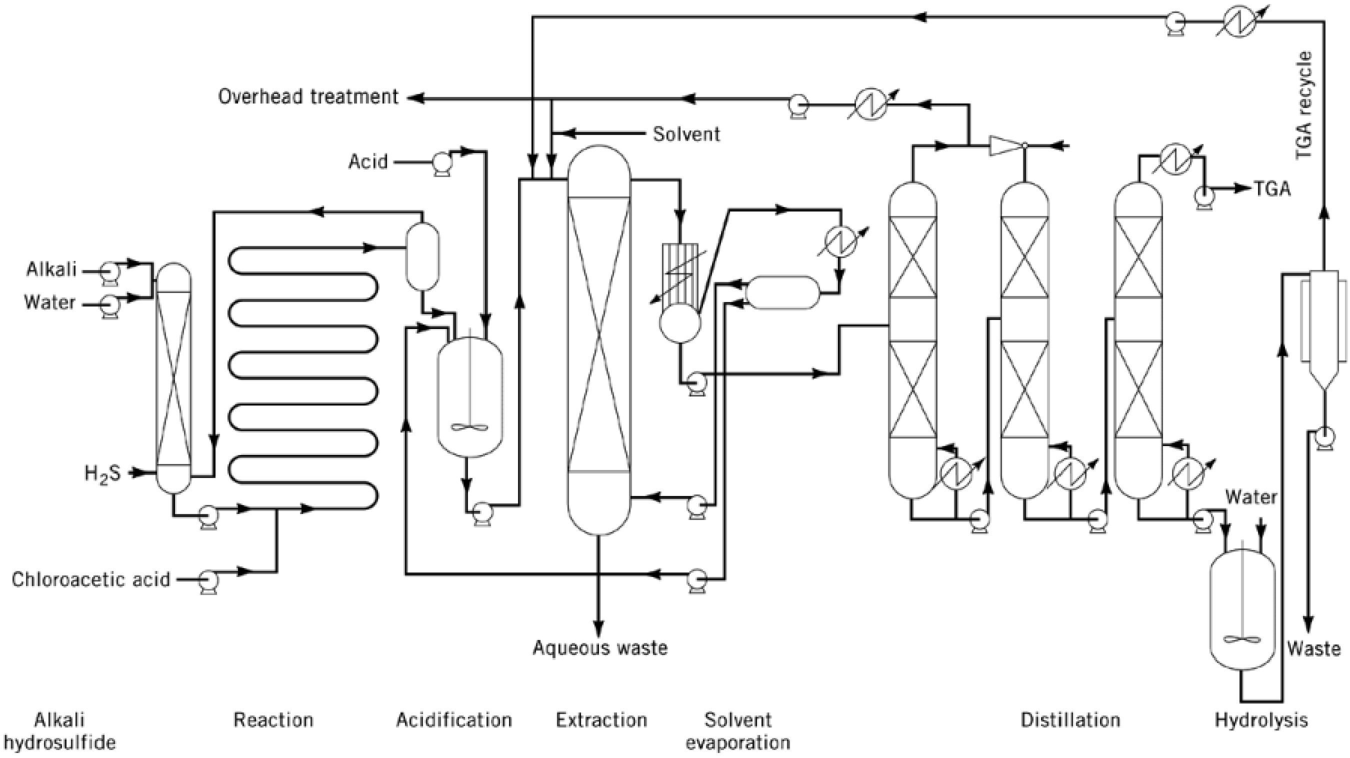


Fig. 1. Thioglycolic acid (TGA) manufacture.

formaldehyde (qv) yields di-*n*-butylmethylene-bisthioglycolate [1433882-0] (MBT ester):

$$2\ \mathrm{HSCH_2COOC_4H_9} + \mathrm{CH_2O} \longrightarrow \mathrm{C_4H_9OOCCH_2SCH_2SCH_2COOC_4H_9} + \mathrm{H_2O} \qquad (3)$$

Thioglycolic acid forms a multiplicity of stable complexes with metal ions. Depending on the particular metal and on experimental conditions, the thioglycolate complexes can be mononuclear or polynuclear and have the structure of carboxylate salts, metal mercaptides, or true chelates. Complexes studied include various metal and rare-earth metals, mercaptocarboxylic acids, and thiodiglycolic acid [123-93-3], $HOOCCH_2SCH_2COOH$. Potentiometric investigations and structural identifications have been carried out to determine properties and stability (6).

3. Manufacturing, Processing, and Storage

Thioglycolic acid is manufactured by the reaction of monochloracetic acid [79-11-8] or its salts with alkali hydrosulfides, eg, NaSH or NH_4SH, in aqueous medium, under controlled conditions of pressure, temperature, pH, concentration, to give a higher yield of thioglycolate salt and minimize the formation of such by-products as thiodiglycolic and dithiodiglycolic acids. The reaction mixture is acidified to liberate thioglycolic acid, which is extracted from the aqueous solution into an organic solvent, such as an ether, and then purified by vacuum distillation (7) (Fig. 1).

Commercial monochloroacetic acid contains many other organic acids, particularly dichloroacetic acid [79-43-6], $Cl_2CHCOOH$, which has to be completely converted into sulfur derivatives to avoid residual chlorine compounds which are harmful for cosmetic applications (8). Thioglycolic acid, which has to meet cosmetic specifications, must be free of metal impurities, and must be pure enough to avoid color and odor problems.

Many other routes to produce thioglycolic acid have been investigated (9). To try to minimize by-products, nucleophilic agents other than alkali sulfhydrates have been claimed, eg, thiosulfates, sodium disulfides, thiourea, xanthogenic acid derivatives, and sodium trithiocarbonates (10). These alternative methods, which require reduction of the disulfides or hydrolysis of carboxymethylthio derivatives, seem less competitive than those using alkali sulfhydrates.

All the processes starting from chloroacetic acid are characterized by the formation of 2 moles of salt per mole of thioglycolic acid produced:

$$ClCH_2COOH + 2\,NaSH \longrightarrow HSCH_2COONa + NaCl + H_2S \qquad (4)$$

$$HSCH_2COONa + HCl \longrightarrow HSCH_2COOH + NaCl \qquad (5)$$

Therefore, manufacture of thioglycolic acid is associated with the production of aqueous salt waste, so problems of waste disposal have to be resolved in each plant.

Where thioglycolic acid is manufactured mainly as an intermediate for conversion to higher alkyl esters, the alcohol of the ester can be used as solvent to extract thioglycolic acid. It is also convenient to manufacture the esters of thioglycolic acid directly and to use the ester of chloroacetic acid and alkali sulfhydrates (10) as raw material.

$$ROOCCH_2Cl + NaSH \longrightarrow ROOCCH_2SH + NaCl \qquad (6)$$

This is a waste-reducing process in comparison with the classical processes, which proceed by the thioglycolic acid esterification route.

Esters of thioglycolic acid are to a large extent manufactured by conventional esterification processes. Manufacture at a larger scale of 2-ethylhexyl thioglycolate [7659-86-1] and isooctyl thioglycolate [25103-09-7] by a continuous process (12) gives esters of higher consistency. Thioglycolic acid is marketed as pure product or at 80–85 wt % aqueous solution. The ammonium salts are available in aqueous solutions containing 50–60 wt % thioglycolic acid; the monoethanolamine salts are available as solutions containing 40–50 wt % thioglycolic acid. Glycerol monothioglycolate is supplied in anhydrous form. Calcium thioglycolate is supplied as a crystalline powder. Potassium thioglycolate [34452-51-2] and sodium thioglycolate [367-51-1] are also available as aqueous solutions.

Thioglycolic acid is stored in reinforced polyethylene or polypropylene tanks or containers. It is advisable to keep thioglycolic acid at low ($<10^\circ C$) temperature to slow down self-esterification. The same care must be taken with drums or tank trucks. Drums are made of polyethylene or polyethylene-lined steel. For transport, thioglycolic acid is classified as a corrosive and toxic liquid. The handling of thioglycolic acid requires the usual precautions observed for strong acid and corrosive chemicals.

Among other mercaptocarboxylic acids, the mercaptopropionic acids have undergone a promising development. Thiolactic acid or 2-mercaptopropionic acid [79-42-5], $HSCH(CH_3)COOH$, is manufactured by using 2-chloropropionic acid [598-78-7]. 3-Mercaptopropionic acid [107-96-0], $HSCH_2CH_2COOH$, competes with thioglycolic acid in plastic additives or as modifiers in various polymers. Mercaptopropionic acid is produced by using acrylic monomers, eg, acrylic acid, acrylonitrile, methyl acrylate, as raw materials (13–19) (Table 1).

Table 1. Mercaptopropionic Acid Syntheses

Process/raw materials	Conversion method	References
$CH_2{=}CHCOOH + HCl \longrightarrow ClCH_2CH_2COOH$		
$ClCH_2CH_2COOH + NaSH$	acidification	13
$CH_2{=}CHCOOH + H_2S$		14
$CH_2{=}CHCOOH + NaSH + CS_2$	acidification	15
$CH_2{=}CHCOOCH_3 + H_2S + S$	reduction hydrolysis	16
$CH_2{=}CHCN + NaSH + S$	reduction hydrolysis	17
$CH_2{=}CHCN + NaSH \longrightarrow NCCH_2CH_2SCH_2CH_2CN$		
$NCCH_2CH_2SCH_2CH_2CN + NaSH + NaOH$	acidification	18
$HOOCCH_2CH_2SCH_2CH_2COOH + NaOH + Na_2S$	acidification	19

4. Economic Aspects

Since its development in cosmetics in the 1940s, thioglycolic acid has become a widespread thiochemical, used all over the world as the acid or in the form of its salts or esters. Because of the several derivatives of thioglycolic acid used, the market size for this chemical is often expressed in terms of thioglycolic acid equivalents. In 1994 the total world market was estimated at around 15,000 to 20,000 metric tons of thioglycolic acid equivalents. Some mercaptocarboxylic acid and esters available are compiled in Table 2.

