Kirk-Othmer Encyclopedia of Chemical Technology.

FLUORINATED ACETIC ACIDS

Fluoroacetic acid [144-49-0], FCH_2COOH, is noted for its high toxicity to animals, including humans. It is sold in the form of its sodium salt as a rodenticide and general mammalian pest control agent. The acid has mp, 33°C; bp, 165°C; heat of combustion, −715.8 kJ/mol(− 171.08 kcal/mol) (1); enthalpy of vaporization, 83.89 kJ/mol (20.05 kcal/mol) (2). Some thermodynamic and transport properties of its aqueous solutions have been published (3), as has the molecular structure of the acid as determined by microwave spectroscopy (4). Although first prepared in 1896 (5), its unusual toxicity was not published until 50 years later (6). The acid is the toxic constituent of a South African plant *Dichapetalum cymosum*, better known as gifblaar (7). At least 24 other poisonous plant species are known to contain it (8).

Chemically, fluoroacetic acid behaves like a typical carboxylic acid, although its acidity is higher ($K_a = 2.2 \times 10^{-3}$) than the average (9). It can be prepared from the commercially available sodium salt by distillation from sulfuric acid (10).

0.1. Sodium Fluoroacetate

Sodium fluoroacetate [62-74-8], FCH_2COONa, known as Compound 1080, is a hygroscopic white solid, mp, 200–202°C, which decomposes when heated above the melting point. Its solubility at 25°C in g/100 g solvent is water, 111; methanol, 5; ethanol, 1.4; acetone, 0.04; and carbon tetrachloride, 0.004. Because its carbon–fluorine bond is unreactive under most conditions, this salt can be converted by standard procedures to typical carboxylic acid derivatives such as fluoroacetyl esters (11, 12), fluoroacetyl chloride [359-06-8] (13), fluoroacetamide (14), or fluoroacetonitrile [503-20-8] (14).

Sodium fluoroacetate is usually made by displacing the halogen from an ester of bromo- or chloroacetic acid with potassium fluoride or, in one instance, antimony fluoride, followed by hydrolysis with aqueous sodium hydroxide (15–17). A commercial process for its manufacture from ethyl chloroacetate and potassium fluoride has been described (18). The ester, purified by distillation to remove traces of acid and water, is treated with oven-dried, finely powdered potassium fluoride in a well-stirred autoclave at 200°C for 11 hours. The resulting ethyl fluoroacetate [459-72-3] is then distilled into an agitated tank containing sodium hydroxide dissolved in methanol. The solid product is isolated by centrifugation, followed by vacuum drying. Through this process, all liquids are handled in a closed system of pipes and vessels, carefully inspected for leaks before each run. This is important since the intermediate fluoroacetate is highly toxic, and the starting chloroacetate is a lacrimator.

0.2. Toxicity

Sodium fluoroacetate is one of the most effective all-purpose rodenticides known (18). It is highly toxic to all species of rats tested and can be used either in water solution or in bait preparations. Its absence of objectionable taste and odor and its delayed effects lead to its excellent acceptance by rodents. It is nonvolatile, chemically stable, and not toxic or irritating to the unbroken skin of workers. Rats do not appear to develop any significant tolerance to this compound from nonlethal doses. However, it is extremely dangerous to humans, to common

household pets, and to farm animals, and should only be used by experienced personnel. The rodent carcasses should be collected and destroyed since they remain poisonous for a long period of time to any animal that eats them.

