Profiling the Oxidative Activation of DMSO-F_6 by Pulse Radiolysis and Translational Potential for Radical C–H Trifluoromethylation

N. Santschi*[a], B. J. Jelier [a], S. Stähelin [a], T. Nauser *[a]

[a]*Eidgenössische Technische Hochschule (ETH) Zürich, Department of Chemistry and Applied Biosciences, Vladimir-Prelog-Weg 1/2, 8093 Zürich (Switzerland)*

E-mail. nicosantschi@gmail.ch; nauser@inorg.chem.ethz.ch
Tel.: +41 44 632 28 73

Supporting Information

General Considerations

A. Materials and Synthetic Methods

All synthetic manipulations were performed under the exclusion of moisture and oxygen using appropriate Schlenk techniques with oven dried glassware under an atmosphere of argon. All starting materials are commercially available and were purchased from Sigma Aldrich or ABCR (Germany) unless otherwise noted.

B. Analytical Methods

Mass spectra were recorded on an Agilent 6890 GC system with a 5975c VL MSD with a triple-axis detector (EI = 70 eV). The experiments were acquired with an injection port 100:1 split ratio mode with the stated injection port temperatures on an Agilent HP-5MS 5% Phenyl Methyl Silox column with dimensions 30m x 250 µm x 0.25 µm using He as a carrier gas. The MSD transfer line was set at 280 °C. NMR spectra were recorded on a Bruker DPX-300 and DPX-400 instruments operating at the denoted spectrometer frequency given in MHz for the specified nucleus. The ^{1}H and ^{13}C chemical shifts are referred to TMS and calibrated with the residual solvent peak. For ^{19}F NMR spectra, $CFCl_3$ was used as an internal standard and the IUPAC specified isotopologue $^{12}CF(^{35}Cl_2)(^{37}Cl)$ was set to 0.261 ppm in $CDCl_3$. The chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). High resolution mass spectra were measured by the MS-service of the "Laboratorium für Organische Chemie der ETH Zürich". Values are given as m/z and the intensity I% of the base peak. IR spectra were recorded on a Thermo Fischer Scientific Nicolet 6700 FTIR equipped with a PIKE technologies GladiATRTM or on a Perkin-Elmer BX II using ATR FT-IR technology and are reported as absorption maxima in cm^{-1}.

C. Pulse Radiolysis

Pulse radiolysis experiments were carried out at the *Rapid Kinetics Facility* at ETH Zürich using equipment featuring a quartz cell with an optical path length $L = 6$ cm.[1] Dosimetry was conducted with ferrocyanide.[2]

Density of DMSO-F_6

A series of volumes of DMSO-F_6 (Material B) were measured out with a 1 mL plastic syringe and the corresponding weights determined gravimetrically. Two separate measurement series were used for the determination of the density, ρ(DMSO-F_6) = 1.42 g / mL.

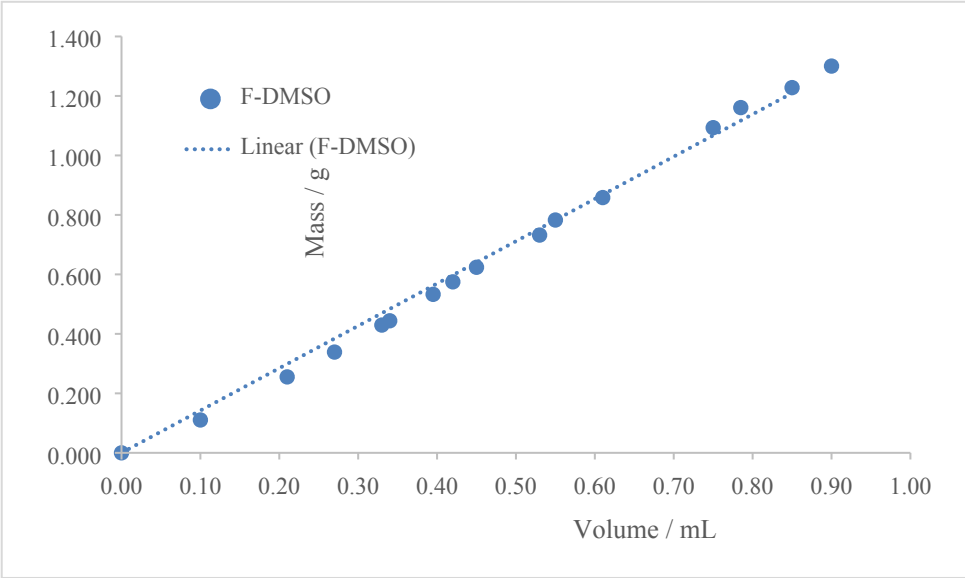
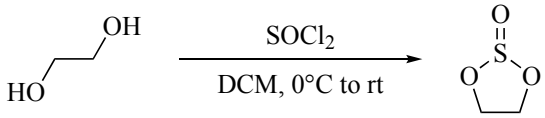


Figure S1. Determination of ρ(DMSO-F_6) = 1.42 g / mL by weighing of specific volumes.

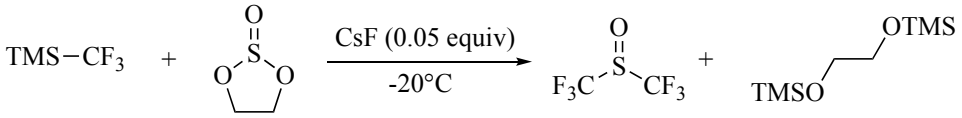
Ethylene sulfite



Adapted from D. Katayev, V. Matoušek, R. Koller, A. Togni. Lewis Acid Catalyzed Synthesis of α-Trifluoromethyl Esters and Lactones by Electrophilic Trifluoromethylation. *Org. Lett.* **2015,** *17*, 5898-5901:

A 500 ml three-neck round bottom flask equipped with a magnetic stirring bar and a 100-ml dropping funnel was charged with anhydrous ethylene glycol (11.30 g, 0.18 mol, 1.0 equiv) and anhydrous dichloromethane (80 ml) under N_2 atmosphere. The effluent gas stream was sent through an impinging bottle filled with aqueous NaOH for neutralization purposes as during the reaction HCl is produced as byproduct. The mixture was then cooled to 0 °C in an ice bath. The dropping funnel was charged with thionyl chloride (16.0 ml, 26.24 g, 0.22 mol, 1.2 equiv) and dichlormethane (20 ml). The thionyl chloride solution was added dropwise to the ethylene glycol solution under vigorous stirring. After complete addition, the mixture was stirred for additional 5 h, after which the solvent was removed in vacuo and the product was purified by distillation (18 mbar, 48 °C) to yield ethylene sulfite (17.07 g, 0.16 mol, 87%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (dm, J = 174 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 67.47 (d, J = 3.7 Hz). IR (neat) 2976, 2909, 1467, 1192, 1121, 1000, 906, 738, 663, 612 cm^{-1}. Elemental analysis percentage by weight calculated [C] 22.22%, [H] 3.73%; found [C] 22.04%, [H] 3.88%.

DMSO-F_6 with CsF initiator neat



CsF was initially dried at 200 °C at 1 × 10^{-2} mbar for 12 h and then backfilled with dry argon and placed in a glovebox. In a glovebox, a 500-mL oven-dried Ace® Glass pressure vessel was charged with anhydrous CsF (978.7 mg, 6.44 mmol, 0.05 equiv) and closed with a septum and placed in a fumehood. Ethylene sulfite (14.09 g, 130.33 mmol, 1.0 equiv) was added under Ar atmosphere and the mixture was cooled to -20 °C by means of externally controlled circulator. Trimethyl(trifluoromethyl)silane (38.20 g, 268.68 mmol, 2.1 equiv) was added and the septum was exchanged with a threaded pTFE plug. The flask was sealed and the contents were stirred -20 °C for 1 h, allowed to warm to RT and stirred for an additional 12 h behind a blast shield. To prevent loss of the volatile DMSO-F_6 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, collecting the fraction with a b.p. of 34 °C at 760 mmHg to furnish hexafluorodimethylsulfoxide (DMSO-F_6) as a colourless, volatile liquid as a colorless liquid with ≥ 95% purity (16.63 g, 89.37 mmol, 69%). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 124.87 (q, J = 338 Hz). **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 298 K, int. ref. to 2.5% w/w $CFCl_3$) δ -68.27 (s) (previously reported at 64.5 ppm). **IR** (ATR-diamond, cm^{-1}): 942, 955, 1100, 1119, 1182, 1244. GC-MS (EI, 70 eV) and IR were also previously reported by Shreeve and are consistent with our observations

Spectroscopic Data for DMSO-F_6

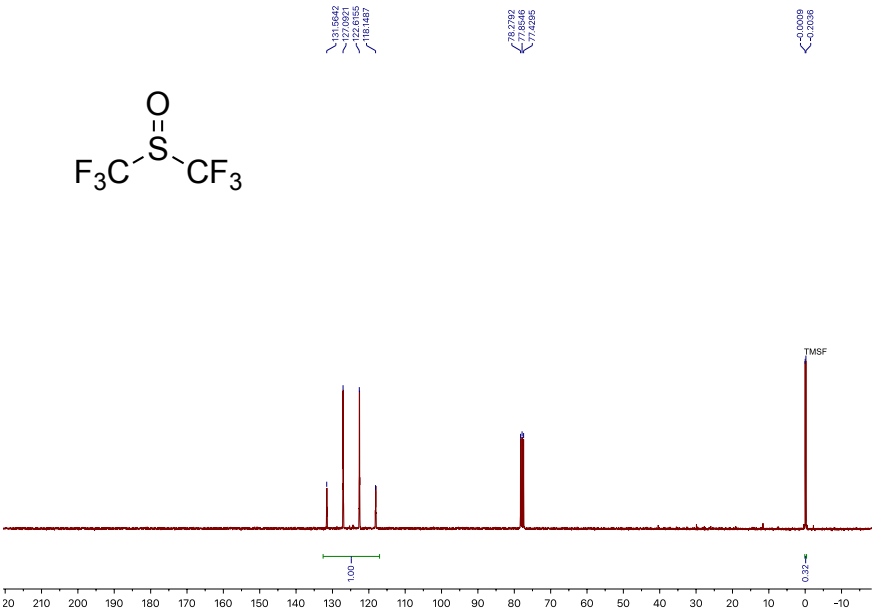


Figure S2. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) Spectra of DMSO-F_6 with residual TMSF.

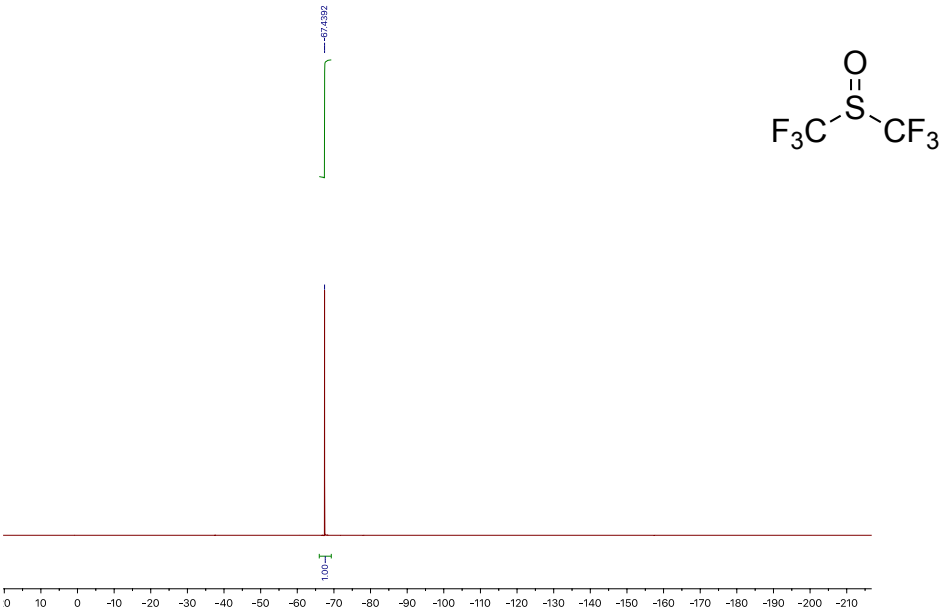


Figure S3. ^{19}F NMR (282 MHz, $CDCl_3$, 298 K) spectra of DMSO-F_6 with 2.5% w/w $CFCl_3$ as internal standard calibrated to neat $CFCl_3$.

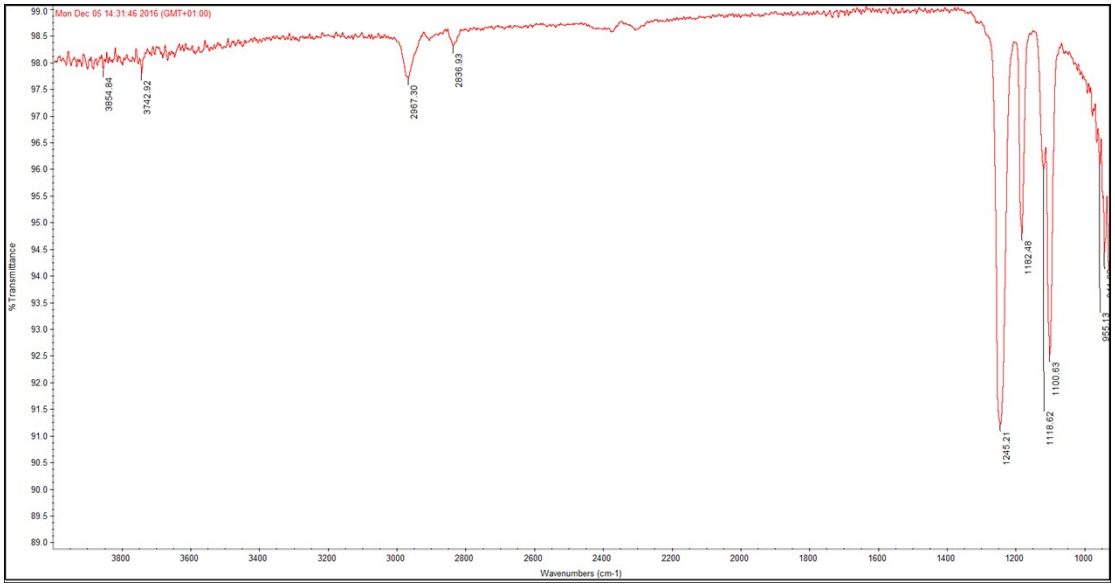


Figure S4. FT-IR (ATR-Diamond, cm^{-1}) spectra of neat DMSO-F_6

Reaction of DMSO-F_6 with $HO^{\bullet}$

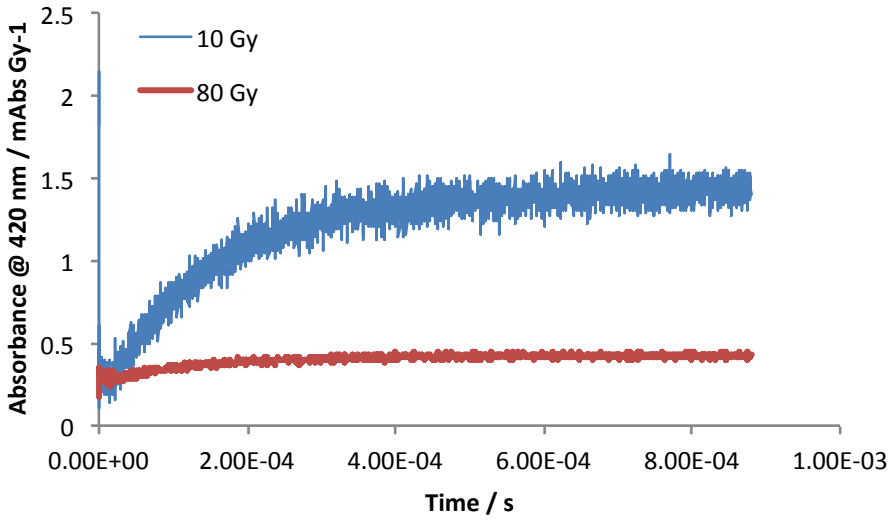


Figure S5. Dose-dependent oxidation kinetics of $Fe^{II}(CN)_6^{4-}$ at longer times for an unbuffered, N_2O saturated solution of $K_4Fe(CN)_6$ (285 µM) and DMSO-F_6 (14.5 µM). The initial absorbance (4-8 µs) is dose-independent and reflects the branching ratio of $HO^{\bullet}$ between $Fe^{II}(CN)_6^{4-}$ and DMSO-F_6.

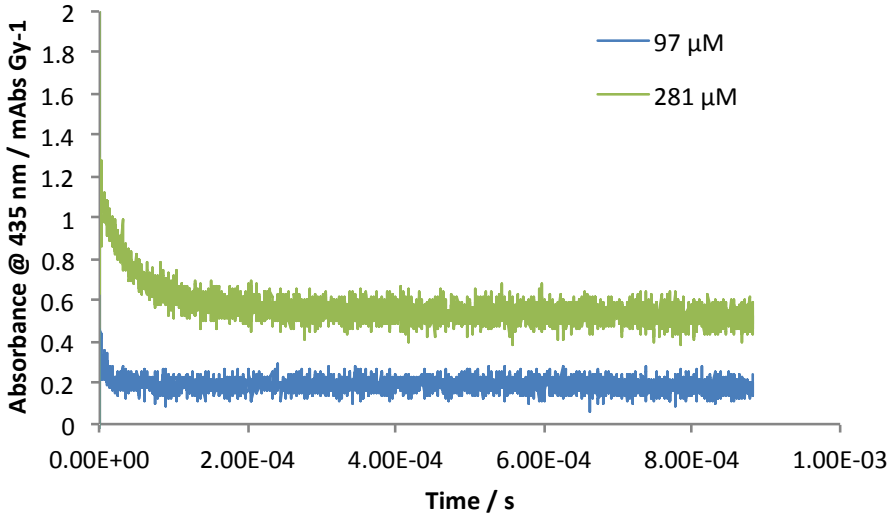


Figure S6. Concentration-dependent decay kinetics of $Ir^{IV}Cl_6^{2-}$ at longer times for unbuffered, N_2O saturated solutions of K_3IrCl_6 and DMSO-F_6 (14.5 µM). The initial absorbance (4-8 µs) reflects the branching ratio of $HO^{\bullet}$ between $Ir^{III}Cl_6^{3-}$ and DMSO-F_6.

$ABTS^{2-}$ as indicator for the reaction mechanism

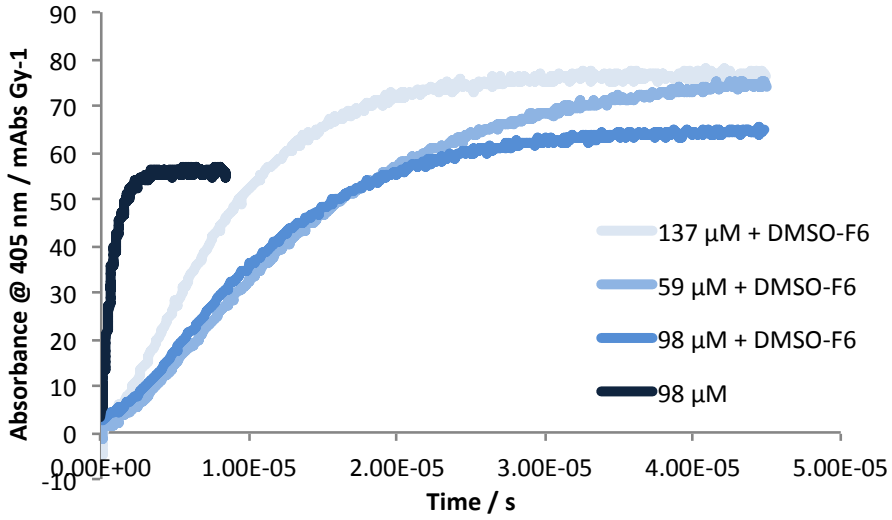


Figure S7. Systematic increase in end-level absorbance at 405 nm in $ABTS^{2-}$ oxidation reactions likely due to an artifact. Experiments were performed in order from dark colors to lighter ones.

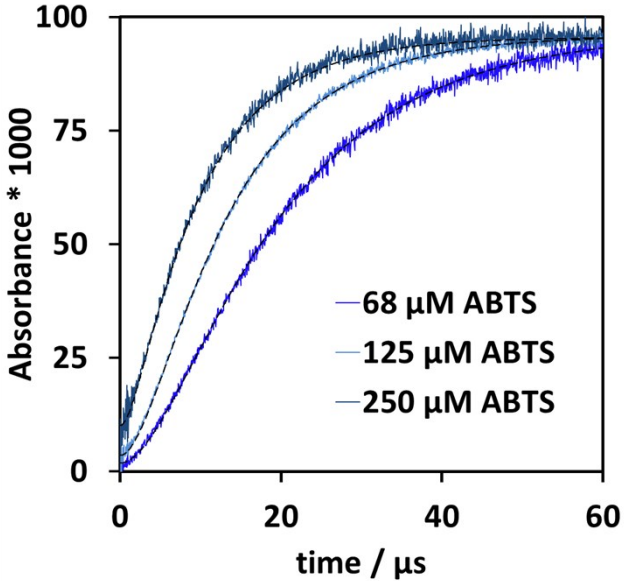
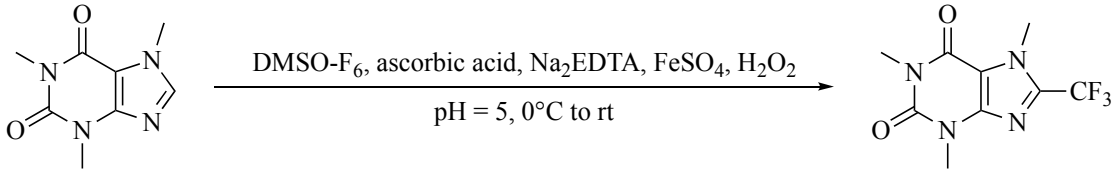


Figure S8. The systematic increase in end-level was not observed in the controls. The end-level was the same within the accuracy of the measurement.

Oxidative functionalization of caffeine[3]



Two 5 ml vials equipped with magnetic stirring bars were charged with caffeine (46.6 mg, 0.24 mmol, 1.0 equiv.), ascorbic acid (84.5 mg, 0.48 mmol, 2.0 equiv.) and

$Na_2EDTA{\cdot}2H_2O$ (44.8 mg, 0.12 mmol. 0.5 equiv.). Phosphate buffer solution consisting of NaH_2PO_4 and Na_2HPO_4 (0.1 ml, pH = 5.0, strength = 1 M) and water (0.9 ml) were added, followed by $FeSO_4{\cdot}7H_2O$ (55.6 mg, 0.20 mmol, 0.8 equiv.). The vials were crimped closed and the two yellow colored solutions were cooled to 0°C in an ice bath. To one of the vials, DMSO (0.17 ml, 187.0 mg, 2.39 mmol, 10.0 equiv.) and to the other DMSO-F_6 (0.14 ml, 274.4 mg, 1.47 mmol, 6.1 equiv.) was added, immediately followed by dropwise addition of H_2O_2 (30 wt% in H_2O, 0.125 ml, 138.75 mg, 1.22 mmol, 5.1 equiv.). In the case of DMSO-F_6, the color of the solution turned from yellow to brown. Both mixtures were stirred for further 30 min at ambient temperature. Afterwards, the organic layer was extracted with EtOAc (2 × 2 ml) and the combined organic layers were analyzed by GC-MS affording a 15% conversion to trifluoromethylated-caffeine.

References

[1] T. Nauser, G. Casi, W. H. Koppenol, C. Schöneich *J. