Kirk-Othmer Encyclopedia of Chemical Technology.

FLUORETHANOLS

Ethanol may be readily fluorinated at C-2. Replacement of H by F at C-1 would lead to unstable compounds which readily form carbonyls by loss of HF.

1. Monofluoro Derivative

2-Fluoroethanol [371-62-0] (ethylene fluorohydrin, β-fluoroethyl alcohol), FCH_2CH_2OH, is a colorless liquid with an alcohol-like odor; mp, $-26.45°C$; bp, 103.55°C; d_4, 1.1297; n_D^{18}, 1.13647; heat of combustion, -1214.0 kJ/mol(-290.16 kcal/mol) (1, 2). It is miscible with water, stable to distillation, and low in flammability. It is the least acidic of the fluoroethanols, although more acidic than ordinary alcohols with a pK_a value of 14.42 ± 0.04 in aqueous solution (3). Its most notable difference from the other fluoroethanols is its extreme toxicity (4–12). In mice an LD_{50} of 10 mg/kg has been measured (10–12). The toxicity is due to its facile oxidation in animals to derivatives of fluoroacetic acid [144-49-0], a known inhibitor of the tricarboxylic acid cycle of respiration. No effective antidote to this poisoning is known, although ethanol appears to diminish the lethal effects of 2-fluoroethanol in rats and monkeys (9).

In its chemical reactions, 2-fluoroethanol behaves like a typical alcohol. Oxidation (12) yields fluoroacetaldehyde [1544-46-3] or fluoroacetic acid; reaction with phosphorus tribromide (12) gives 1-bromo-2-fluoroethane [762-49-2]; addition to olefins results in ethers (13); and additions to isocyanates give carbamates (14). The alcohol can be prepared in 50% yield by the reaction of potassium fluoride with 2-chloroethanol at 175°C in high boiling glycol solvents (15). Alternatively, the addition of hydrogen fluoride to ethylene oxide (16) or the fluorination of 2-bromoethyl or 2-chloroethyl acetate with silver, potassium, or mercuric fluoride followed by hydrolysis gives the alcohol (1, 2). 2-Fluoroethanol is not currently produced in commercial quantities, although (in 1992) it was available in research quantities for ca $3/g.

Because of its high toxicity, special procedures should be followed by users of 2-fluoroethanol. Suggested precautions include working with it in sealed reactors at subatmospheric pressure and careful monitoring to ensure that contamination of the surroundings is minimized (17). Another potential hazard is the formation of the alcohol as a minor by-product in reactions such as those involving boron trifluoride and ethylene oxide (18). Despite these problems, several potential uses for the alcohol and its derivatives have been reported. The alcohol has been used to control rodent populations (19) and, when labeled with ^{18}F, as a radiodiagnostic agent (20). Various derivatives have shown promise as herbicides or as agents to control mites and other plant pests (14, 21–24).

2. Difluoro Derivative

2,2-Difluoroethanol [359-13-7], F_2CHCH_2OH, is a colorless liquid with an alcohol-like odor; mp, 28.2°C, bp, 96°C; d_1^{17}, 1.3084; n_D^{17}, 1.3320; heat of combustion, -1026 kJ/mol(-245.3 kcal/mol). It is stable to distillation and miscible with water and many organic solvents. As expected, its acidity lies between that of 2-fluoroethanol and 2,2,2-trifluoroethanol both in the gas phase (25) and in 50% aqueous ethanol solution (26), where its K_a of 1.0×10^{-12} is about 4.8 times smaller than that of trifluoroethanol.

2,2-Difluoroethanol is prepared by the mercuric oxide catalyzed hydrolysis of 2-bromo-1,1-difluoroethane with carboxylic acid esters and alkali metal hydroxides in water (27). Its chemical reactions are similar to those of most alcohols. It can be oxidized to difluoroacetic acid [381-73-7] (28); it forms alkoxides with alkali and alkaline-earth metals (29); with alkoxides of other alcohols it forms mixed ethers such as 2,2-difluoroethyl methyl ether [461-57-4], bp 47°C, or 2,2-difluoroethyl ethyl ether [82907-09-3], bp 66°C (29). 2,2-Difluoroethyl difluoromethyl ether [32778-16-8], made from the alcohol and chlorodifluoromethane in aqueous base, has been investigated as an inhalation anesthetic (30, 31) as have several ethers made by addition of the alcohol to various fluoroalkenes (32, 33). Methacrylate esters of the alcohol are useful as a sheathing material for polymers in optical applications (34). The alcohol has also been reported to be useful as a working fluid in heat pumps (35). The alcohol is available in research quantities for ca $6/g (1992).

3. Trifluoroethanol

2,2,2-Trifluoroethanol [75-89-8], CF_3CH_2OH, is a colorless liquid with an ethanol-like odor; mp, $-45°C$; bp, 73.6°C; d_4^{25}, 1.3823; n_D^{20}, 1.2907; flash point (open cup), 41°C; flash point (closed cup), 33°C; no fire point (36); heat of combustion, -886.6 kJ/mol(-211.9 kcal/mol) (36); and dielectric constant (25°C), 26.14 (37). Many other physical and thermodynamic properties of the alcohol and its solutions have been published (36, 38–41). It is the most acidic fluoroethanol with an ionization constant of 4.3×10^{-13} (42). It is stable to distillation and miscible with water and many organic solvents. It has the unusual property of dissolving most polyamides, both nylons (43) and polypeptides (44), at room temperature. Because of its excellent combination of physical and thermodynamic properties, 2,2,2-trifluoroethanol–water mixtures (also known as fluorinols) have application as working fluids in Rankine-cycle engines for recovering energy from waste heat sources (36, 45, 46). Its high ionizing power and low specific conductance make the alcohol useful as a solvent for ionic reactions and conductometric titrations (47), and basic research into solvolysis mechanisms (48–50).

Chemically, 2,2,2-trifluoroethanol behaves as a typical alcohol. It can be converted to trifluoroacetaldehyde [75-90-1] or trifluoroacetic acid [76-05-1] by various oxidizing agents such as aqueous chlorine solutions (51) or oxygen in the presence of a vanadium pentoxide catalyst (52). Under basic conditions, it adds to tetrafluoroethylene and acetylene to give, respectively, 1,1,2,2-tetrafluoroethyl 2′,2′,2′-trifluoroethyl ether [406-78-0] (53) and 2,2,2-trifluoroethyl vinyl ether [406-90-6] which was used as the inhalation anesthetic Fluroxene. Its alkoxides react with bromoethane to give trifluoroethyl ethyl ether [461-24-5], bp 50.3°C. Similarly prepared is bis(trifluoroethyl) ether used as the convulsant drug Flurothyl as a substitute for electric shock therapy. As the trichlorosulfonate ester, trifluoroethanol is used to introduce the trifluoroethyl group into the anxiolytic drug Halazepam [23092-17-3] (54). 2,2,2-Trifluoroethanol is also the starting material for the anesthetic Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether [26675-46-7]) (55, 56) and Desflurane (2-difluoromethoxy-1,1,1,2-tetrafluoroethane [57041-67-5]) (57).

Trifluoroethanol was first prepared by the catalytic reduction of trifluoroacetic anhydride [407-25-0] (58). Other methods include the catalytic hydrogenation of trifluoroacetamide [354-38-1] (59), the lithium aluminum hydride reduction of trifluoroacetyl chloride [354-32-5] (60) or of trifluoroacetic acid or its esters (61, 62), and the acetolysis of 2-chloro-1,1,1-trifluoroethane [75-88-7] followed by hydrolysis (60). More recently, the hydrogenation of 2,2,2-trifluoroethyl trifluoroacetate [407-38-5]over a copper(II) oxide catalyst has been reported to give the alcohol in 95% yield (63).

The largest producer of trifluoroethanol is Halocarbon Products Corp. Other producers include Japan Halon and Rhône-Poulenc. Commercial quantities sell for approximately $20/kg (1992).

Toxicity studies on trifluoroethanol show acute oral LD_{50}, 240 mg/kg; acute dermal LD_{50}, 1680 mg/kg; and acute inhalation $L(ct)_{50}$, 4600 ppmh . Long-term subchronic inhalation exposure to 50–150 ppm of the alcohol has caused testicular depression in male rats, but no effects were noted at the 10 ppm level (32). Although the significance of the latter observations for human safety is unknown, it is recommended that continuous exposure to greater than 5 ppm or skin contact with it be avoided.

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