The unusually high toxicity of fluoroacetic acid and of other monofluorinated organic compounds that can be metabolized to fluoroacetate has stimulated much research into the mechanism of this toxicity (8, 19–23). Fluoroacetate mimics acetate by being incorporated into the tricarboxylic acid cycle of cellular respiration where it becomes converted into fluorocitric acid. This acid inhibits the enzyme, aconitate hydratase, which normally catalyzes the dehydration of citric acid. As a result, citric acid accumulates in the organism and the energy-producing cycle is interrupted. Because of the time it takes for the fluorocitrate to form and accumulate, there is usually a latent time of at least an hour before the appearance of symptoms of fluoroacetate poisoning, eg, ventricular fibrillation or convulsions. This is advantageous in its use as a pesticide. One characteristic of fluoroacetate toxicity is the wide range in lethal doses for different species ranging from (LD_{50}, mg/kg) 0.06 in dogs, 0.2 in cats, 0.4 in sheep or rabbits, 2–10 in humans, 5 in rats, 7 in mice, to about 400 in toads (20, 24). The only suggested antidotes for the poisoning are 1,2,3-propanetriol monoacetate (20, 23), acetamide (20), and other acetate donors, but these only have an effect if administered before significant amounts of fluoroacetate have been converted to fluorocitrate. To determine if fluoroacetate poisoning has occurred, it is often desirable to detect the presence of small amounts of the poison in animal tissue. Although difficult, this can be done by spectrochemical methods (25), processes involving ion-selective fluoride electrodes (21, 26), or gas chromatography often combined with mass spectrometry (27). A microbial detection of fluoroacetate utilizing DNA technology and bioluminescence has been reported (28).

0.3. Fluoroacetamide

Fluoroacetamide [640-19-7], FCH_2CONH_2, is a white water-soluble solid having mp 108°C (14). It has been used as a rodenticide and has been reported to have a better acceptability to rats than sodium fluoroacetate (29). However, like the latter compound, its misuse has caused deaths to farm animals and pets (20).

Tull Chemical Co. (Oxford, Alabama) is the only producer of sodium fluoroacetate. It is sometimes colored with the black dye nigrosine. It is usually packed in 8 oz (227 g) or 5 kg cans and is almost exclusively exported. There is very limited use in the United States.

1. Difluoroacetic Acid

Difluoroacetic acid [381-73-7], $F_2CHCOOH$, is a colorless liquid with a sharp odor; mp, 35°C; bp, 134°C; $d^{10}{}_4$, 1.539 g/mL; $n^{20}{}_D$, 1.3428 (30, 31); flash point, 78°C (95% aqueous solution); enthalpy of vaporization, 67.82 kJ/mol (16.21 kcal/mol); and enthalpy of solution in water of the undissociated acid, −7.03 kJ/mol(− 1.68 kcal/mol) (2). It is a moderately strong acid; determinations of its acid dissociation constant are 4.6×10^{-2} (32) and 3.5×10^{-2} (33). Its molecular structure in the gas phase has been determined by electron diffraction studies (34). Details of the acid's ir (35) and nmr (36) spectra also have been reported.

Difluoroacetic acid undergoes reactions typical of a carboxylic acid such as forming an ester when heated with an alcohol and sulfuric acid. Typical esters are methyl difluoroacetate [433-53-4], bp, 85.2°C, and ethyl difluoroacetate [454-31-9], bp, 99.2°C. It can also be photochemically chlorinated to chlorodifluoroacetic acid [76-04-0] or brominated in the presence of iron to bromodifluoroacetic acid [667-27-6] (37, 38).

The acid can be synthesized in several different ways. The reaction of tetrafluoroethylene with ammonia to give 2,4,6-tris(difluoromethyl)-*s*-triazine, followed by its alkaline hydrolysis, has been reported to give the acid in 80% overall yield (31). The addition of diethylamine to tetrafluoroethylene gives, after partial hydrolysis, a 49% yield of amide *N,N*-diethyldifluoroacetamide [56425-08-2], $F_2CHCON(C_2H_5)_2$, which can be hydrolyzed in excellent yield to the acid (39). The same amide can be prepared in 60% yield by the addition of diethylamine to

