Introduction

The generation of C-centered radical species R' under laboratory conditions requires suitable precursors, P(R), and a matched set of activating conditions, A, since most of the members of this class of molecules cannot be stored in bottles (Scheme 1). For example, methyl radicals (H₃C·) may be accessed most conveniently by the oxidative activation of readily available laboratory solvents, e.g. dimethyl sulfoxide (DMSO). For example, the hydroxyl radical (HO·) readily generated under traditional Haber–Weiss or Fenton conditions with a suitable Fe(II) additive and hydrogen peroxide liberates the methyl radical from the parent radical precursor. Even though this process is not efficient in terms of yield, its striking operational simplicity allowed studying the important methylation of nucleic acid bases under conditions inspired by Nature. Remarkably, the introduction of a single methyl group into a molecular scaffold can drastically alter a compound’s biological profile, typically noted as the magic methyl effect. As a consequence, synthetic organic chemists have dedicated considerable efforts towards expanding and optimizing the arsenal of radical methylation strategies available. For example, Baran and co-workers reported the use of methyl group surrogate radicals (PhSO₂CH₂·) accessed by oxidative activation, and Antonchick and co-workers successfully modified the Fenton chemistry approach to achieve introduction of the CD₃ motif on synthetically relevant scales.

Similar to the methyl radical, the installation of the trifluoromethyl analogue has garnered significant attention, especially in the past decade. Thus, the sagacious introduction of a single trifluoromethyl group into a organic scaffold typically increases the lipophilicity of a drug candidate (ϕ = 0.88) and together with this moiety’s chemical inertness, has spurred the design of a host of matched precursor/activator pairs to provide F₃C· radicals (Scheme 1). Two general paradigms exist for the unfettering of the reactive intermediate: (1) reductive activation (RA) of a CF₃-reagent is often employed with photochemical strategies and exploits readily available bulk chemicals such as trifluoroacetic acid derivatives and sulfonic chlorides whereas (2) oxidative activation (OA) depends on sulfoxide or sulfinate derivatives, e.g. Langlois’ reagent, which are also inexpensive and readily available. The latter strategy is widely adaptable and by tuning of the sulfinate’s substituents, can readily provide access to other alkyl radicals, as most recently demonstrated by Baran and co-workers. Activation of the sulfoxide motif is most often achieved using tBuOOH as stoichiometric reactant and apart from an isolated example by Antonchick and co-workers, we are not aware of a hydroxyl radical being used as a promoter in Fenton-like chemistry. Furthermore, the direct application of the largely unknown, fully fluorinated analogue of the common laboratory solvent, dimethyl sulfoxide, DMSO-F₆, as radical precursor to F₃C·, i.e. in analogy to DMSO serving as precursor to H₃C·, is conspicuously absent from the literature. Specifically, in the context of radiolysis experiments, which are carried out in water, the HO· radical constitutes one of the primary products and DMSO-F₆ could potentially provide a convenient entry point into studying the kinetics of F₃C· radicals.

Moreover, DMSO-F₆ would not necessitate specialized handling or additives as required for previously employed gaseous CF₃I or Togni’s reagents, nor would we expect any undesired cross-reactivity with commonly employed metal reagents.
salts. Furthermore, the abovementioned commercial zinc sulfinate radical precursors are of limited use due to the formation of a precipitate with K₄[Fe²⁺(CN)₆], one of the standard indicators for HO radicals. Herein, we explored the chemical kinetics of DMSO-F₆ with primary radiolysis products, juxtapose these values with parameters available for DMSO in the literature, and perform preliminary activation test of DMSO-F₆ with Fenton's reagent as a foundational study for an alternative radical trifluoromethylation reagent.

Materials and methods

Synthesis of DMSO-F₆

The synthesis of perfluorodimethylsulfoxide, DMSO-F₆, is based on a sole literature report from 1972. However, the reported procedure (A) (requiring heating substantially above the boiling point of the product, and a substantial but delayed exotherm) required significant improvements to negate an unsafe and questionable protocol, to remove ambiguity, and update key spectroscopic details of DMSO-F₆. Spectroscopic examination only available by extended ¹³C NMR experiments revealed that product A was only about 70% estimated purity (measured against an internal standard by ¹⁹F NMR with a pulse delay value, d₁, of 10 s) using the reported procedure as the by-products including TMS-F and Me₃SiOMe form an inseparable ternary azeotropic mixture. We were not able to purify the mixture properly by any number of fractional distillations or liquid–liquid extraction. Therefore, an alternative synthesis strategy (B) was developed which led to the desired product with a purity of >95% based on GC-MS analysis (Scheme 2).

Thus, a 350 mL oven-dried Ace Glass pressure vessel was charged with CsF (0.978 g, 6.44 mmol, 0.05 equiv.) and a large pTFE stirbar and subsequently dried at 200 °C at 1 × 10⁻² mbar for 12 h and then backfilled with dry argon. The reaction vessel was cooled to RT and then to −20 °C in an EtOH bath by means of externally controlled circulator. 1,3,2-Dioxathiolane 2-oxide (14.09 g, 130 mmol, 1.0 equiv.) and TMSCF₃ (38.20 g, 269 mmol, 2.1 equiv.) were added under an argon atmosphere. The flask was sealed and the contents were stirred at −20 °C for 1 h, warmed to RT and stirred for an additional 22 h behind a blast shield. To prevent loss of the volatile DMSO-F₆ during post-reaction workup, the light-yellow crude reaction mixture was cooled to 0 °C, and the contents transferred to a distillation apparatus containing a 25 cm rectifying column. The product was fractionally distilled twice, collecting the fraction with a b.p. of approx. 34 °C at 760 mmHg to afford hexafluorodimethylsulfoxide (DMSO-F₆) as a colourless, volatile liquid (16.63 g, 69% yield) still containing trace trimethylsilyl impurities (<5% by GC-MS).

