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Hydrolytic instability of C–F bonds in 2,2,2-trifluoroethyl-phosphinic acid systems: formation of carboxymethylphosphinic acid derivatives

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The trifluoromethyl group in 2,2,2-trifluoroethylphosphonic acid remains stable against hydrolysis. However, in contrast, 2,2,2-trifluoroethylphosphinic acid and its derivatives display unexpectedly low hydrolytic stability of the C–F bond in alkaline solutions. When treated with bases such as alkali metal hydroxides or tetramethylammonium hydroxide, these compounds undergo hydrolysis of the R–CF$_3$ group, producing R–COO$^-$ and F$^-$ quantitatively. This phenomenon is easily observed using ^{19}F NMR spectroscopy, which provides a clear analytical signature of the transformations. Although the resulting carboxymethylphosphinic acid derivatives somewhat resemble malonic or phosphonoacetic acid derivatives, they demonstrate remarkable stability in both strong acidic and alkaline solutions, where decarboxylation analogous to the malonic ester synthesis or dephosphorylation similar to the Horner–Wadsworth–Emmons reaction would be expected. The observed hydrolytic instability of the 2,2,2-trifluoroethylphosphinic acid fragment brings the possibility to introduce a bifunctional carboxymethylphosphinic acid chelating group(s) in, *e.g.*, chelators used in radiomedicine.

Introduction

Fluorinated carbon compounds, characterised by the carbon–fluorine (C–F) bond, are notable for their exceptional stability and resistance to environmental degradation. This resilience is attributed to the significant electronegativity difference between carbon and fluorine, resulting in highly polar and very short bonds with substantial orbital overlap. Consequently, fluorinated compounds persist in the environment, leading to their accumulation in living organisms and raising ecological concerns.

While naturally occurring fluorinated compounds are relatively rare,[1] certain microorganisms, such as *Streptomyces cattleya*, synthesise fluoroacetate and fluorinated fatty acids by incorporating environmental fluoride ions.[1,2] Recent research has identified enzymes capable of catalysing the hydrolysis of the C–F bonds, including fluorinases and dehalogenases.[3] These enzymes offer potential pathways for the biodegradation of fluorinated compounds; however, their practical application remains in the early stages of development. Fluorine-containing derivatives of natural metabolites (fluoroacetate, fluorocitrate, fluorinated fatty acids) are used by some plants (*e.g.* several species of genus *Dichapetalum*) as a poisonous chemical weapon to protect from grazing.[4–7]

Another fluorine-containing analogue of a naturally occurring compound, 2-fluoro-2-deoxy-glucose (2-FDG),[8] was

originally suggested as a cytostatic agent; unfortunately, it was found to be too toxic to be utilised in this capacity. However, as concentrations used for radiodiagnostic purposes are (from a "chemical" point of view) negligible, its radioactive 18-fluoro analogue (2-[18F]FDG) was found to be a very effective tracer in positron emission tomography (PET).[9] As the compound structurally resembles glucose, it is uptaken by the cells, and due to the stability of the C–F bond, it cannot be further metabolised, which leads to its accumulation in the metabolically active tissues.

Nowadays, of particular concern are the so-called "forever chemicals", such as trifluoroacetic acid (TFA), hydrofluorocarbons (HFCs) and polytetrafluoroethylene (PTFE, commonly known as Teflon). These substances are renowned for their environmental persistence and potential adverse effects. TFA has been detected in increasing concentrations across multiple environmental media, including groundwater. Its perseverance and mobility raise concerns about potential ecological and health effects. Studies have reported TFA concentrations exceeding proposed regulatory limits in a significant proportion of water samples, indicating widespread contamination.[10] HFCs, widely used in refrigerators or air-conditioners, contribute significantly to global warming due to their high global warming potential and prolonged atmospheric lifetimes. Although introduced as substitutes for ozone-depleting substances like chlorofluorocarbons (freons, CFCs), HFCs have been recognised for their substantial climatic impact, and the U.S. Environmental Protection Agency has established ambitious goals to reduce their production and

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emissions. Under the Kigali Amendment to the Montreal Protocol, a phased reduction has been agreed, reflecting the urgent need to mitigate emissions of fluorinated greenhouse gases.[11]
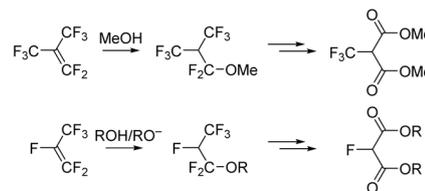
A significant threat currently arises from nano- and microplastics. These tiny plastic particles, often invisible to the naked eye, can accumulate in organisms and ecosystems, disrupting biological processes and potentially releasing toxic chemicals.[12–14] In this respect, attention is also paid to particles of polyfluoroalkanes.[15,16]