Table 1. Physical Properties of Trifluoroacetic Acid

Property	Value	References
freezing point, °C	−15.36	42
boiling point, °C	71.8	43
water azeotrope (20.6% H_2O) bp, °C	105.5	44
density at 25°C, g/mL	1.4844	45
heat of vaporization, kJ/mol[a]	33.26	43
viscosity at 25°C, mPas(= cP)	0.813	46
dielectric constant at 25°, ϵ	42.1	47
conductivity at 25°C, 1/Ωcm	2600	46
surface tension at 25°C mN/m(=dyn/cm)	13.44	48
heat of formation, liquid, kJ/mol[a]	-1060 ± 2	49

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

chlorotrifluoroethylene followed by hydrolysis and fluorination with KF in diethylene glycol. Another method that gives the acid in 86% yield is the permanganate oxidation of $CHF_2CH{=}CCl_2$ (40).

Difluoroacetic acid is much less toxic than fluoroacetic acid (LD_{50} = 180 mg/kg mouse iv) (41). It is available in research quantities for about $5/g (1992).

2. Trifluoroacetic Acid

2.1. Physical Properties

Trifluoroacetic acid [76-05-1], CF_3COOH, is a colorless liquid with a sharp odor resembling that of acetic acid. Its physical properties are shown in Table 1. It is a strong carboxylic acid with an acid dissociation constant at 25°C of 0.588 (9) or 0.32 (32). It is miscible with water, fluorocarbons, and most common organic solvents including methanol, benzene, carbon tetrachloride, acetone, ether, and hexane. Compounds with limited solubility in the acid include alkanes with more than six carbon atoms and carbon disulfide. It is a good solvent for proteins (50) and polyesters. The viscosities, densities, and conductivities of solutions of the acid in acetic acid, water, and several other liquids have been studied (46).

2.2. Chemical Properties

Trifluoroacetic acid undergoes reactions typical of a carboxylic acid. The trifluoromethyl group is inert to most common reducing agents, including lithium aluminum hydride, which give trifluoroacetaldehyde [75-90-1] and 2,2,2-trifluoroethanol [75-89-8] (51, 52). Common oxidizing agents do not attack the acid at room temperature except for potassium permanganate, which slowly oxidizes the anhydrous acid to carbon dioxide and other products (53). The acid is also slowly attacked by boiling 25% aqueous sodium hydroxide to yield oxalate and fluoride ions (44). Although the acid is stable to temperatures above 250°C, its sodium salt decomposes above 205°C to give sodium fluoride, trifluoroacetyl fluoride [354-34-7], carbon monoxide, carbon dioxide, and other products (44). In ethylene glycol solution at 180°C the sodium salt can be made to decompose quantitatively to trifluoromethane [75-46-7] and carbon dioxide if a boric acid buffer is present (54). Except for a few instances like these, the reactions of trifluoroacetic acid closely parallel those of other carboxylic acids, but there are important differences: eg, its amides and esters are more easily hydrolyzed than is typical for carboxylic acids. This has led to the use of the acid and its anhydride [407-25-0] (55) in making derivatives of carbohydrates (56), amino acids (57), and peptides (57) from which the trifluoroacetyl protective group can be removed with relative ease. Peroxytrifluoroacetic acid [359-48-8], formed from the reaction of trifluoroacetic anhydride and hydrogen

peroxide, is a stronger oxidizing agent than other peroxycarboxylic acids and gives better yields of epoxides from alkenes (58), esters from ketones (59), and nitrobenzenes from anilines (60). Trifluoroacetic acid and its anhydride are also useful as catalysts for reactions involving other carboxylic acids such as esterifications of alcohols or acylations of aromatic or other unsaturated compounds (45). The acid has been reported to be superior to sulfuric acid as a catalyst for the Beckmann rearrangement of oximes to amides (61). Owing to its low nucleophilicity, the acid has been used as a solvent for basic research into solvolysis mechanisms (62).