Most experiments with DMSO-F₆ were carried out with product derived from Method A. If the contaminants were less reactive than DMSO-F₆, then kinetics results are expected to be essentially unaffected. Alternatively, if the trimethylsilyl fluoride contaminants were significantly more reactive than DMSO-F₆, then the derived reaction rates will be too high.
Specifically, the yields (\textit{G-values}) of 
\[
G(\text{e}_{\text{aq}}^{-}) = 2.65, \quad G(\text{HO}^{+}) = 2.65, \quad \text{and} \quad G(\text{H}^{+}) = 0.55 \quad \text{with} \quad G-values \text{ given in species per 100 eV deposited dose.}
\]
If the sample solution is saturated with \(\text{N}_{2}\text{O}\) prior to radiolysis (at 298.15 K; \(x_{1} = 4.367 \times 10^{-4}\), \([\text{N}_{2}\text{O}]_{\text{sat}} = 24.2 \text{ mM}\)), then the solvated electrons \(\text{e}_{\text{aq}}^{-}\) can also be converted to \(\text{HO}^{+}\) according to eqn (2), thereby doubling the yield of this oxidizing species.

\[
\text{N}_{2}\text{O} + \text{e}_{\text{aq}}^{-} \rightarrow \text{H}^{+} \rightarrow \text{HO}^{+} + \text{N}_{2} \quad (2)
\]

Note, that if other fast reactions with \(\text{e}_{\text{aq}}^{-}\) do occur, they may compete with reaction (2). In particular and in analogy with other halogenated substances and carbonyl-derivatives, \(\text{DMSO-F}_6\) is also expected to react quickly with \(\text{e}_{\text{aq}}^{-}\). As a consequence, for our kinetics analyses we aim for a ratio

\[
\frac{[\text{MV}^{2+}]/[\text{MV}^{2+}]}{[\text{MV}^{2+}]} \quad \text{for DMSO based}
\]

![Image](https://example.com/image.png)

**Fig. 1** (A) Temporal evolution of dose-normalized absorbance at 605 nm after irradiation (10 Gy) of an argon saturated solution of methyl viologen \(\text{MV}^{2+}\) (135 \(\mu\text{M}\)) and \(\text{tBuOH}\) (10%, 1.1 mM) in absence (black) and presence (maroon) of \(\text{DMSO-F}_6\) (14.5 mM). (B) The ratio \([\text{MV}^{2+}]/[\text{MV}^{2+}]_0\) varies non-linearly with the ratio \([\text{DMSO-F}_6]/[\text{MV}^{2+}]_0\). At \([\text{DMSO-F}_6]/[\text{MV}^{2+}]_0 = 35.2\), half the solvated electrons \(\text{e}_{\text{aq}}^{-}\) are intercepted by \(\text{DMSO-F}_6\). In light grey, predicted ratios \([\text{MV}^{2+}]/[\text{MV}^{2+}]_0\) for DMSO based on kinetic data available in the literature. Error bars represent two standard deviations.
stant if DMSO-F6 was used.

In certain experiments BuOH was used as a HO· scavenger to avoid interferences by this oxidizing species (eqn (3)).

\[(CH_3)_2COH + HO· \rightarrow (CH_3)_2C(OH)CH_2^+ + H_2O\]  (3)

The rate constant of the reaction of a CF₃⁻precursor with a radical was always determined by competition with an indicator reaction. As example see reaction (4) and competitor in reaction (5). The product yield is given by eqn (6a) and results are shown in Fig. 1B. The data were not linearized for analysis, because such treatment would amplify the influence of measurement errors. Instead, a least squares fit according to eqn (6b) was performed by variation of the parameter \(r\). Thus, errors were dominated by the uncertainties in the rate constants used as references.

**Results**

**Reaction of DMSO-F₆ with eₐq⁻⁻**

The rate constant \(k_1\) was determined by competition with methyl viologen (MV²⁺), reaction (5), observing the intensely blue colored methyl viologen radical (MV⁻⁺) at 605 nm \(\varepsilon_{605} = 1.31 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}\).¹⁷

\[\text{DMSO-F}_6 + e_{aq}^- \rightarrow \text{products} \]  (4)

\[\text{MV}^2+ + e_{aq}^- \rightarrow \text{MV}^+ \]  (5)

Addition of DMSO-F₆ to a solution of MV²⁺ suppresses the formation of MV⁻⁺ (Fig. 1) and competition predicts

\[\text{[MV}^+\text{]} = \frac{[\text{MV}^+]_0 \times (k_5[\text{MV}^2+] + k_4[\text{DMSO-F}_6])}{k_5[\text{MV}^2+] + k_4[\text{DMSO-F}_6]} \]  (6a)

\[\frac{[\text{MV}^+]_0}{[\text{MV}^+]_0} = \frac{r[\text{MV}^2+]}{r[\text{MV}^2+]} + [\text{DMSO-F}_6] \]  (6b)

\[r = \frac{k_5}{k_4} \]  (6c)

with \([\text{MV}^+]_0\) the yield in absence of DMSO-F₆. The product concentration was measured as temporal average over 4–6 µs after the pulse. When 14.5 mM DMSO-F₆ was introduced to an argon saturated solution containing 135 µM MV²⁺ and 10% BuOH, the absorbance at 605 nm was lowered by 74% from 23.8 to 6.3 mAbs Gy⁻¹ (Fig. 1A). A variation of \([\text{MV}^2+]\) (0.135, 0.24, 0.35, 1.05 mM) at constant [DMSO-F₆] leads to Fig. 1B and to \(k_5/k_4 = 35.2\) with a least squares fit of eqn (6b). With \(k_5 = (5.4 - 9.0) \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}\) and \(r = 1.8 \times 10^{-10} \text{ M}^{-1} \text{ s}^{-1}\), we derive \(k_4 = (1.5 - 2.6) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}\).

Based on the rate constant \(k_2 = (8.0 - 9.6) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}\) and the solubility of N₂O in water at 298.15 K, \([\text{N}_2\text{O}]_{\text{sat}} = 24.2 \text{ mM}\), we calculate that 84–91% of the solvated electrons are scavenged by N₂O in presence of 14.5 mM DMSO-F₆,¹⁹a,b in close agreement to our aim. In consequence, \(G(\text{HO}·) = 4.87\) and \(G(\text{reaction (4)}) = 0.23 - 0.43\). Note, however, that this does not affect our competition experiments because the branching ratio for electrons through reactions (2) and (4) was always constant if DMSO-F₆ was used.

**Reaction of DMSO-F₆ with HO·**

The rate constant \(k_7\) was determined by competition with hexacyanoferrate(4-) ("ferrocyanide") and hexachloroiridate(3-) (Fig. 2, maroon and green, respectively). Each data point is an average of >4 single determinations:

\[\text{DMSO-F}_6 + \text{HO}· \rightarrow ([\text{CF}_3]_2\text{S(OH)O})^+ \]  (7)

\[\text{Fe}^{II}(\text{CN})_6^{4-} + \text{HO}· \rightarrow \text{Fe}^{II}(\text{CN})_6^{3-} + \text{HO}^- \]  (8)

\[\text{Ir}^{III}\text{Cl}_6^{3-} + \text{HO}· \rightarrow \text{Ir}^{IV}\text{Cl}_6^{2-} + \text{HO}^- \]  (9)

DMSO-F₆ (14.5 mM) was added to aqueous, unbuffered and N₂O saturated solutions of Fe²⁺(CN)₆⁴⁻ (0.11–1 mM). After pulse irradiation with doses of 10–20 Gy yields were compared to reference measurements with 0.11 mM Fe²⁺(CN)₆⁴⁻ in the absence of DMSO-F₆. The reaction was followed spectrophotometrically at 420 nm \(\varepsilon_{420}(\text{Fe}^{III}(\text{CN})_6^{3-}) = (0.9 - 1.1) \times 10^8 \text{ M}^{-1} \text{ cm}^{-1}\) and the final absorption ("yield") was determined as a temporal average over 4–8 µs after the pulse.²¹ Alternatively, 14.5 mM DMSO-F₆ was added to aqueous, unbuffered, N₂O saturated solutions of 97, 291 and 873 µM Ir³⁺Cl₆³⁻. Solutions were pulse-irradiated, the kinetics was followed at 435 nm and plotted with reference to a solution of 97 µM Ir³⁺Cl₆³⁻ in the absence of reagent. Both, reaction (8) and (9), are diffusion controlled with \(k_8 = (0.92 - 1.1) \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}\) and \(k_9 = (0.47 - 1.3) \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}\).²² Given \(k_8/k_7 = 4.8\) and \(k_9/k_7 = 6.4\) (Table 1), we derive \(k_7 = (0.73 - 2.5) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}\). The uncertainty in \(k_7\) originates from the large uncertainty in \(k_8\) (see Table 1) and, therefore, the upper limit of the given range has the higher probability of being correct.

At longer timescales we observe in both cases additional processes, which we cannot explain quantitatively (see ESI†). The processes are clearly dose-dependent, suggestive for invol-

![Fig. 2 Relative yield of reference oxidation reaction for different [Precursor]/[Reference] ratios. Precursors to F₃C⁻ employed as competitors: DMSO-F₆ (magenta, green), Langlois’ reagent (black) and trifluoroacetate (light and dim grey). Error bars represent two standard deviations.](image-url)
Table 1. Compilation of literature reference rates, $k(\text{Ref.} + \text{HO})$, and thereof derived rate constants for oxidative activation of $\text{F}_3\text{C}$ precursors, $k(\text{P} + \text{HO})$.

| Precursor (P) | Reference (Ref.) | $k(\text{Ref.} + \text{HO})$ ($10^{9}$ M$^{-1}$ s$^{-1}$) | $k(\text{P} + \text{HO})$ ($10^{9}$ M$^{-1}$ s$^{-1}$) |
|---------------|-----------------|-----------------|-----------------|
| DMSO-F$_6$    | $\text{Fe}(\text{CN})_6^{3-}$ | 0.92–1.1         | 4.8             |
|               | $\text{I}^{-}\text{Cl}^{-}$  | 0.47–1.3         | 6.4             |
| $\text{F}_3\text{COSO}_2$ | $\text{Fe}(\text{CN})_6^{3-}$ | 0.92–1.1         | 2.0             |
| $\text{F}_3\text{CCOO}$ | $\text{Fe}(\text{CN})_6^{3-}$ | 0.92–1.1         | 15 140          |
| SCN$^-$       | 1.4 (ref. 24)   | 7460             | $1.8 \times 10^6$ |

The rate constant $k_1$ of reaction (7) was derived, i.e. consequence of reaction (7). Therefore, the absorption increase is due to reaction (8) and the slower is a concentration change of oxidized indicator.

**Controls with product B**

Competition according to section 1 was reproduced and $r = 17.9$ was derived, i.e. $k_4 = (3 - 5) \times 10^9$ M$^{-1}$ s$^{-1}$. For the determination of the vapor pressure and the concentration of DMSO-F$_6$ in a given Schlenk-tube, we measured the yield of $\text{Fe}(\text{CN})_6^{3-}$ (see above). Experiments were carried out with 0, 50 µl and 100 µl DMSO-F$_6$. With $\text{N}_2\text{O}$ saturated solution of 3 mM $\text{Fe}(\text{CN})_6^{3-}$ we derived $k_4$ using the branching of solvated electrons via reactions (2) and (4). We observe a two stage reaction, a fast initial reaction followed by a slower process of pseudo-first order with $k_{3\text{obs}} = 2 \times 10^4$ s$^{-1}$. Under the assumption that the total yield $G(\text{Fe}(\text{CN})_6^{3-})_{\text{tot}} = G(\text{OH})$ and that $G(\text{OH}) + G(\text{e}_{\text{aq}}^{-}) = 5.9$, we estimate $k_4 = (3.4 - 4.1) \times 10^9$ M$^{-1}$ s$^{-1}$. This assumption implies also that, the initial, fast absorption increase is due to reaction (8) and the slower is a consequence of reaction (7). Therefore, $G(\text{Fe}(\text{CN})_6^{3-})_{\text{initial}}/G(\text{Fe}(\text{CN})_6^{3-})_{\text{tot}} = k_{4\text{b}}/k_{4\text{f}} = k_{4\text{b}}/(k_{4\text{f}} + k_{5\text{DMSO-F}6})$. We derive a rate constant of $k_2 = (0.83 - 1.0) \times 10^9$ M$^{-1}$ s$^{-1}$. If 10 ml of a $\text{N}_2\text{O}$ saturated solution of 3 mM $\text{Fe}(\text{CN})_6^{3-}$ was directly spiked in the sample-lock syringe with 50 µl DMSO-F$_6$, we derive $k_4 = (1.7 - 4.7) \times 10^9$ M$^{-1}$ s$^{-1}$ and $k_2 = (0.63 - 2.0) \times 10^9$ M$^{-1}$ s$^{-1}$.

**Reaction of $\text{CF}_3\text{SO}_2$ (langlois’ reagent) with HO$^-$**

The rate reaction was measured in competition with reaction (8):

$$\text{CF}_3\text{SO}_2^- + \text{HO}^- \rightarrow [\text{CF}_3\text{SO}_2\text{OH}]^-$$

Unbuffered, $\text{N}_2\text{O}$ saturated, aqueous solutions of 10.4 mM $\text{CF}_3\text{SO}_2\text{Na}$ and varying concentration of $\text{K}_4\text{Fe}(\text{CN})_6$ were pulse-irradiated with doses of 10–20 Gy. Two independent experimental series were measured, (1) $[\text{K}_4\text{Fe}(\text{CN})_6] = 0.4–6.3$ mM and (2) $[\text{K}_4\text{Fe}(\text{CN})_6] = 0.63–3$ mM. As reference a solution of 1.1 mM $\text{K}_4\text{Fe}(\text{CN})_6$ was used. Results are shown in Fig. 2 (black) and for the obtained value of $r = 2$ we arrive at $k_{10} = (4.6 - 5.5) \times 10^9$ M$^{-1}$ s$^{-1}$ (Table 1).

Also with Langlois’ reagent we observed reactions at later times, however, the reproducibility of those measurements was unsatisfactory. We suspect a non-negligible influence of impurities on our measurements at times >20 µs after pulse. While the corresponding Zn-salt is also commercially available and is typically provided in much better quality, its use is prohibited by the formation of Zn$^{2+}$ precipitates with ferrocyanide (vide infra).13

**Reaction of $\text{CF}_3\text{CO}_2$ with HO$^-$**

The rate constant of this reaction was measured versus ferrocyanide and thiocyanate:

$$\text{CF}_3\text{CO}_2^- + \text{HO}^- \rightarrow \text{CF}_3\text{C}^- + \text{CO}_2 + \text{HO}^-$$

$$\text{SCN}^- + \text{HO}^- \rightarrow \text{SCN}^- + \text{HO}^-$$

$$\text{SCN}^- + \text{SCN}^- \rightarrow (\text{SCN}_2)^-$$

The ratio $k_6/k_{11} = 15 140$ was determined in unbuffered, $\text{N}_2\text{O}$ saturated aqueous solutions containing either 0.11 mM $\text{K}_4\text{Fe}(\text{CN})_6/0.5$ M $\text{CF}_3\text{CO}_2$ or 0.05 mM $\text{K}_4\text{Fe}(\text{CN})_6/1$ M $\text{CF}_3\text{CO}_2$ (Fig. 2, light grey). As reference, a solution of 0.11 mM $\text{K}_4\text{Fe}(\text{CN})_6$ was chosen.

Thiocyanate is often used as dosimeter in pulse radiolysis, reaction (13) is an equilibrium reaction, and (SCN)$_2^-$ has a known molar absorptivity of $\varepsilon_{257}(\text{SCN})_{2^-} = 7580$ M$^{-1}$ cm$^{-1}$.$^{26}$ Unbuffered, $\text{N}_2\text{O}$ saturated solutions of 510 mM $\text{CF}_3\text{CO}_2$ and 0.05–5 mM KSCN were pulse-irradiated and $k_{13}/k_{11} = 7460$ determined. It is noteworthy that (pseudo-)halogenide radicals tend to form complexes with anions, e.g. reaction (13), and for chlorine atoms even the diffusion-controlled reaction with hydroxide is described.$^{27}$ Possibly, SCN$^-$ will react with the 0.5 M carboxylate present and such an equilibrium would compete with equilibrium (13) resulting, in turn, in an overestimation of $k_{11}$.

2,2’-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS$^{2^-}$) as indicator for the reaction mechanism

One-electron oxidation of ABTS$^{2^-}$ produces a strongly colored radical, ABTS$^-$$^-$$^,$ with $k_{14} = 3.6 \times 10^4$ M$^{-1}$ cm$^{-1}$.$^{28}$ It is a convenient reagent to test for a moderately or strongly one-electron oxidizing species in a solution. We suspect $[(\text{CF}_3)\text{S(OH)}\text{O}]^-$ (reaction (7)) to be of low reactivity and wished to gain kinetics information on reaction (14). Reaction (16) is very fast, $k_{16} = (1.2 - 1.9) \times 10^9$ M$^{-1}$ s$^{-1}$, and we suspect $k_{17}$ to be of similar magnitude, large enough to possibly monitor reactions (14) and/or (15).

$$[(\text{CF}_3)\text{S(OH)}\text{O}]^- \rightarrow \text{CF}_3\text{SO}_2^- + \text{F}_3\text{C}^- + \text{H}^+$$

$$\text{F}_3\text{C}^- + \text{O}_2 \rightarrow \text{F}_3\text{COO}^-$$

$$\text{ABTS}^{2^-} + \text{Cl}_2\text{COO}^- \rightarrow \text{ABTS}^- + \text{Cl}_2\text{COOH} + \text{HO}^-$$

$$\text{ABTS}^{2^-} + \text{F}_2\text{COO}^- \rightarrow \text{ABTS}^- + \text{F}_2\text{COOH} + \text{HO}^-$$


\[
\text{ABTS}^{2-} + \text{HO}^+ \rightarrow \text{ABTS}^- + \text{HO}^+ \quad (18)
\]

\[
\text{H}^+ / \epsilon_{\text{aq}}^- + \text{O}_2 \rightarrow \text{O}_2^2- / \text{HO}_2^+ \quad (19)
\]

Solutions were saturated with a gas mixture of N\textsubscript{2}O:O\textsubscript{2} \approx 5:1. This will change the yields of the different radicals compared to experiments with N\textsubscript{2}O saturation, as we have an additional reaction (19). If gas-saturation were perfectly reproducible, no variation of starting conditions after the pulse is expected. We measured DMSO-F\textsubscript{6} (14.5 mM) in presence of ABTS\textsuperscript{2-} (59, 98, 137 µM) and, as a reference in absence of DMSO-F\textsubscript{6} we used 98 µM ABTS\textsuperscript{2-} (Fig. 3, black). For this latter case, we determined \( k_{1a} = 1.3 \times 10^{10} \text{ M}^{-1} \text{s}^{-1} \), in agreement with the reported value.\(^{28}\) The initial absorption of the kinetics traces, directly after the pulse, increases with increasing [ABTS\textsuperscript{2-}], consistent with the aforementioned rate constant \( k_{1a} \). Also, we observe that the yield of [ABTS\textsuperscript{2-}] in reaction (18) is only about 57%, in full agreement with the work of Willson.\(^{28}\)

The gas was mixed manually for every stock solution. We observed slightly increased yields of ABTS\textsuperscript{2-} with each new solution. The effect was not dependent on the ABTS\textsuperscript{2-} concentration, as the different concentrations were measured in random order. The total signal increase over the whole day was approximately 15% (see ESIF). We judged that we were observing an artifact and, therefore, normalized the curves for the same end-absorption.\(^{\dagger}\) Normalization does not influence the derived rate constants. Kinetics traces can be seen in Fig. 3. The kinetics change dramatically in the presence of DMSO-F\textsubscript{6}, and there are three important qualitative observations: (i) the reactions are distinctly slower, (ii) instead of a 1\textsuperscript{st} order growth we observe a lag-phase followed by an absorption increase to the level observed before and (iii) the rate of increase is dependent on [ABTS\textsuperscript{2-}]. The lag-phase (ii) is typical for multi-step reactions, in support of our assumptions. We infer to observe consecutive reactions of (7), presumably reactions (14), (15) and (17). It even seems, that the total yield of ABTS\textsuperscript{2-} is independent whether ABTS\textsuperscript{2-} is oxidized directly via reaction (18) or indirectly via a reaction cascade starting at reaction (7).

Based on these qualitative observations we set out to model the kinetics traces. Again, we suspect a reaction cascade involving reactions (7), (14), (15) and (17). For our simulation of the shape of the curve, reaction (7) is irrelevant for the kinetics because it has a half-life of only \( t_2 = \ln(2)/(k_2 \times [\text{DMSO-F}_6]) < 80 \text{ ns} \) (for \( k_2 > 0.6 \times 10^4 \text{ M}^{-1} \text{s}^{-1} \)). We know that reaction (17) is relevant, because the rate of absorption build up in Fig. 3 (color) is clearly dependent on [ABTS\textsuperscript{2-}].

Because we want to limit the number of parameters in our model, we tried to model reactions (14) and (15) together using one single first order rate constant \( k_{\text{calc}} \). With [O\textsubscript{2}] \( \gg \) [F\textsubscript{6}C\textsubscript{5}], this would imply that either \( k_{\text{calc}} = k_{14} > k_{15} [\text{O}_2] \) or \( k_{\text{calc}} = k_{15} [\text{O}_2] > k_{14} \). In the case that \( k_{\text{calc}} = k_{15} [\text{O}_2] \), the process of gas saturation would govern the results. The oxygen concentration, [O\textsubscript{2}], in the samples were not analytically quantified between samples of DMSO-F\textsubscript{6} and therefore different oxygen concentrations could additionally provide a rationale for slightly different values observed between experimental series (Table 2). It is foreseeable that measured values for reactions (14) and (17) will also be subject to the analytical quality of DMSO-F\textsubscript{6} used.

The corresponding least-square fitted curves can be seen in Fig. 3. The corresponding parameters are shown in Table 2.

### Table 2: Compilation of model parameters for modeling the system comprising of eqn (14), (15) and (17)

| ABTS\textsuperscript{2-}/µM | \( k_{\text{calc}}^{a} / 10^{3} \text{ s}^{-1} \) | \( k_{15}^{b} / 10^{3} \text{ M}^{-1} \text{s}^{-1} \) | Offset/10\textsuperscript{3} Gy |
|--------------------------------|---------------------------------|---------------------------------|-----------------------------|
| 59\textsuperscript{a}         | 2.7 ± 0.7\textsuperscript{b}    | 1.5 ± 0.3\textsuperscript{b}    | 2.4                         |
| 98\textsuperscript{a}         | 2.7 ± 0.2\textsuperscript{b}    | 1.2 ± 0.0\textsuperscript{b}    | 5.6                         |
| 137\textsuperscript{e}        | 3.6 ± 0.4\textsuperscript{b}    | 1.2 ± 0.1\textsuperscript{b}    | 4.0                         |
| 68\textsuperscript{a}         | 0.6 ± 0.02\textsuperscript{b}   | 2.9 ± 0.1\textsuperscript{b}    | 2.7                         |
| 125\textsuperscript{a}        | 0.9 ± 0.08\textsuperscript{b}   | 2.3 ± 0.2\textsuperscript{b}    | 4.5                         |
| 250\textsuperscript{a}        | 1.1 ± 0.02\textsuperscript{b}   | 2.6 ± 0.1\textsuperscript{b}    | 10                          |

\textsuperscript{a} First order intermediate step. \textsuperscript{b} Standard deviations based on fitting. \textsuperscript{e} Experiments performed with product A. \textsuperscript{d} Experiments performed with product B.

**Fenton reaction in presence of DMSO-F\textsubscript{6} and product analysis**

We characterized the radical species generated by oxidative activation by its reaction with caffeine. This xanthine is an ideal substrate: it is water soluble, features only one reactive

\(^{\dagger}\) In the controls, this effect was not observed anymore.
site for radical addition and is reminiscent of purine nucleobases. Thus, the well-established oxidative activation of DMSO by the Fenton protocol for methylating adenine and guanidine should provide an ideal blue print.29 To mixtures of caffeine, ascorbic acid, Na2EDTA and Fe(SO4)2 · 7H2O in phosphate buffer we added at 0 °C a DMSO derivative followed by drop-wise addition of H2O2. Products were extracted with ethyl acetate and analyzed by GC-MS (Fig. 4). Besides unreacted starting material (tR = 11.0 min; 194 m/z, grey) only the functionalized products occur, i.e. CF3-caffeine (tR = 9.8 min; 262 m/z, green) or CH3-caffeine (tR = 11.6 min; 208 m/z, magenta), as well as minor amounts of a decomposition product likely arising from oxidative imidazole cleavage (tR = 11.6 min, 112 m/2). The product CF3-caffeine was quantified by 19F NMR spectroscopy through addition of PhCF3 as internal standard to the organic extract and furnished a value of approximately 16%.

Discussion

Rates constants for the reaction of DMSO-F6 with eaq− and HO−

Perfluorination has two distinct effects on the reactivity of DMSO. The inductive effect exerted by fluorine will decrease electron density around the sulfur center. Additionally, the C–F bond is easier to reduce than the C–H bond because of the very low lying σCF* orbital,30 and the resulting instability of perfluorinated materials towards strongly reducing conditions is well documented.31 The reaction of the solvated electron with DMSO-F6, k1 = (2 – 5) × 108 M−1 s−1, is three orders of magnitude larger than with ordinary DMSO (calculated curve depicted in light grey in Fig. 1B). Conversely and as inferred, the oxidation of DMSO-F6 with HO−, k2 = (0.6 – 2.5) × 109 M−1 s−1, is an order of magnitude slower than that of DMSO.32

Reagents for production of F3C− radicals in pulse radiolysis

Experiments with Langlois’ reagent and trifluoroacetate yielded unsatisfactory results for different reasons but serve as valuable references due to the reagents’ commercial availability. The oxidation of trifluoroacetate with HO− is simply too slow for fast production of F3C− needed in time-resolved mechanistic studies. We find k11 = (6 – 7) × 105 M−1 s−1 in agreement with published data from flash photolysis experiments (<106 M−1 s−1).33 Langlois’ reagent is kinetically ideal for our purposes, k10 = 5 × 109 M−1 s−1. The corresponding Zn-salt (Baran modification) is stable and available in high purity, however, Zn2+ has a rich complex chemistry that distinctly limits the use of this compound. In our case, the low solubility of Zn[Fe(CN)6] precluded certain measurements.13 On the other hand, the sodium salt proved to be either unstable or not pure: experiments yielded distinctly different kinetics traces for timescales >20 µs from day to day, which is not acceptable for future mechanistic investigations. In addition, earlier experiments with reductive activation of CF3I showed several disadvantages associated with this gas, such as the necessity of signal deconvolution.34

DMSO-F6 has the drawback of not being commercially available. Its rate of reaction with HO− is lower than that of Langlois’ reagent by half an order of magnitude. On the other hand, liquid handling is comparatively easy, and the reagent proved to be robust in daily use. This makes DMSO-F6 the currently best, though not optimal, choice for time-resolved mechanistic studies. We therefore investigated the mechanism of the oxidative activation more closely, because in principle, fragmentation of the oxidized intermediate [(CF3)2S(OH)O]− may not only occur via reaction (14), but also via reactions (20) and (21), also producing a moderately oxidizing radical.

\[
[(CF_3)_2S(OH)O]^− \rightarrow [(CF_3)_2S(O)O]^− + H^+ \quad (20)
\]

\[
[(CF_3)_2S(O)O]^− \rightarrow CF_3SO_2^− + F_3C^− \quad (21)
\]

Kinetics experiments as well as product analysis were carried out to confirm the hypothesis of fragmentation via reaction (14). Product analysis, demonstrating trifluoromethylation of caffeine after oxidative activation of DMSO-F6 by the Fenton reagent, indeed supports the notion of F3C− radical production, reaction (14), very clearly, albeit at low yield. In this regard, it is noteworthy that the addition of ascobrate proved critical to observing the functionalized product. However, ascorbate (“antioxidant”) may reduce the F3C− radical, thereby preventing oxidative functionalization of caffeine.35 Because perfluoroalkyl radicals exhibit a very low molar absorptivity, we decided to monitor kinetics with a reporter molecule, ABTS2−. In the presence of oxygen, we observe a double-exponential be...
havior (Fig. 3), i.e. two sequential (pseudo)-first order reactions can be resolved. In aqueous environment F$_3$C and Cl$_3$C radicals have a similar electronegativity.\textsuperscript{24,26} Similarly, F$_3$COO\textsuperscript{-} and Cl$_3$COO\textsuperscript{-} show comparable kinetic behavior.\textsuperscript{27} While the former is a stronger oxidant, the overall reactivity of both molecules is dominated by the electron-withdrawing effect exerted by the halogen substitution pattern. With the ascorbate anion (triborohalogen)methylperoxyl radicals have a reactivity H$_2$COO\textsuperscript{-} ≪ Cl$_3$COO\textsuperscript{-} ≤ F$_3$COO\textsuperscript{-} corresponding relative rate constants of 1 : 100 : 100.\textsuperscript{38} For the reaction with Trolox C the corresponding rate constants have a relative magnitude of 1 : 2400 : 4700. Oxygen will cause formation of F$_3$COO\textsuperscript{-} radicals, reaction (15), which we expect to exhibit a comparable reactivity as Cl$_3$COO\textsuperscript{-}, $k_{15} = (1.2 - 1.9) \times 10^9$ M$^{-1}$ s$^{-1}$.\textsuperscript{28} This is indeed the case: $k_{17} = (1 - 3) \times 10^8$ M$^{-1}$ s$^{-1}$ (Table 2) is the remaining rate constant, with $k_{\text{calculated}} = (0.5 - 3) \times 10^5$ s$^{-1}$, to be attributed to reaction (14) or reaction (15)? Based solely on our data we cannot decide unequivocally. Nevertheless, reaction (15) is the more probable candidate for two reasons: (A) given [O$_2$] $\approx$ 200 µM,\textsuperscript{39} we would calculate $k_{13} = (0.3 - 1.5) \times 10^9$ M$^{-1}$ s$^{-1}$, in agreement with the corresponding rate constants for the reactions of H$_2$C and Cl$_3$C with O$_2$ of (3.0 - 4.7) $\times 10^8$ M$^{-1}$ s$^{-1}$ and $3.3 \times 10^8$ M$^{-1}$ s$^{-1}$, respectively.\textsuperscript{40} (B) Compared to a reported value of $k_{11} = 1.5 \times 10^7$ s$^{-1}$ we consider a value of $k_{14} = (0.5 - 3) \times 10^5$ s$^{-1}$ too low.\textsuperscript{41} 

\[
[(\text{CH}_3)_2\text{S(OH)}\text{O}]^+ \rightarrow \text{CH}_3\text{SO}_2^- + \text{H}_3\text{C}^- + H^+ \quad (21)
\]

The [S $\rightarrow$ C] substitution from Langlois’ reagent to trifluoroacetate underpins the importance of a nucleophilic central atom to achieve significant scavenging rates of the HO$^-$ radical. A loss in reactivity of over three orders of magnitudes was observed and this innocuous substitution was likely accompanied by a fundamental change in mechanism. Furthermore, the comparison of trifluoroacetate with acetate is an illustrative example for the often-quoted increase in metabolic stability achieved by the [CH$_3$ $\rightarrow$ CF$_3$] modification. In acetate, $\alpha$-hydrogen abstraction predominates over oxidation ($k(\text{H}_2\text{COO}^- + \text{HO}) = (7.9 - 10) \times 10^7$ M$^{-1}$ s$^{-1}$).\textsuperscript{22a,33,34} Similarly, the [H $\rightarrow$ F] substitution in DMSO causes reactivity changes. As abovementioned, perfluorination of DMSO decreases the rate constant of its reaction with HO$^-$ about half an order of magnitude. The CF$_3$-group is a relatively strongly $\sigma$-withdrawing moiety and may, in addition, allow for stabilizing $n \rightarrow \sigma_{*}$ interactions.\textsuperscript{20} The lone pair at sulfur in DMSO-F$_6$ may thus be rendered less electron-rich and presumably overall less available than in DMSO. A lower reactivity appears only reasonable. If oxidative activation occurs via addition of the HO$^-$ radical to sulfur, reaction (7), an additional steric argument should be considered: the electron density at the fluorine atoms gives rise to shielding. This may hinder the trajectory of an incoming radical. The comparison of the behavior of DMSO-F$_6$ and of Langlois’ reagent suggests that the replacement of a single CF$_3$ group in DMSO-F$_6$ fully reconstitutes the reactivity lost due to the perfluorination of native DMSO. However, whether this effect is mostly electronic in nature (e.g., anionic vs. neutral) or whether it also features a (pronounced) steric component cannot be deduced from the data at hand.

**Conclusions**

In analogy to the oxidative activation of DMSO with HO$^-$ providing H$_2$C, we explored the feasibility of using DMSO-F$_6$ as a precursor to F$_3$C. Pulse-radiolysis studies in conjunction to laboratory experiments corroborated that DMSO-F$_6$ undergoes a rapid reaction with HO$^-$ with $k_F = (0.6 - 2.5) \times 10^9$ M$^{-1}$ s$^{-1}$, followed by a fragmentation reaction to furnish F$_3$C. In comparison to other commercially available precursors (Langlois’ reagent, trifluoroacetate), DMSO-F$_6$ proved stable, easier to handle and overall more robust and therefore, is well suited for time-resolved kinetics studies of F$_3$C. The major caveat is the requirement for its laboratory synthesis and hitherto time-consuming purification.

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**

1. (a) J. O. Kang, K. S. Gallagher and G. Cohen, *Arch. Biochem. Biophys.*, 1993, 306, 178–182; (b) K. Kawai, Y.-S. Li, M.-F. Song and H. Kasai, *Bioorg. Med. Chem. Lett.*, 2010, 20, 260–265.

2. H. Schönherr and T. Cernak, *Angew. Chem., Int. Ed.*, 2013, 52, 12256–12262.

3. J. Gui, Q. Zhou, C.-M. Pan, Y. Yabi, A. C. Burns, M. R. Collins, M. A. Ornelas, Y. Ishihara and P. S. Baran, *J. Am. Chem. Soc.*, 2014, 136, 4853–4856.

4. R. Caporaso, S. Manna, S. Zinken, A. R. Kochnev, E. R. Lukyanenko, A. V. Kurkin and A. P. Antonchick, *Chem. Commun.*, 2016, 52, 12486–12489.

5. C. Hansch, A. Leo and D. Hoekmann, *QSAR: Volume 2: Hydrophobic, Electronic, and Steric Constants*, American Chemical Society, Washington DC, 1995.

6. K. Müller, C. Faeh and F. Diederich, *Science*, 2017, 317, 1881–1886.

7. A. Studer, *Angew. Chem., Int. Ed.*, 2012, 51, 8950–8958.

8. (a) J. W. Beatty, J. J. Douglas, K. P. Cole and C. R. J. Stephenson, *Nat. Commun.*, 2015, 6, 7919; (b) N. Kamigata, T. Fukushima and M. Yoshida, *Chem.
Paper

Let., 1990, 19, 649–650; (c) Y. Ouyang, X.-H. Xu and F.-L. Qing, Angew. Chem., Int. Ed., 2018, 57, 6926–6929.
9 Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, Nature, 2012, 492, 95–99.
10 K. Matcha and A. P. Antonchick, Angew. Chem., Int. Ed., 2014, 53, 11960–11964.
11 A. Henglein, W. Schnabel and J. Wendenburg, Einführung in die Strahlenchemie, Verlag Chemie GmbH, Weinheim, 1969.
12 (a) G. Bullock and R. Cooper, Trans. Faraday Soc., 1970, 66, 2055–2064; (b) N. Santschi and T. Nauser, J. Fluorine Chem., 2017, 203, 218–222.
13 G. Jander and E. Blasius, Lehrbuch der analytischen und präparativen anorganischen Chemie, S. Hirzel Verlag, Stuttgart, 1969.
14 (a) From dimethyl sulfite: D. T. Sauer and J. M. Shreeve, J. Fluorine Chem., 1971/72, 1, 1–11; (b) P. Maruthamuthu and S. Steenken, J. Fluorine Chem., 1999, 64, 2873–2876.
15 A similar protocol from thionyl fluoride, see: N. Patel and R. Kirchmeier, Inorg. Chem., 1992, 31, 2537–2540.
16 W. M. Haney, CRC Handbook of Chemistry and Physics, CRC Press/Taylor&Francis, Boca Raton, Florida, 97th edn, 2016.
17 H. Shiraishi, G. V. Buxton and N. D. Wood, Int. J. Radiat. Appl. Instrum., Part C. Radiat. Phys. Chem., 1989, 33, 519–522.
18 (a) M. A. J. Rodgers, D. C. Foyt and Z. A. Zimek, Radiat. Res., 1978, 75, 296–304; (b) A. Horvath, O. Horvath and K. L. Stevenson, J. Photochem. Photobiol., A, 1992, 68, 155–163.
19 (a) A. M. Koulkes-Puvo, B. D. Michael and E. J. Hart, Int. J. Radiat. Phys. Chem., 1971, 3, 333–344; (b) D. Razem and W. H. Hamill, J. Phys. Chem., 1977, 81, 1625–1631.
20 A. J. Elliot, Radiat. Phys. Chem., 1989, 34, 753–758.
21 (a) W. N. Perera and G. Hefter, Inorg. Chem., 2003, 42, 5917–5923; (b) J. J. Alexander and H. B. Gray, J. Am. Chem. Soc., 1968, 90, 4260–4271.
22 (a) R. L. Willson, C. L. Greenstock, G. E. Adams, R. Wageman and L. M. Dorfman, Int. J. Radiat. Phys. Chem., 1971, 3, 211–220; (b) W. L. Waltz, S. S. Akhtar and R. L. Eager, Can. J. Chem., 1973, 51, 2525–2529.
23 (a) C. L. Crawford, M. R. Gholami, S. L. Roberts and R. J. Hanrahan, Radiat. Phys. Chem., 1992, 40, 205–212;
24 (b) N. Selvarajan and N. V. Raghavan, J. Chem. Soc., Chem. Commun., 1980, 336–337.
25 B. H. Milosavljevic and J. A. LaVerne, J. Phys. Chem. A, 2005, 109, 165–168.
26 R. H. Schuler, A. L. Hartzell and B. Behar, J. Phys. Chem., 1981, 85, 192–199.
27 R. H. Schuler, L. K. Patterson and E. Janata, J. Phys. Chem., 1980, 84, 2088–2089.
28 U. K. Klanning and T. Wolff, Ber. Bunsenges. Phys. Chem., 1985, 89, 243–245.
29 (a) J. O. Kang, K. S. Gallagher and G. Cohen, Arch. Biochem. Biophys., 1993, 306, 178–183; (b) K. Kawai, Y.-S. Li, M.-F. Song and H. Kasai, Bioorg. Med. Chem. Lett., 2010, 20, 260–265.
30 D. O’Hagan, Chem. Soc. Rev., 2008, 37, 308–319.
31 K. Brace, C. Combellas, M. Delamar, A. Fritsch, E. Kanoufi, M. E. R. Shanahan and A. Thiébault, Chem. Commun., 1996, 403–404.
32 D. Veltwisch, E. Janata and K. D. Asmus, J. Chem. Soc., Perkin Trans. 2, 1980, 146–153.
33 P. Maruthamuthu, S. Padmaja and R. E. Huie, Int. J. Chem. Kinet., 1995, 27, 605–612.
34 N. Santschi and T. Nauser, ChemPhysChem, 2017, 18, 2973–2976.
35 T. Nauser and J. Gebicki, Arch. Biochem. Biophys., 2017, 633, 118–123.
36 F. De Vleeschouwer, V. Van Speybroeck, M. Waroquier, P. Geerlings and F. De Proft, Org. Lett., 2007, 9, 2721–2724.
37 R. E. Huie, D. Brault and P. Neta, Chem.-Biol. Interact., 1987, 62, 227–235.
38 (a) X. Shen, J. Lind, T. E. Eriksen and G. Merenyi, J. Phys. Chem., 1989, 93, 553–557; (b) P. Neta, R. E. Huie, P. Maruthamuthu and S. Steenken, J. Phys. Chem., 1989, 93, 7654–7659.
39 R. Sander, Atmos. Chem. Phys., 2015, 15, 4399–4391.
40 (a) A. Sauer, H. Cohen and D. Meyerstein, Inorg. Chem., 1989, 28, 2511–2512; (b) J. K. Thomas, J. Phys. Chem., 1967, 71, 1919–1925; (c) M. Moenig, D. Bahmann and K. D. Asmus, Chem.-Biol. Interact., 1983, 47, 15–27.
41 R. Herscu-Klusa, A. Masarwa, M. Sapheir, H. Cohen and D. Meyerstein, Chem. – Eur. J., 2008, 14, 5880–5889.