The worldwide growth of thioglycolic acid and its derivatives is primarily driven by the market growth of PVC, and more particularly by the demand for the tin stabilizers used in this thermoplastic. The demand for cold wave permanents and chemical depilatories is the second driving force for production of thioglycolic acid and its derivatives. The progress of thioglycolic acid within this sector is closely linked to local hair fashion, changes in cultural habits, and the development of average purchasing power. The world market for thioglycolic acid and its derivatives is thought to experience an average annual growth of 2%.

Manufacturing plants for thioglycolic acid and derivatives are found in Europe, the United States, and Asia. Producers in Europe are B. Bock (Germany), Elf Atochem (France), and Merck (Germany); in the United States Elf Atochem, Hampshire, and Witco; and in Japan, Daicel. Production capacity is expected to be sufficient to supply world demand for five years.

5. Specifications

Table 3 lists some properties and commercial specifications of thioglycolic and its salts.

6. Analytical and Test Methods

Thioglycolic acid can be identified by its ir spectrum or by gas chromatography. Most of the by-products and self-esterification products are also detected by liquid chromatography, eg, thiodiglycolic acid, dithiodiglycolic acid, linear dimers, and polymers. Iron content can be assayed by the red sensitive complex of 1,10-phenanthroline [66-71-7] and ferrous ion of a mineralized sample. Ferric ion turns an aqueous ammonia solution deep red-violet.

6.1. Assay

Thioglycolic acid is determined by its quantitative reaction with iodine. Depending on the storage conditions and time, thioglycolic acid tends to form thioglycolides with formation of water. This process is reversible by

Table 2. Mercaptocarboxylic Esters Derivatives

Compound	CAS Registry Number	Structural formula	Bp,[a] °C
methyl thioglycolate	[2365-48-2]	$HSCH_2COOCH_3$	148
methyl 3-mercaptopropionate	[2935-90-2]	$HSCH_2CH_2COOCH_3$	166
ethyl thioglycolate	[623-51-8]	$HSCH_2COOC_2H_5$	155
n-butyl thioglycolate	[10047-28-6]	$HSCH_2COOC_4H_9$	$110_{5.3}$
n-butyl 3-mercaptopropionate	[16215-21-7]	$HSCH_2CH_2COOC_4H_9$	$101_{1.6}$
2-ethylhexyl thioglycolate	[7659-86-1]	$HSCH_2COOC_8H_{17}$	$106_{0.4}$
2-ethylhexyl 3-mercaptopro-pionate	[50448-95-8]		$85\text{–}87_{0.27}$
isooctyl thioglycolate	[25103-09-7]		$107_{0.53}$
isooctyl 3-mercaptopropionate	[30774-01-7]		$95_{0.30}$
ethylene glycol dimercapto-acetate	[123-81-9]	$(CH_2OOCCH_2SH)_2$	$137_{0.26}$
ethylene glycol dimercaptopro-pionate	[22504-50-3]	$(CH_2OOCCH_2CH_2SH)_2$	$101_{0.04}$
pentaerythritol-tetrakis-thioglycolate	[10193-99-4]	$C(CH_2OOCCH_2SH)_4$	[b]
pentaerythritol-tetrakis-3-mercaptopropionate	[7575-23-7]		[b]
di-*n*-butyl methylene bis thioglycolate	[14338-82-0]	$CH_2(SCH_2COOC_4H_9)_2$	[c]
thiodiglycolic acid	[123-93-3]	$S(CH_2COOH)_2$	128[d]
dithiodiglycolic acid	[505-73-7]	$S_2(CH_2COOH)_2$	100–102[d]
dithiodipropionic acid	[1119-62-6]	$S_2(CH_2CH_2COOH)_2$	152–156[d]
thiodipropionic acid	[111-17-1]	$S(CH_2CH_2COOH)_2$	130[d]
dimethyl thiodipropionate	[4131-74-2]	$S(CH_2CH_2COOCH_3)_2$	$130_{0.26}$
dilauryl thiodipropionate	[123-28-4]	$S(CH_2CH_2\text{–}COOC_{12}H_{25})_2$	40[d]
distearyl thiodipropionate	[693-36-7]	$S(CH_2CH_2COOC_{18}H_{37})_2$	63–68[d]
3-mercaptopropionic acid	[107-96-0]	$HSCH_2CH_2COOH$	15.5[d] 111_2
2-mercaptopropionic acid	[79-42-5]	$HSCH(CH_3)COOH$	$85_{0.66}$
thiomalic acid	[70-49-5]	$HSCH(CH_2COOH)COOH$	150[d]

[a] Pressure other than atmospheric given as subscript in kPa. To convert to mm Hg, multiply by 7.5.
[b] Material assays at 95%.
[c] Viscosity at 20°C is $14-18$ mPa·s(= cP).
[d] Value given is melting point.

hydrolysis at elevated temperature or by alkalies or acids. Thioglycolides can be completely reconverted to thioglycolic acid. Therefore, for the assay determination of the initial thioglycolic acid, it is necessary to carry out hydrolysis with ammonia prior to iodometric titration.