2.3. Preparation

Because of its stability to further oxidation, trifluoroacetic acid can be prepared by the oxidation of compounds containing a trifluoromethyl group bonded to carbon. Although first prepared in 1922 by the oxidation of trifluoromethylcyclohexane or 3-aminobenzotrifluoride, later better results were obtained from the alkaline permanganate oxidation of olefins such as 1,1,2-trichloro-3,3,3-trifluoropropene (40), or more economically, 2,3-dichlorohexafluoro-2-butene which gives an 87% yield of the acid (63). The acid has been prepared by photochemical oxidation of ethanes such as 2-chloro-1,1,1-trifluoroethane or 2,2-dichloro-1,1,1-trifluoroethane with oxygen to give high yields of trifluoroacetyl-chloride[354-32-5] which easily hydrolyzes to the acid (64, 65). Another process involves the trimerization of trichloroacetonitrile to a triazine which can be fluorinated with a mixture of SbF_3 and $SbCl_5$ and then hydrolyzed to the acid (66). The reaction of trichloroacetyl chloride with hydrogen fluoride at 320°C over a chromium and nickel oxide catalyst has been reported to give trifluoroacetic acid in 92% yield (67).

Trifluoroacetic acid was produced commercially by 3M Co. by the electrolysis of mixtures containing acetyl fluoride, hydrogen fluoride, and sodium fluoride to give trifluoroacetyl fluoride, which upon hydrolysis gave the acid (68). Although a 71% yield is claimed, isolation of the low boiling acid fluoride product from by-product hydrogen is costly. Improvements in this process have been patented (69, 70) as well as processes involving the electrochemical fluorination of 2-chloroethanol (71) or chloroacetyl fluoride (72).

2.4. Health and Safety Factors

Unlike fluoroacetic acid, trifluoroacetic acid presents no unusual toxicity problems. However, owing to its strong acidity, its vapors can be irritating to tissue, and the liquid acid can cause deep burns if allowed to contact the skin. The acid can be safely stored in containers made of glass or common corrosion-resistant alloys and metals such as stainless steel or aluminum.

2.5. Economic Aspects

Halocarbon Products Corp. is the largest producer of trifluoroacetic acid. The commercial grade is of very high purity with the main impurity being ca 0.2% water. A grade, which has a low residue specification, intended for use in protein synthesis (Biograde) is available. Other producers include Rhône-Poulenc and Solvay. The 1992 price was ca $15/kg.

BIBLIOGRAPHY

"Monofluoroacetic Acid" under "Fluorine Compounds, Organic," in *ECT* 1st ed., Vol. 6, pp. 764–766, by E. E. Hardy and J. H. Saunders, Monsanto Chemical Co.; "Difluoroacetic Acid" under "Fluorine Compounds, Organic," in *ECT* 1st ed., Vol. 6, pp. 766–767, by M. G. Gergel and M. Revelise, Columbia Organic Chemicals Co.; "Trifluoroacetic Acid" under "Fluorine Compounds, Organic," in *ECT* 1st ed., Vol. 6, pp. 767–768, by M. G. Gergel and M. Revelise, Columbia Organic Chemicals Co.; "Monofluoroacetic Acid" under "Fluorine Compounds, Organic," in *ECT* 2nd ed., Vol. 9, pp. 767–770, by E. Hardy, Monsanto Research Corp., J. H. Saunders, Mobay Chemical Co., and J. B. Hynes, Hynes Chemical Research Corp.;

"Difluoroacetic Acid" under "Fluorine Compounds, Organic," in *ECT* 2nd ed., Vol. 9, pp. 770–771, by J. B. Hynes, Hynes Chemical Research Corp.; "Trifluoroacetic Acid" under "Fluorine Compounds, Organic," in *ECT* 2nd ed., Vol. 9, pp. 771–772, by C. Woolf, Allied Chemical Corp.; "Fluorinated Acetic Acids" under "Fluorine Compounds, Organic," in *ECT* 3rd ed., Vol. 10, pp. 891–896, by G. Astrologes, Halocarbon Products Corp.

Cited Publications

1. F. Swarts, *Bull. Acad. R. Belg.* **35**, 849 (1898).
2. P. Haberfield and A. K. Rakshit, *J. Am. Chem. Soc.* **98**, 4393 (1976).
3. M. V. Kaulgud and G. H. Pandya, *Indian J. Chem. Sect. A.* **14A**(2), 91 (1976).
4. B. P. Van Eijck, P. Brandts, and J. P. M. Maas, *J. Mol. Struct.* **44**, 1 (1978)
5. F. Swarts, *Bull. Acad. R. Belg.* **31**, 675 (1896).
6. F. L. M. Pattison, *Toxic Aliphatic Fluorine Compounds*, Elsevier Publishing Co., New York, 1959, p. 16.
7. M. J. J. Meyer and N. Grobbelaar, *J. Plant Physiol.* **138**, 122 (1991).
8. G. W. Miller, M. H. Yu, and M. Psenak, *Fluoride* **6**(3), 203 (1973).
9. A. L. Henne and C. J. Fox, *J. Am. Chem. Soc.* **73**, 2323 (1953).
10. F. L. M. Pattison, J. B. Stothers, and R. G. Woolford, *J. Am. Chem. Soc.* **78**, 2255 (1956).
11. F. L. M. Pattison, S. B. D. Hunt, and J. B. Stothers, *J. Org. Chem.* **21**, 883 (1956)
12. C. C. Price and W. G. Jackson, *J. Am. Chem. Soc.* **69**, 1065 (1947).
13. F. L. M. Pattison and co-workers, *Can. J. Technol.* **34**, 21 (1956).
14. F. J. Buckle, R. Heap, and B. C. Saunders, *J. Chem. Soc.*, 912 (1949).
15. B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 1773 (1948).
16. E. D. Bergmann and I. Blank, *J. Chem. Soc.*, 3786 (1953).
17. Ref. 6, 21–22.
18. Ref. 6, p. 167.
19. D. D. Clarke, *Neurochem. Res.* **16**, 1055 (1991).
20. R. A. Peters, *Fluoride* **6**(3), 189 (1973).
21. M. N. Egyed, *Fluoride* **6**(3), 215 (1973).
22. P. Buffa, V. Guarriero-Bobyleva, and R. Costa-Tiozzo, *Fluoride* **6**, 224 (1973).
23. Ref. 6, 27–56, 208–210.
24. Ref. 6, 3–4.
25. I. Schoenfeld and M. Lidji, *J. Forsensic Sci.* **13**, 267 (1968).
26. J. A. Peters and K. J. Baxter, *Bull. Environ. Contam. Toxicol.* **11**(2), 177 (1974).
27. H. M. Stahr, W. B. Buck, and P. F. Ross, *J. Assn. Off. Anal. Chem.* **57**, 405 (1974).
28. S. Lee and co-workers, *Anal. Chim. Acta.* **244**, 201 (1991).
29. T. Kusano, *J. Fac. Agric. Tottori Univ.* **10**, 15 (1975).
30. F. Swarts, *Bull. Soc. Chim. Fr.*, 597 (1903).
31. A. L. Henne and R. L. Pelley, *J. Am. Chem. Soc.* **74**, 1426 (1952).
32. J. L. Kurz and J. M. Farrar, *J. Am. Chem. Soc.* **91**, 6057 (1969).
33. M. M. Kreevoy and co-workers, *J. Am. Chem. Soc.* **89**, 1201 (1967).
34. J. M. Bijen and J. L. Derissen, *J. Mol. Struct.* **27**, 233 (1975).
35. J. R. Barcelo and C. Otero, *Spectrochim. Acta* **18**, 1231 (1962).
36. V. Barboiu, *Rev. Roum. Chim.* **19**, 363 (1974).
37. F. Swarts, *Chem. Zentr.* **II**, 709 (1903).
38. F. Swarts, *Chem. Zentr.* **I**, 1237 (1906).
39. N. N. Yarovenko and co-workers, *Obschei Khim.* **27**, 2246 (1957).
40. A. L. Henne, T. Alderson, and M. S. Newman, *J. Am. Chem. Soc.* **67**, 918 (1945).
41. Ref. 6, 62–63.
42. H. H. Cady and G. E. Cady, *J. Am. Chem. Soc.* **76**, 915 (1954).
43. M. D. Taylor and M. B. Templeman, *J. Am. Chem. Soc.* **78**, 2950 (1956).
44. F. Swarts, *Bull. Acad. R. Belg. Classe Sci.* **8**, 343 (1922).
45. *Trifluoracetic Acid Brochure*, Halocarbon Products Corp., Hackensack, N.J., 1967.