Due to the chemical stability of the C–F bond mentioned above, fluorine-containing organic compounds are generally expected to be hydrolytically stable. It can be documented by extremely harsh conditions (30% aq. KOH, reflux) used for the hydrolysis of fluoroacetic acid to glycolic acid when Marais studied the toxicity of *Dichapetalum cymosum*.[4] However, it was shown that the trifluoromethyl group can undergo formal hydrolytic defluorination (*i.e.* substitution for an electronegative atom with elimination of F⁻) if activated by a specific position in the molecule.[17] For example, condensation of 1-trifluoromethyl-2-phenyl-ethene activated by the presence of an ester, alkynyl or aryl group on carbon-1 with substituted acetylacetones leads to the leaving of two fluoride ions and affords 2-fluoro-4H-pyranes as the products (Scheme 1).[18] In a similar reaction with N-tosyl-aminomalonates, the hydrolytic lability of the CF_3 group bound to the vinyl fragment activated by ester, carbonyl or alkynyl was used in the synthesis of a series of 2-fluoro-2-pyrrolines (Scheme 1).[19] It should be noticed that the fluorine atom in such heterocyclic products can be further formally hydrolysed (exchanged for an electronegative atom: X = O, S or N, Scheme 1).[18,19]

As other examples of hydrolytic instability of the C–F bonds, the synthesis of fluoro-substituted malonates starting from perfluoroalkenes can be mentioned. For example, perfluoro-*iso*-butene is known to undergo alcohol addition, and gentle acid hydrolysis of the intermediate affords bis(trifluoromethyl)acetic acid ester. It can, upon addition of the base, undergo further dehydrofluorination, and the intermediate olefin can react with another molecule of the alcohol, affording – after next defluorination – 2-trifluoromethyl malonate diester (Scheme 2).[20] In another example, the addition of ammonia to perfluoropropene leads to 1,1,1,2-tetrafluoropropionic nitrile, which, after its dehydrofluorination by alcoholate, followed by addition of alcohol and gentle acid hydrolysis, afforded 2-fluoromalonate diester.[21] Alcoholysis of perfluoropropene works in a similar way (Scheme 2).[21,22]
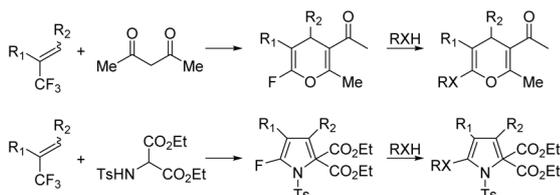
Scheme 2 Alcoholysis of perfluoroalkenes.[20–22]

It was also shown that direct alkaline hydrolysis of α-trifluoromethylcarboxylic fatty acids led to 2-alkyl malonate derivatives.[23] For these reasons, the methods for the synthesis of CF_3-substituted quaternary carbon centres cannot employ alkylation of 2-trifluoromethyl-malonates and bis(trifluoromethyl)acetates in the presence of a base, as β-defluorination of the α-carbanion intermediate occurs. Although it can be overcome by deprotonation with an electrochemically generated non-metallic base (pyrrolidone anion) under mild conditions,[24] alternative methods, as metallo- or organo-catalysed allylic alkylation or Michael addition, are usually used.[25–28]

The instability of the afore-mentioned compounds and intermediates clearly arises from the presence of the hydrogen atom bound to the α-carbon bearing both trifluoromethyl and carboxy or some other activating group. Such a constellation undergoes dehydrofluorination with a base, affording a reactive 1,1-difluoroolefin.[29] However, if no hydrogen atom is present on the α-carbon, as in the case of, *e.g.,* trifluoropyruvate, no defluorination occurs and compounds of R–C(CF_3)(OH)(CO_2R') type can be obtained by allylic alkylation of trifluoropyruvate ester.[30]

During our previous studies on potential ¹⁹F MRI contrast agents,[31–33] we observed a surprising hydrolytic instability of C–F bonds in some 2,2,2-trifluoroethylphosphinic acid derivatives. We decided to gain a more detailed understanding of this phenomenon and chose different 2,2,2-trifluoroethylphosphorus derivatives 1–6 (Fig. 1) to study their potential hydrolysis. To find

Scheme 1 Reactivity of activated 1-trifluoromethyl-alkenes.[18,19] For $R_{1,2}$ see the text.
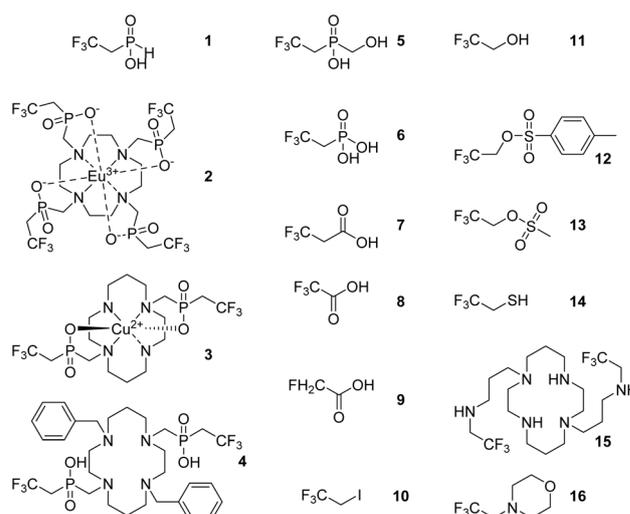
Fig. 1 Structural formulas of the compounds tested for the hydrolysis of the C–F bond.

out whether the hydrolytic instability is related exclusively to the phosphorus derivatives, we also studied behaviour of representative compounds containing the 2,2,2-trifluoroethyl group bound to different heteroatoms (nitrogen, oxygen, sulphur and halogen; compounds **10–16**), as well as derivatives with the C–F bond(s): 3,3,3-trifluoropropionic acid **7**, trifluoroacetic acid **8**, and fluoroacetic acid **9** for comparison (Fig. 1). Here, we present the results of this investigation.