Titration of thioglycolate esters is also realized by iodine in alcoholic solution. Titration of thioglycolic acid (acid number) in thioglycolate esters is effected by potentiometric titration with potassium hydroxide.

7. Health and Safety Factors

A safety assessment of ammonium and glyceryl thioglycolates and thioglycolic acid has been published (20). Hair products containing ammonium thioglycolate and glyceryl thioglycolate may be used safely, at infrequent intervals, at concentrations of ammonium thioglycolate and glyceryl thioglycolate up to 14.5% (as thioglycolic acid). Hairdressers should avoid skin contact and minimize consumer skin exposure.

7.1. Metabolism

Absorption, distribution, metabolism, and excretion of thioglycolic acid have been reviewed (20). In summary, ^{35}S-thioglycolic acid was absorbed significantly after application to the skin of rabbits. After intravenous

Table 3. Specifications for Thioglycolic Acid and Some Derivatives

Property	Thioglycolic acid	Thioglycolic acid	Ammonium thioglycolate	Glyceryl monothioglycolate	Monoethanolamine thioglycolate	Calcium thioglycolate
CAS Registry Number	[68-11-1]	[68-11-1]	[5421-46-5]	[30618-84-9]	[126-97-6]	[814-71-1]
EINECS[a]	2006774	2006774	2265409	2502648	2048154	
assay as TGA, %	98–99	80.0–80.3	60.0–60.3	75–76	50.0–50.4	50
specific gravity, 20°C	1.32	1.26–1.27	1.205	1.285	1.25	
iron[b], ppm	0.4	0.3	0.4	2	0.4	
pH			7.0–7.2		6.9–7.3	11–12
refractive index, 20°C	1.5030			1.5020–1.5030		
appearance	water-white	water-white	clear	clear, colorless	clear	white crystalline powder

[a] EINECS = European Inventory of Existing Commercial Chemical Substances.
[b] Value is maximum.

injection, the greatest counts of radioactivity were found in the kidneys, lungs, and spleen of monkey and in the small intestine and kidneys of rat. Most of the radioactivity was rapidly excreted in the urine in the form of inorganic sulfate and neutral sulfur.

7.2. Acute Toxicity

Thioglycolic acid, its esters and 3-mercaptopropionic acid are considered moderately toxic on the basis of acute toxicity studies. These are presented in Table 4.

7.3. Local Effects

Pure thioglycolic acid and 3-mercaptopropionic acid are stronger acids than acetic acid, and they must be handled with precautions appropriate for strong acids. Application of thioglycolic acid in a single patch test in rabbits resulted in necrosis in 5 min. This was accompanied by hyperemia and edema (23). 3-Mercaptopropionic acid induced corrosive dermatolysis after 24-h patch on rabbit skin (21). Thioglycolic acid esters induced at most a moderate irritation after 4-h contact on rabbit skin and are not classified as irritants under European regulations.

Instillation of pure thioglycolic acid into the eyes of a rabbit resulted in severe pain, severe conjunctival inflammation, dense corneal opacity, and severe iritis. These effects had not improved at the end of 14 d after exposure. Washing immediately after exposure did not modify the response (23). These kinds of injuries correspond to those observed in one accident in which part of the contents of a bottle of concentrated thioglycolic acid were splashed into the eyes (25). Diluted (10% in water) thioglycolic acid is considered only as irritating according to the European criteria (26).

3-Mercaptopropionic acid induced immediate necrosis of the eye (21). Thioglycolic esters, eg, ethyl, isooctyl, 2-ethylhexyl, and glyceryl, are far less dangerous to rabbit eyes than free thioglycolic acid. They are not classified as irritants, whereas methyl thioglycolate is classified as an irritant according to European regulations (21).

7.4. Sensitization

The skin irritation and sensitization potentials of 9.0% thioglycolic acid were evaluated using the open epicutaneous test. Reactions were not observed during the challenge phase. Thioglycolic acid was an irritant, but not a sensitizer (20).