46. Y. Y. Fialkov and V. S. Zhikarev, *Zh. Obshch. Khim.* **33**, 3466, 3471, 3790 (1963).
47. J. H. Simons and K. E. Lorentzen, *J. Am. Chem. Soc.* **72**, 1426 (1950).
48. J. J. Jasper and H. L. Wedlick, *J. Chem. Eng. Data* **9**, 446 (1964).
49. V. P. Kolesov, G. M. Slavutskaya, and T. S. Papino, *Zh. Fiz. Khim.* **46**, 815 (1972).
50. J. J. Katz, *Nature* **174**, 509 (1954).
51. M. Braid, H. Iserson, and F. E. Lawlor, *J. Am. Chem. Soc.* **76**, 4027 (1954).
52. O. R. Pierce and T. G. Kane, *J. Am. Chem. Soc.* **76**, 300 (1954).
53. G. S. Fujioka and G. H. Cady, *J. Am. Chem. Soc.* **79**, 2451 (1957).
54. I. Auerbach, F. H. Verhoek, and A. L. Henne, *J. Am. Chem. Soc.* **72**, 299 (1950).
55. J. M. Tedder, *Chem. Rev.* **55**, 787 (1955).
56. E. J. Bourne and co-workers, *J. Chem. Soc.*, 2976 (1949).
57. F. Weygand, *Bull. Soc. Chim. Biol.* **43**, 1269 (1961).
58. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.* **77**, 89 (1955).
59. W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.* **77**, 2287 (1955).
60. W. D. Emmons, *J. Am. Chem. Soc.* **76**, 3470 (1954).
61. U.S. Pat. 2,721,199 (Oct. 18, 1955), M. L. Huber (to E. I. du Pont de Nemours & Co., Inc.).
62. P. E. Peterson and co-workers, *J. Am. Chem. Soc.* **87**, 5169 (1965).
63. A. L. Henne and P. Trott, *J. Am. Chem. Soc.* **69**, 1820 (1947).
64. R. N. Haszeldine and F. Nyman, *J. Am. Chem. Soc.*, 387 (1959).
65. U.S. Pat. 3,883,407 (May 13, 1975), A. L. Dittman (to Halocarbon Products Corp.).
66. T. R. Norton, *J. Am. Chem. Soc.* **72**, 3527 (1950).
67. Ger. Offen. 2,221,849 (Nov. 16, 1972), Ramanadin (to Rhone-Progil).
68. U.S. Pat. 2,717,871 (Sept. 13, 1965), H. M. Scholberg and H. G. Bryce (to Minnesota Mining and Manufacturing Co.).
69. U.S. Pat. 4,022,824 (May 10, 1977), W. V. Childs (to Phillips Petroleum Co.).
70. Jpn. Kokai 75 30,827 (Mar. 27, 1975), T. Suzuki and S. Yahara (to Mitsubishi Gas Chemical Co., Inc.).
71. USSR Pat. 329,165 (Feb. 9, 1972), N. M. Arakelyan and S. E. Isabekyan.
72. Czech. Pat. 119,682 (Sept. 15, 1966), D. Frantisek.

ARTHUR J. ELLIOTT
Halocarbon Products Corporation

Related Articles

Fluorine compounds, organic, introduction; Acetic acid; Pesticides