Results and discussion

Synthesis of studied compounds

Most of the chosen compounds for our study are commercially available, were available from our previous studies or could be prepared according to the literature. Two crucial derivatives are new compounds that were not available yet – 2,2,2-trifluoroethyl(hydroxymethyl)phosphinic acid **5** and 2,2,2-trifluoroethylphosphonic acid **6**. Their synthesis had to be established and optimised, and is discussed below.

Synthesis of 2,2,2-trifluoroethyl(hydroxymethyl)phosphinic acid 5. Synthesis proceeded according to Scheme 3.

In general, hydroxymethylation of the P–H bond proceeds in an acidic medium (aq. HCl, elevated temperature), as used, *e.g.*, in the preparation of hydroxymethylphosphinic acid.[34] Similar conditions have been often used in Mannich-type reaction between an (alkyl)phosphinic acid, formaldehyde and a secondary amine to introduce an (alkyl)phosphinic acid–methyl pendant arm to the amine skeleton. In such reactions, the hydroxymethyl(alkyl)phosphinic derivative is usually formed as a by-product.[35–38] In this respect, 2,2,2-trifluoroethylphosphinic acid was found to be a very reactive substrate,[33] and also the reaction with formaldehyde proceeds easily in acidic media (6 M HCl) at slightly elevated temperature (60 °C). It was found that removal of ammonia from starting 2,2,2-trifluoroethylphosphinic acid (which was previously isolated as the ammonium salt) is crucial for a clean course of the reaction, as if some traces of ammonia were present in the reaction mixture, Mannich-type reaction also proceeded, resulting in the formation of tris{[2,2,2-trifluoroethyl(hydroxy)phosphoryl]methyl}amine **17** side product (Scheme 3), whose identity was confirmed by X-ray diffraction analysis (Fig. S2).

Oxidation of 2,2,2-trifluoroethylphosphinic acid 1 to 2,2,2-trifluoroethylphosphonic acid 6. Synthetic approaches employed are overviewed in Scheme 4.
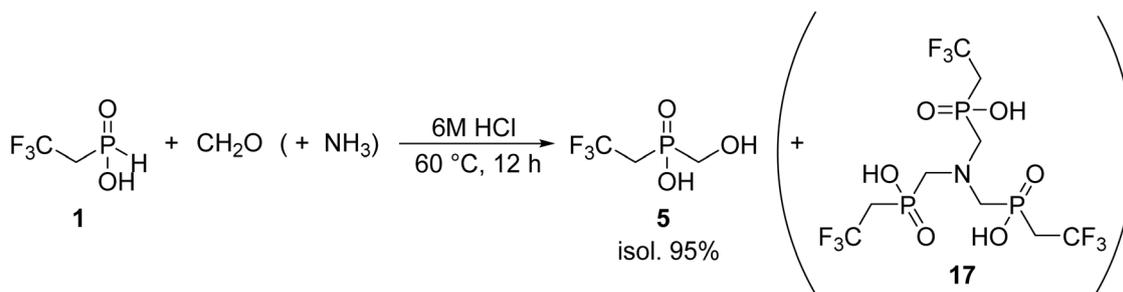
The P–H bond in 2,2,2-trifluoroethylphosphinic acid **1** was found to be surprisingly very stable towards oxidation, as the presence of the 2,2,2-trifluoroethyl group makes the phosphorus atom electronically poor due to a strong electron-withdrawing effect. The compound was found to be fully stable upon heating in 10% aq. hydrogen peroxide at 90 °C overnight and was quantitatively recovered after evaporation. Similarly, heating compound **1** with iodine excess in aqueous–ethanolic solvent in a closed vial to 70 °C overnight had no effect. The compound can be successfully oxidised with $(NH_4)_2S_2O_8$ at elevated temperature; however, the reaction mixture cannot be easily worked up due to the presence of salts. Clean and quantitative oxidation was observed when compound **1** was heated in hexamethyldisilazane as a solvent in air. Hexamethyldisilazane is standardly used as a trimethylsilylation agent, forming trimethylsilyl esters of phosphinic acids.[39,40] The electron-donating properties of the silyl group enable the successful oxidation of the intermediate ester by oxygen. The product – 2,2,2-trifluoroethylphosphonic acid **6** – was isolated as white crystalline material by evaporation and recrystallisation from water–ethanol in the form of mono-ammonium hydrogen salt $NH_3 \cdot \mathbf{6}$ as confirmed by single crystal X-ray diffraction analysis (Fig. 2).

Basic hydrolysis of the CF_3 group

NMR cleavage scale. A potential for hydrolysis of the C–F bonds was studied across 16 substrates shown in Fig. 1. The selection of substrates included compounds with trifluoroethyl
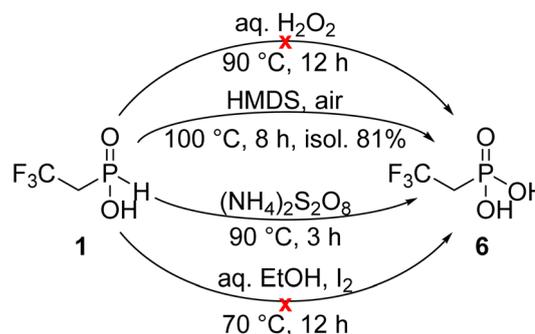
Scheme 4 Synthetic approaches used for the synthesis of 2,2,2-trifluoroethylphosphonic acid **6**.

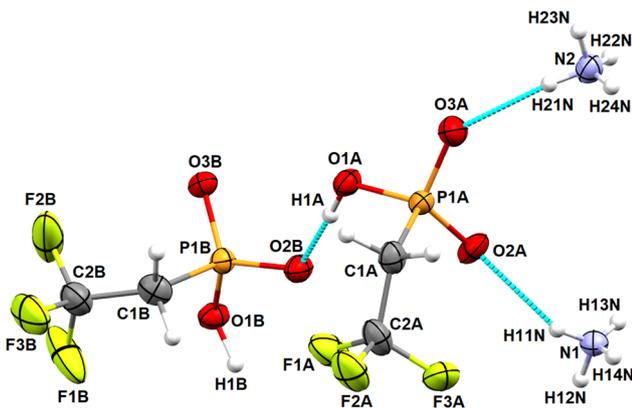**Scheme 3** Synthesis of 2,2,2-trifluoroethyl(hydroxymethyl)phosphinic acid **5**.

Fig. 2 Structurally independent part found in the crystal structure of ammonium hydrogen-2,2,2-trifluoromethylphosphonate (NH$_3$·**6**). Two formula units are present in the independent part. All hydrogen atoms bound to the nitrogen and oxygen atoms, respectively, are involved in an intermolecular hydrogen bond network; however, only hydrogen bonds within the independent part are shown for clarity reasons (turquoise).

groups bound to different heteroatoms. Besides the title phosphorus derivatives (alkyl- and dialkyl-phosphinic acids, phosphonic acid), also derivatives where the group was bound to nitrogen (different amines), oxygen (alcohol and sulfonate esters), sulphur (thiol) and halogen (iodide as generally the most reactive from the halide family) atoms were chosen, together with "just carbon" derivatives – fluoroacetic acid, trifluoroacetic acid (TFA) and 3,3,3-trifluoropropionic acid.

Preliminary hydrolytic experiments (pH 11–12, 50 °C) followed by ^{19}F NMR spectroscopy over several days clearly show that all phosphinic acid derivatives – *i.e.* compounds **1–5** – undergo hydrolysis of the CF$_3$ group, and free fluoride ion is formed as clearly detected by a typical chemical shift *ca.* −120 ppm. Besides these compounds, only 3,3,3-trifluoropropionic acid **7** was hydrolysed, as could be expected based on the literature data,[17] and all other compounds remained unchanged. Surprisingly, 2,2,2-trifluoroethylphosphonic acid **6** was also found to be fully stable under the chosen reaction conditions. To characterise possible intermediates in the hydrolytic reaction, the experiments with several compounds were repeated, and the ^{19}F NMR spectra were recorded in short time intervals. However, no intermediates were detected, and the compounds hydrolysed to produce only fluoride ions. If proceeded, the reaction lasted several hours at pH 11 and 50 °C, or a few days when the reaction mixture was left at room temperature. For substrates containing more trifluoroethylphosphinic groups (especially compound **2**), the reaction was slowed down in time by released fluoride ions, as they neutralised the starting base. However, after increasing the pH, the reaction proceeded quantitatively also in these cases. A time course of the hydrolysis of 2,2,2-trifluorophosphinic acid **1** is shown in Fig. 3 as an example. Fig. S16–S30 demonstrate the hydrolytic lability of compounds **2–5** and **7**, and stability of other substrates, with the exception of 2,2,2-trifluoroethanethiol **14**, where some minor decomposition products were formed under the reaction conditions, but

a release of the fluoride ions was not observed (Fig. S28). In the hydrolytic reactions, no significant role of the cation present in the reaction mixture was observed – the reactions proceeded with NMe$_4$OH, LiOH, NaOH and KOH with similar efficiency.

From an analogy to 2,2,2-trifluoroethylcarboxy derivatives,[17] where hydrolysis of the trifluoromethyl group produces carboxylic acid, one can expect that the carboxymethylphosphinic fragment is formed during hydrolysis of 2,2,2-trifluoroethylphosphinic derivatives (Scheme 5). To confirm this suggestion, hydrolysis of **1** was followed by multinuclear NMR spectroscopy. Indeed, the NMR spectra unambiguously revealed, besides the release of the fluoride ions, the formation of carboxymethylphosphinic acid **18** (Fig. S31–S35).

Based on the mechanism suggested for the hydrolysis of the trifluoromethyl group in 2,2,2-trifluoroethylcarboxy derivatives,[17] one can expect that the first step of the hydrolysis of 2,2,2-trifluoroethylphosphinic derivatives is elimination of HF and formation of a terminal difluoromethylene fragment, which is further hydrolysed by a hydroxide nucleophile (Scheme 5), analogously as reported for perfluoroalkenes.[20–22] As no intermediate was detected within the course of the reaction, the subsequent hydrolytic steps proceed very fast. The initial mechanism thus very probably involves elimination of the hydrogen atom from the α-carbon atom. This process is possible in phosphinate derivatives, as the phosphinic group (–P(R)O$_2^-$) has a generally electron-withdrawing character and enforces splitting of the hydrogen. On the contrary, phosphonic acid (fully deprotonated to phosphonate –PO$_3^{2-}$ under the reaction conditions) is double negatively charged and, thus, serves as an electron-donating group and increases electron density on the α-carbon atom. As a result, trifluoroethylphosphonic acid is fully stable towards alkaline hydrolysis.

Preparative isolation of selected products of hydrolysis. Carboxymethylphosphinic acid **18** was isolated on a preparative scale – after hydrolysis of **1**, released fluoride ions were precipitated in the form of CaF$_2$ on addition of a slight excess of CaCl$_2$, and the resulting solution was passed through a strong
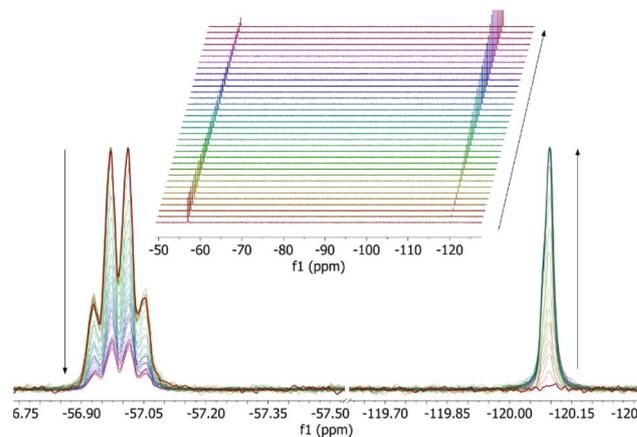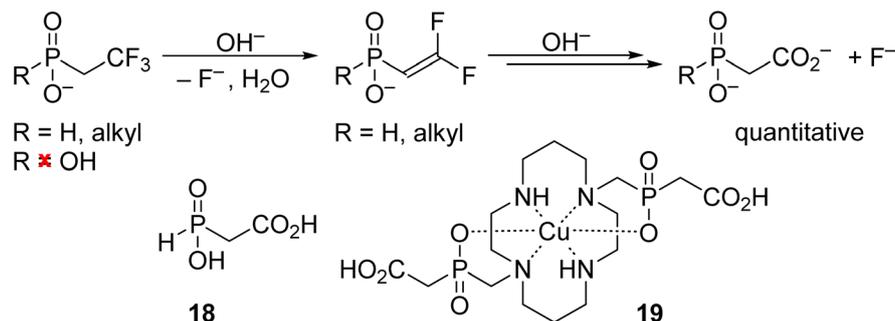

Fig. 3 ^{19}F NMR PAD spectra showing hydrolysis of **1** under highly basic conditions (starting pH 11) and formation of fluoride. 282 MHz, 50 °C, duration 10 h.

Scheme 5 Top: general hydrolysis of 2,2,2-trifluorophosphinic acid derivatives showing the structure of the expected intermediate. Bottom: structural formulas of isolated examples of hydrolysis products **18** and **19**.

cation exchange resin in H⁺-form to remove cations. The acid eluate was evaporated, affording pure **18** in a high yield. The identity of **18** was confirmed by multinuclear NMR spectroscopy. The compound undergoes deuteration of the P–H as well as C–H bonds in both acid and alkaline D_2O media (Fig. S36–S39). However, it was fully stable towards possible decarboxylation/dephosphorylation.

The general course of the hydrolytic reaction was also confirmed by the isolation of complex **19** from the hydrolysis of complex **3**. The identity of **19** was confirmed by X-ray diffraction (Fig. 4).

The synthesis charts a clean and convenient route to carboxymethylphosphinic derivatives, which were only scarcely reported in the literature. Until now, related derivatives were obtained by hydrolysis of cyanomethylphosphinic derivatives.[41] The new procedure can lead to TRAP-like analogues (macrocyclic ligands with carboxyethylphosphinic pendant arms)[42,43] with a shorter carboxylate linker, and could find a potential use in radiomedicinal applications as the parent TRAPs.[44]

Experimental

Materials and methods

Thin-layer chromatography (TLC) was performed on silica-coated aluminium sheets Silica gel 60 F254 (Merck). Spots
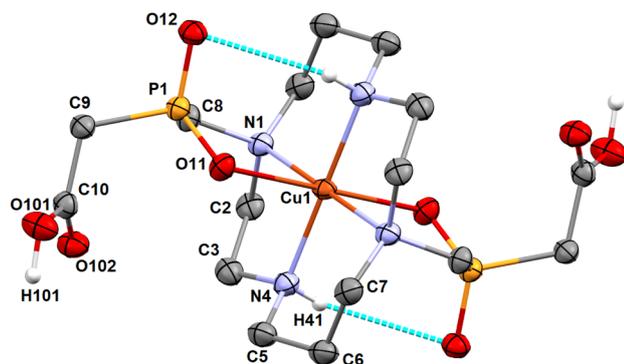

Fig. 4 The molecular structure of complex **19** found in the crystal structure of **19**·2H₂O. Carbon-bound hydrogen atoms are omitted for the sake of clarity. The intramolecular hydrogen bonds between the amino group and the pendant arm are shown in turquoise. The molecule possesses a centre of symmetry; thus, only one half is labelled.

were visualised by dipping in a 0.75% aq. solution of $KMnO_4$ in 5% K_2CO_3 + 1% KOH. NMR spectra were recorded on a Varian VNMRS300 (frequencies 299.9 MHz for ¹H, 282.2 MHz for ¹⁹F and 121.4 MHz for ³¹P) and Bruker Avance III 600 MHz (frequencies 600.2 MHz for ¹H, 150.9 MHz for ¹³C). The spectra were acquired at 25 °C unless stated otherwise. Internal references for ¹H and ¹³C NMR spectra were t-BuOH for D_2O solutions (1.24 ppm for ¹H and 30.29 ppm for ¹³C). Aq. H_3PO_4 (3%) was used as the external reference for ³¹P NMR (0.5 ppm) and ca. aq. 1% trifluoromethanesulfonic (triflic) acid for ¹⁹F NMR (−78.9 ppm). These secondary references were referenced to 85% H_3PO_4 (0.0 ppm) and Freon-11 (0.0 ppm), respectively. Chemical shifts are given in ppm and coupling constants in Hz. Multiplicities of the signals are expressed as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet). Details on single-crystal X-ray crystallography are given in the SI.

Synthetic procedures

Tested substrates 3,3,3-trifluoropropionic acid **7**, trifluoroacetic acid **8**, fluoroacetic acid **9**, 1,1,1-trifluoro-2-iodoethane **10**, 2,2,2-trifluoroethanol **11** and 2,2,2-trifluoroethanethiol **14** were purchased from commercial sources (Sigma-Aldrich, Fluorochem) and used as received. Substrates 2,2,2-trifluoroethylphosphinic acid **1**,[33] Eu(III)–DOTP^tfe complex **2**,[31] Cu(II)–TE2P^tfe complex **3**,[32] 4,11-dibenzyl-1,8,-bis{[2,2,2-trifluoroethyl(hydroxy)phosphoryl]methyl}-1,4,8,11-tetraazacyclotetradecane **4**,[32] 2,2,2-trifluoroethyl-tosylate **12**,[33] 2,2,2-trifluoroethyl-mesylate **13**,[45] 1,8-bis[N-(2,2,2-trifluoroethyl)-3-aminopropyl]-1,4,8,11-tetraazacyclotetradecane **15** (ref. 46) and N-(2,2,2-trifluoroacetyl)morpholine[47] were synthesized according to published literature or were available from our previous studies. N-(2,2,2-trifluoroethyl)morpholine **16** was prepared by reduction of **15** with BH_3 generated in situ by reaction of $NaBH_4$ and $BF_3·Et_2O$ in etheric solvent analogously as used in syntheses of other N-trifluoroethyl derivatives.[46,48] For detailed procedure, see SI. Substrates 2,2,2-trifluoroethyl(hydroxymethyl)phosphinic acid **5** and 2,2,2-trifluoroethylphosphonic acid **6** were synthesised according to the procedures described below.

Synthesis of 2,2,2-trifluoroethyl(hydroxymethyl)phosphinic acid 5. Ammonium salt of 2,2,2-trifluoroethylphosphinic acid (NH₃·**1**, 500 mg, 3.03 mmol) was dissolved in 5 mL of H_2O, and the solution was poured onto a column of a strong ion exchange

resin (Dowex 50, 25 mL) in the H^+-form. The free acid **1** was eluted with water (150 mL), and the water was evaporated on a vacuum rotary evaporator, and the residue was transferred into a 25-mL tear-shaped flask. Free acid **1** was dissolved in aq. HCl (6 M, 10 mL) and a large excess of aq. formaldehyde solution (30%) was added (3 mL). The mixture was heated to 60 °C overnight. The volatiles were evaporated on a vacuum rotary evaporator (with repeated addition of a small amount of water) to a constant mass of the residue **5** as a yellowish oil. Yield 512 mg (*ca.* 95%).

NMR: (D_2O, pD 0.6): ^1H: 2.93 (2H, pseudo-p, PCH_2CF_3, $^2J_{HP}$ ≈ $^3J_{HF}$ ≈ 13); 3.84 (2H, d, PCH_2OH, $^2J_{HP}$ = 5.5). $^{13}C\{^1H\}$: 32.6 (dq, PCH_2CF_3, $^1J_{CP}$ = 85, $^2J_{CF}$ = 28); 59.8 (d, PCH_2OH, $^1J_{CP}$ = 118); 125.3 (q, CF_3, $^1J_{CF}$ = 276). ^{19}F: −57.6 (m). ^{31}P: 35.8 (m). $^{31}P\{^1H\}$: 35.8 (q, $^3J_{PF}$ = 8.4). See Fig. S3–S7.

TLC (iPrOH:conc. aq. NH_3 : H_2O 5 : 1 : 1): 0.9 (yellowish spot).

When traces of ammonia were present in the reaction mixture, tripodal tris{[2,2,2-trifluoroethyl(hydroxy)phosphoryl] methyl}-amine **17** was isolated as the by-product, as identified by X-ray diffraction analysis (Fig. S2).

Synthesis of 2,2,2-trifluoroethylphosphonic acid 6. Ammonium salt ammonium salt of 2,2,2-trifluoroethylphosphinic acid (NH$_3$·**1**, 500 mg, 3.03 mmol) was suspended in a 25-mL tear-shaped flask in hexamethyldisilazane (10 mL). The flask was equipped with a condenser, and the mixture was heated in an oil bath to 100 °C for 8 h under air. After cooling, volatiles were evaporated on a vacuum rotary evaporator and the solid residue was dissolved in water (1 mL). The solution was layered with anhydrous EtOH (5 mL) and left overnight. The white product – monoammonium salt of **6** – was isolated by filtration. Yield 444 mg (81%).

NMR: (D_2O, pD 7.5): ^1H: 2.93 (2H, dq, PCH_2CF_3, $^2J_{HP}$ = 17, $^3J_{HF}$ = 12). $^{13}C\{^1H\}$ 34.7 (dq, PCH_2CF_3, $^1J_{CP}$ = 122, $^2J_{CF}$ = 27); 126.9 (q, CF_3, $^1J_{CF}$ = 274). ^{19}F: −58.40 (pseudo-q, $^3J_{FH}$ ≈ $^3J_{FP}$ ≈ 13). ^{31}P: 8.5 (m). $^{31}P\{^1H\}$: 8.5 (q, $^3J_{PF}$ = 12). See Fig. S8–S12.

TLC (iPrOH:conc. aq. NH_3 : H_2O 5 : 1 : 1): 0.2 (yellowish spot).

Single crystals suitable for X-ray diffraction study were selected from the bulk.

In an alternative approach, **1** (50 mg, 0.30 mmol) was dissolved together with $(NH_4)_2S_2O_8$ (138 mg, 0.60 mmol, 2 equiv.) in water (1.0 mL). The mixture was divided into two NMR cuvettes; the first was allowed to stand at laboratory temperature, and the second was heated to 90 °C. After 3 h, the ^{31}P and ^{19}F NMR spectra were acquired, revealing *ca.* 20% conversion to **6** at room temperature, whereas the reaction processed at 90 °C was completed. At room temperature, the reaction was completed within 24 h.

Hydrolytic study

The samples were prepared by dissolving a sufficient amount of the studied compound to reach a concentration of fluorine atoms of *ca.* 20 mM in water (0.5 mL) or 90% aq. EtOH (0.5 mL) in the cases where the compound (**4**, **14**) was insoluble/immiscible with pure water. The pH was adjusted to 11–11.5 (uncorrected electrode reading) by several drops of 10% aq. NaOH. The hydrolysis experiments were carried out in closed

NMR tubes in an oil bath heated up to 50 °C, and after a chosen time period, the NMR spectra were measured. The measurement was performed at ambient temperature. From these preliminary experiments, hydrolytically non-stable compounds were identified. For them, Pre-acquisition delay (PAD) kinetic NMR experiments were performed directly in the spectrometer at 50 °C and spectra were measured at conveniently chosen time increments to cover the course of the reaction. Selected results are shown in the Results and Discussion part (Fig. 3) and in SI (Fig. S16–S30). Temperature was calibrated using the MeOH-d_4 method.[49,50]

Identification of the products of hydrolysis

Identification of the product of the hydrolysis of 1: carboxymethylphosphinic acid 18. Ammonium salt of 2,2,2-trifluoroethylphosphinic acid (NH$_3$·**1**, 20 mg) was dissolved in water (0.5 mL), and the pH was adjusted to 11 by the addition of several drops of 10% aq. NaOH. After heating overnight to 50 °C, ^1H, $^{13}C\{^1H\}$, ^{19}F, ^{31}P and $^{31}P\{^1H\}$ NMR were acquired.

NMR: (H_2O, pH 11): ^1H: 2.50 (2H, dd, $HPCH_2CO_2$, $^2J_{HP}$ = 19, $^3J_{HH}$ = 2); 7.01 (1H, d, $HPCH_2OH$, $^1J_{HP}$ = 531). $^{13}C\{^1H\}$: 43.8 (d, PCH_2CO_2, $^1J_{CP}$ = 78); 175.6 (d, PCH_2CO_2, $^2J_{CP}$ = 4.0). ^{19}F: −119.6 (s, F$^-$). ^{31}P: 23.0 (dt, $^1J_{PH}$ = 531, $^2J_{PH}$ = 19). $^{31}P\{^1H\}$: 23.0 (s). See Fig. S31–S35.

Synthesis of carboxymethylphosphinic acid 18. Ammonium salt of 2,2,2-trifluoroethylphosphinic acid (NH$_3$·**1**, 500 mg, 3.03 mmol) was dissolved in water (5 mL), and the solution was alkalised by the addition of aq. NaOH (10%) to pH *ca.* 11.5. The mixture was stirred at 50 °C for 8 h. The ^{19}F NMR revealed full hydrolysis of the starting compound as only the signal of fluoride ions (*ca.* −120 ppm) was present in the spectrum. A solution of $CaCl_2$ (0.5 M, 11 mL, 20% excess with respect to the fluoride ions) was added, and the mixture was left overnight to complete crystallisation of CaF_2. The precipitate was filtered off using a cotton ball, and the filtrate was passed through a column of strong cation exchange resin in H^+-form (Dowex 50, 50 mL) with water as an eluent were removed using a rotary vacuum evaporator, affording compound **18** as a yellowish oil. Yield 320 mg (*ca.* 85%).

NMR: (D_2O, pH 0.9): ^1H: 2.93 (2H, d, $HPCH_2CO_2$, $^2J_{HP}$ = 18); 7.21 (<1H, intensity partially lowered due to a P–H exchange for P–D in D_2O, d, $HPCH_2OH$, $^1J_{HP}$ = 565). $^{13}C\{^1H\}$: 40.0 (d, PCH_2CO_2, $^1J_{CP}$ = 78); 177.8 (d, PCH_2CO_2, $^2J_{CP}$ = 4.7). ^{31}P: 21.7 (dt, $^1J_{PH}$ = 565, $^2J_{PH}$ = 18), 21.4 (partially deuterated P–H to P–D, non-binomial tt, $^1J_{PD}$ = 86, $^2J_{PH}$ = 18). $^{31}P\{^1H\}$: 21.7 (s), 21.4 (partially deuterated P–H to P–D, non-binomial t, $^1J_{PD}$ = 86). See Fig. S36–S39.

The cuvette with the sample in D_2O was heated overnight at 90 °C. Deuterations of P–H bond and CH_2 group were observed (as revealed by an intensive non-binomial triplet in the ^{31}P NMR spectra and complicated pattern of the $CH_2/CHD/CD_2$ group in the ^{13}C spectra, as well as intensity lowering of the CH_2 group in the ^1H spectra together with a signal split of the CHD group), but decarboxylation did not.

Isolation of the product of the hydrolysis of complex 3: complex 19. The reaction mixture after hydrolysis of Cu(II)–

TE2P^{tfe} complex **3** (starting from 30 mg, *ca.* $5 \cdot 10^{-5}$ mol) with composition analogous to the final spectrum shown in Fig. S17 was mixed with a solution of $CaCl_2$ (0.5 M, 360 µl, 20% excess with respect to the fluoride ions) and the mixture was left to stand overnight. Precipitated CaF_2 was filtered off using a cotton ball, and the filtrate was passed through a column of strong cation exchange resin (Dowex 50, 5 mL) with water as an eluent. The volatiles were evaporated. Single crystals of **19**·2H$_2$O with quality suitable for X-ray diffraction analysis were obtained by crystallisation from a small amount of hot water, slow cooling, and concentration at room temperature.

Conclusions

A broad study of the hydrolytic stability/lability of the 2,2,2-trifluoroethyl group was performed depending on the substrate structure; the substrates included derivatives where the 2,2,2-trifluoroethyl group is bound to iodine, oxygen, sulphur, nitrogen or phosphorus atoms, as well as fluoroacetate, trifluoroacetate and 3,3,3-trifluoropropionate. Two new compounds – 2,2,2-trifluoroethyl(hydroxymethyl)phosphonic acid **5** and 2,2,2-trifluoroethylphosphonic acid **6** – were prepared for the purpose, and *N*-(2,2,2-trifluoroethyl)morpholine **16** was prepared in a more convenient way than reported previously.[52–54]

Despite the widely accepted notion of the stability of the C–F bond, which renders fluorinated organic compounds prone to accumulation in the environment, the compounds containing 2,2,2-trifluoroethylphosphinic groups undergo clean hydrolysis of the CF_3 group in alkaline solutions (pH > 10) to produce a carboxy group and free fluoride ions. Some of the studied (or related) compounds have been previously suggested as potential ^{19}F MRI contrast agents,[31–33] and this potential application still remains feasible, as the conditions needed for a successful hydrolysis are disjunct from those biologically relevant. However, from a sustainability and biodegradability standpoint, this feature of fluorine-containing compounds can be considered an advantage. On the contrary, 2,2,2-trifluoroethylphosphonic acid was found to be fully stable towards hydrolysis, as the double negatively charged phosphonate moiety obviously donates electron density to the neighbouring α-carbon atom and disables dehydrofluorination. Other model compounds, where 2,2,2-trifluoroethyl group is bound to iodine, oxygen, sulphur or nitrogen atoms, were found to be fully stable towards basic hydrolysis of the C–F bonds.

Besides 2,2,2-trifluoroethylphosphinic acid derivatives, basic hydrolysis was also observed in the case of 3,3,3-trifluoropropionic acid, as could be expected from the literature data, although this fact was not explicitly reported yet.[17] Conversely, trifluoroacetate and fluoroacetate are fully stable under our reaction conditions. However, it should be noted that fluoroacetate was found to be hydrolysed enzymatically[51] or in extremely harsh alkaline conditions.[4]

From the perspective of studying these compounds, the revealed hydrolytic instability of the 2,2,2-trifluoroethylphosphinic acid fragment presents a pathway for the synthesis of derivatives related to TRAP ligands currently used in human radiomedicine.[42–44] Pre-formed scaffolds containing 2,2,2-trifluoroethylphosphinic acid groups can be potentially modified to a carboxymethylphosphinic arm if the scaffold stability is sufficient to withstand the conditions of hydrolysis. Therefore, the 2,2,2-trifluoroethylphosphinic group represents a very promising synthon for the potential applications in, *e.g.*, nuclear medicine, enabling the introduction of a carboxymethylphosphinate bifunctional moiety into the molecular structure of the ligands, and it warrants further investigation.

Author contributions

Conceptualisation F. K. and J. K.; investigation F. K., I. C. and J. K., methodology F. K and J. K.; validation F. K. and J. K.; formal analysis F. K. and I. C.; data curation F. K. and I. C.; writing—original draft preparation F. K.; writing—review and editing J. K.; visualisation F. K. and J. K.; supervision J. K.; project administration J. K.; funding acquisition J. K.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2489251–2489254 contain the supplementary crystallographic data for this paper.[55a–d]

The NMR spectra supporting this article have been included in the supplementary information (SI). Supplementary information: synthetic procedure for compound **16**, NMR spectra of new compounds, ^{19}F NMR kinetic traces, details on crystallographic study, discussion of crystal structures of **16**·HCl and **17**. See DOI: https://doi.org/10.1039/d5ra07303k.

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