Table 4. Toxicity of Thioglycolic Acid and Derivatives[a]

Sex[b]	Route	Dosing sol'n, %	LD$_{50}$, mg/kg	Clinical signs	References
Thioglycolic acid					
M,F	oral	0.2–1	73	ptosis, decrease respiratory rate, prostaration	21
M	oral	2.5	114		22
M,F	inhalation/4 h (aerosol)		0.21[c]	irritation of the eyes and the lungs	21
[d]	dermal	10	848		23
Methyl thioglycolate					
F	oral	10	209		22
M,F	dermal	100	>2000[e]	no deaths, hypoactivity,	21
Ethyl thioglycolate					
				piloerection, no cutaneous reaction	
F	oral	10	178		22
Isooctyl thioglycolate					
	oral		348–391		24
M,F	dermal	100	>2000[e]	no deaths, no clinical signs,	21
2-Ethylhexyl thioglycolate					
				no cutaneous reactions	
M	oral	10	303		21
M,F	inhalation/6 h		[f]		21
M,F	dermal	100	>2000	20% mortality, hypo-activity,	21
Glyceryl thioglycolate					
				no cutaneous reactions	
M,F	oral	68	>25 <200	sedation, coma, dyspnea, piloerection	21
Mercaptopropionic acid					
	oral		96–400		24
[g]	inhalation/1 h		[h]		21

[a] Tests carried out on rats, unless otherwise noted.
[b] Of animals used. F = female; M = male.
[c] Value is LC$_{50}$ and units are mg/L.
[d] Rabbits; no sex information given.
[e] Value is LD$_0$.
[f] No mortality at 0.51 mg/L.
[g] Mice.
[h] No death at saturated vapor.

The potential of 3-mercaptopropionic acid and thioglycolic acid esters to induce delayed-contact hypersensitivity following intradermal injection and cutaneous application was evaluated in guinea pigs according to the maximization method of Magnusson and Kligman. Mercaptopropionic acid and methyl thioglycolate did not induce sensibilization. Glyceryl thioglycolate is a very weak sensitizer; isooctyl thioglycolate is a weak sensitizer; and 2-ethylhexyl thioglycolate is a moderate sensitizer (21).

7.5. Genotoxicity

Thioglycolic acid (27), sodium thioglycolate (28), 2-ethylhexyl thioglycolate (21), isooctyl thioglycolate (21), and glyceryl thioglycolate (21) were not mutagenic in the Ames test when tested with and without metabolic activation. 3-Mercaptopropionic acid showed mutagenic activity in the Ames test strain TA1535, both with and without metabolic activation (21). In the sex-linked recessive lethal mutation test, thioglycolic acid and sodium thioglycolate were not mutagenic (20, 28). Thioglycolic acid (21) and sodium thioglycolate (28) also were not clastogenic when evaluated in the *in vitro* human lymphocytes chromosomal aberrations assay and the *in vivo* micronucleus test in bone marrow of mice, respectively.

7.6. Carcinogenicity

Very few data are available on the carcinogenic potential of thioglycolic acid and derivatives. There was no evidence of carcinogenicity in mice and rabbits that received dermal application of 1.0% sodium thioglycolate (in acetone) twice per week throughout the study. Mice were allowed to die spontaneously, whereas rabbits were killed during the 85th week of treatment (29).

7.7. Ecotoxicity

Thioglycolic acid is harmful to fish. The LC_{50}, 96 h for *Pimephales promelas* was found to be 30 mg/L. A biodegradation of 21% was achieved within 28 d in a closed bottle test based on the consumption of oxygen (21); thus, thioglycolic acid cannot be considered as readily biodegradable. But the acid was found to be inherently biodegradable in a MITI (Japanese) test based on the biological oxygen demand with a biodegradation rate of 70% after 28 days (30). It is not expected to bioaccumulate, owing to its low (log $P = 0.06$) *n*-octanol/water partition coefficient.

In the case of mercaptopropionic acid, biodegradation of 96% was achieved within 28 d in a closed bottle test based on the consumption of oxygen. The pass level of 60% was reached within 10 d of exceeding the 10% level; thus, mercaptopropionic acid can be considered as readily biodegradable. It is not expected to bioaccumulate, owing to the low (log $P = 0.09$) *n*-octanol/water partition coefficient.

2-Ethylhexyl thioglycolate is toxic to fish. The LC_{50}, 48 h to *Leuciscus idus* was found to be 9 mg/L (21). As a biodegradation of 22% was achieved within 28 d in a closed bottle test based on the biological oxygen demand (21), 2-ethylhexyl thioglycolate cannot be considered as readily biodegradable. From its *n*-octanol/water partition coefficient, log $P = 2.43$, low bioaccumulation potential is expected.

8. Uses

8.1. Thioglycolic Acid in Cosmetics

In the 1940s the first patents were issued for the use of mercaptans in cold waving of human hair, and some time later thioglycolic acid-based formulations were put on the market. Thioglycolic acid rapidly became preferred, and as of the mid-1990s the thioglycolates continue to be the most commonly used active ingredient in permanent waving, in hair straightening lotions, and in depilatory creams.

The greater part of hair is made of an insoluble protein material, called keratin, composed of amino acids (qv) that form large condensed polymeric structures by the formation of amide links. The polypeptide chains are cross-linked by the disulfide bond of cystine. The purpose of the reducing step, in which thioglycolic acid is involved, is the cleavage of the disulfide bond of cystine (see eq. 1), so that hair becomes deformable. In a further step, the bonds are restored by a neutralizer, and curls are made permanent. Aqueous and dry neutralizers contain hydrogen peroxide, sodium perborate, and sodium and potassium bromate; as well as citric, tartaric, or phosphoric acids for pH adjustments; wetting agents, eg, fatty alcohols; protective agents; specifiers; and perfumes (31). Because the thioglycolates are not effective at low pH, the balance between buffer and ammonium hydroxide to get the right (from 7–9.5) pH is very important. The maximum thioglycolic acid concentration permitted under European regulations (32) is 8% for home formulations and 11% for professional use.

The majority of available depilatories are based on mercaptans like thioglycolic acid, which is used in the presence of alkaline reacting material. These preparations have less odor and are safer on the skin than other sulfides. Like waving lotions, the depilatory creams use various raw materials, thickening agents, fat compounds, chalk, alkaline salt of thioglycolic acid (2.5–5% as thioglycolic acid), chelating agent, perfume. The maximum concentration permitted under the European regulations is 5% and the pH must be in the range from 7 to 12.7 (32).

Many attempts have been made to reduce the ammoniacal and sulfurous odor of the standard thioglycolate formulations. As the cosmetics market is very sensitive to the presence of impurities, odor, and color, various treatments of purification have been claimed to improve the olfactory properties of thioglycolic acid and its salts, such as distillation (33), stabilization against the formation of H_2S using active ingredients (34), extraction with solvents (35), active carbon (36), and chelate resin treatments (37).

8.2. Polymerization Catalysts, Modifiers, and Chain-Transfer Agents

Properties of polymers obtained by free-radical polymerization depend on their molecular weight and molecular weight distribution, and substances capable of regulating these are called chain transfer agents. Owing to the thiol function, thioglycolic acid and its esters, or mercaptopropionic acids and their esters, can play such a role. Depending on the purpose for which a thioglycolate additive is used in polymerization, it is called a catalyst, a promoter, an accelerator, or a chain transfer agent.

Mercaptocarboxylic acids are also an easy means of introducing a polar function into the polymer for a further grafting, to influence the properties of the final polymer, and sometimes to obtain processing advantages (38). Thioglycolic acid, used as a chain transfer agent in various polymers, is useful for improving the dispersion properties of pigments and basic fillers in paints (39), or for increasing the affinity of polymer latexes with fillers in coatings for paper (40). Thioglycolic acid can also be used as a water-soluble chain transfer agent in aqueous solution polymerization, which mainly concerns acrylic and acrylamide polymerization, as retention agents (flocculants) in paper and water treatments, or as charge dispersants for paper.

Various polymers, such as polythiourethanes, polythioethers, and polythioacrylates, are used to produce resins which are transparent, colorless and have a high refractive index and good mechanical properties, useful for the production of optical lenses. Higher refractive indices are promoted by sulfur compounds and especially by esters of mercaptocarboxylic acids and polyols such as pentaerythritol (41) (see Polymers containing sulfur).

The mercaptans are known to be efficient curing agents for epoxy resins for adhesives applications. Esters of thioglycolic acid or mercaptopropionic acid and polyols (42) are used as epoxy hardeners. They have several advantages such as low temperature curing properties, fast curing rate, lower toxicity than amines, and excellent color. They are also considered to be coupling agents, improving adhesion between metals and resins (43). 1,2,6-Hexanetriol trithioglycolate [19759-80-9] is known to exert a chelating action (44).

The stabilizing of halogen resins against the adverse effects of ionizing radiation has been obtained by using an ester of glycerol and thioglycolic acid (45).

8.3. Tin Stabilizers for Vinyl Chloride Polymers

The most important development of thioglycolic acid, and especially its isooctyl and 2-ethylhexyl esters, concerns its use as raw material for tin stabilizers, to prevent discoloration during thermal processing of PVC, and also to assure good compatibility and diffusion of the stabilizers through the resins (46). Commercial organotin stabilizers are typically tetravalent tin having one or two alkyl groups and two or three mercaptides or other basic ligands. The alkyl groups are usually methyl, butyl, or octyl. The choice of type and number depends largely on the use. Methyl and octyl derivatives are often used in food contact applications, but this varies by local custom and governmental regulations (FDA approval).

The alkyl group also produces subtle changes in the processing of the PVC, the use level and cost of the stabilizer, and in some cases even the final properties of the article, especially the heat distortion temperature or Vicat softening point. Overall, methyl derivatives are most widely used. Butyls are second and octyls a distant third.

Mercaptides are unchallenged as the ligand of choice for the other entities bonded to the tin, but carboxylates can also be used. Whereas a variety of mercaptans are used, the thioglycolic acid derivatives remain the largest single mercaptan. Dibutyltin bis(isooctyl thioglycolate) [25168-24-5] and butyltin tris(isooctyl thioglycolate) [25852-70-4] are two common examples. These materials are produced by the reaction of the appropriate alkyltin chloride or oxide, and the mercaptan.

$$\mathrm{R'_{\mathit{p}}Sn\,(Cl)_{4-\mathit{p}} + (4-\mathit{p})\ HSCH_2COOR \longrightarrow R'_{\mathit{p}}Sn\,(SCH_2COOR)_{4-\mathit{p}} + (4-\mathit{p})\ HCl} \qquad (7)$$

$$\mathrm{R'_2SnO + 2\ HSCH_2COOR \longrightarrow R'_2Sn\,(SCH_2COOR)_2 + H_2O} \qquad (8)$$

Whereas other metal salts, especially lead stearates and sulfates, or mixtures of Groups 2 and 12 carboxylates (Ba–Cd, Ba–Zn, Ca–Zn) are also used to stabilize PVC, the tin mercaptides are some of the most efficient materials. This increased efficiency is largely owing to the mercaptans. The principal mechanism of stabilization of PVC, in which all types of stabilizers participate, is the adsorption of HCl, which is released by the PVC during degradation. This is important because the acid is a catalyst for the degradation, thus, without neutralization the process is autocatalytic.

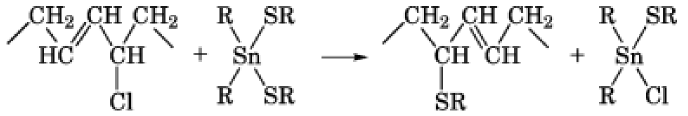
However, because PVC is largely composed of alternating $\mathrm{CH_2}$ and CHCl groups, each elimination of HCl also produces an allylic chlorine (eq. 9). The allylic chlorine is less stable than the alkyl chlorine, ie, the production of allylic chlorine lowers the overall stability.

$$\mathrm{(CH_2{-}CHCl{-}CH_2{-}CHCl{-}CH_2)_{\mathit{n}} \longrightarrow (CH_2{-}CH{=}CH{-}CHCl{-}CH_2)_{\mathit{n}} + HCl} \qquad (9)$$

Degradation then continues at adjacent sites to form conjugated olefins. This does not, however, eliminate the allylic chlorine (eq. 10). Rather the sequence leads to the zipper effect (46), in which long series of conjugated olefins are quickly produced. These series begin to adsorb light in the visible region when there are about 6 alternating double bonds and thus quickly degrade the appearance of the article.

$$\mathrm{(CH_2{-}CH{=}CH{-}CHCl{-}CH_2{-}CHCl)_{\mathit{n}} \longrightarrow (CH_2{-}CH{=}CH{-}CH{=}CH{-}CHCl)_{\mathit{n}} + HCl} \qquad (10)$$

Unlike other stabilizers, tin mercaptide, or the mercaptan that is formed after the HCl reacts with the mercaptide, can react with the allylic chlorine to produce a sulfide (47), thus eliminating the labile chlorine groups and stopping the unzipping.



(11)

The mercaptan or mercaptide can also add directly to the olefin to break up or shorten the conjugation.

Additionally, organotin mercaptides can act as antioxidants, as they can sequester free-radical degradation mechanisms (48). The one drawback of mercaptide-based tin stabilizers is the discoloration of the sulfur after exposure to uv-radiation. Special precautions or formulations need to be developed for outdoor applications.

The type of stabilizer used is greatly influenced by the specifics of the final products and the customs in the region of use. Lead- and tin-based stabilizers are mostly used in rigid opaque applications such as building materials (see Building materials, plastic). Lead-based stabilizers predominate in Europe because the PVC formulations are low in uv-blockers (titanium dioxide). However, the higher uv-blocker needed in the US allows the use of tin mercaptides, eliminating the hazards associated with the handling of the lead-based products and affording a larger processing latitude than that available with the lead-based materials.

Because of the stringent U.S. requirements on handling lead-based powders, these stabilizers are only found in flexible electrical wire insulation in the United States because no other stabilizers have been developed which have the low conductivity afforded by these materials.

However, most recently, mixed metal stabilizers are being introduced into this area. Whereas some mixed metal stabilizers are used in rigid applications, it is difficult for these newer materials to compete with lead and tin based stabilizers on a cost/efficiency basis. These materials find their largest applications in flexible compounds, especially those requiring good stability to uv exposure.

8.4. Miscellaneous

In the leather industry, dehairing is a specific step in the treatment of animal skins, where the reducing properties of thioglycolic salts for the disulfide links of keratins are exploited along side those of other reducing agents such as sodium sulfide and sodium hydrosulfide. Thioglycolic acid formulations have the advantage over simple sodium sulfide formulations regarding process safety issues, better quality of the final leather, reduction of waste, and recovery of hair (49).

Wool treatment by thioglycolic acid improves elongation, elasticity, and strength properties of fibers; prevents shrinkage; and makes dyeing easier. These improvements result from the interchange reactions between disulfides and the HS group of thioglycolic acid, observed on the fiber (50).

In wood industries, addition of thioglycolic acid to pulping liquor during alkaline cooking of pinewood led to an increase in the degree of delignification of wood. Thioglycolic acid has facilitated the cleavage of lignins, gives higher pulp yields, and leads to lower alkali consumption (51).

Thioglycolic acid is recommended as a cocatalyst with strong mineral acid in the manufacture of bisphenol A by the condensation of phenol and acetone. The effect of the mercapto group (mercaptocarboxylic acid) is attributed to the formation of a more stable carbanion intermediate of the ketone that can alkylate the phenol ring faster. The total amount of the by-products is considerably reduced (52).

Thioglycolic acid is described in descaling compositions for iron oxide removal. It can also be used as ammonium or ethanolamine salts to remove rust without attacking the metal substrate (53) (see Metal surface treatments). Thioglycolic acid can modify the fluidity of concretes and cements in a new class of superplasticizers, where the polymeric melamine structures are grafted with a sulfur atom instead of nitrogen in the case of the well-known sulfanilic acid [121-57-3], 4-$(H_2N)C_6H_4SO_3H$, (54). This newer way of linking using an S atom modifies the structure of the resin and is responsible to a great extent for high fluidity values, a water-reducing content in concrete, and an improvement in mechanical properties (see Cement).

In the oil field industry, in drilling activities the sequestering properties of thioglycoic acid for iron are reflected in its use as an iron-controlling agent, for acidizing in well stimulation, and also as corrosion inhibitors in high density completion fluids (55). The oxazoline derivative of thioglycolic acid has been claimed, in water-based drilling muds, as a lubricant additive (56). In the catalytic cracking of hydrocarbons, in petroleum refining activities, mercaptides of thioglycolic acid are effectively added as a heavy metal passivator to counteract the adverse effects of metal (Ni, V, Fe) contaminants on catalysts. This is the case for antimony tris(2-ethylhexyl thioglycolate) [26888-44-4] or the isooctyl analogue [27288-44-4]. Other antimony, stannous, or phosphorous derivatives in various combinations have also been used (57).

In the lightening of petroleum hydrocarbon oil, esters of mercaptocarboxylic acids can modify radical behavior during the distillation step (58). Thioesters of dialkanol and trialkanolamine have been found to be effective multifunctional antiwear additives for lubricants and fuels (59). Alkanolamine salts of dithiodipropionic acid [1119-62-6] are available as water-soluble extreme pressure additives in lubricants (60).

Sulfur compounds are traditionally used as rubber and plastic additives. Esters of thioglycolic acid and various glycols, eg, ethylene glycol, propylene glycol, pentaerythritol, and particularly the butyl ester of methylene bisthioglycolic acid, $(C_4H_9OOCCH_2S)_2CH_2$, are used as a polar plasticizer and softener for synthetic rubber, especially for nitrile rubber and chloroprene. Dodecylthioacetic acid, $C_{12}H_{24}SCH_2COOH$ is a viscosity modifier (61). Esters of thiodipropionic acid [111-17-1], $(HOOCCH_2CH_2)_2S$, and long-chain alcohols, in the C_{12}–C_{18} range, are largely used as thioester antioxidant additives in polyolefins and styrene–butadiene latex resins.

The pentaerythritol ester of dodecylthiopropionic acid [1462-52-8], $C_{12}H_{25}SCH_2CH_2COOH$, is marketed for the same purpose.

Thioglycolic acid and esters are used in the manufacture of sulfur dyes (qv), thioindigo pigments, and as additives for dyeing baths (62). Examples are 2,5-dichlorophenylthioglycolic acid [6274-27-7] (63) for thioindigo pigment and 2-naphtylthioglycolic acid as dyestuff intermediate (64).

8.5. Pharmaceuticals and Agrochemicals

Thioglycolic acid and its esters are useful as a raw material to obtain biologically active molecules. In cephalosporine syntheses, (4-pyridyl)thioacetic acid [10351-19-8] (65) and trifluoromethane (ethyl) thioglycolate [75-92-9] (66) are used as intermediates. Methyl-3-amino-2-thiophene carboxylate can be used as intermediate for herbicidal sulfonylureas (67) and various thiophenic structures (68).

Various other cyclic compounds can be built using thioglycoic acid, eg, thiazolidinone, thiazole, isothiazole, and thiazine-type structures, leading to intermediates for the agricultural and pharmaceutical industries (69). Fungicidal organotin mercaptocarboxylates have also been claimed (70).

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Related Articles

Cosmetics; Heat stabilizers; Leather; Vinyl chloride polymers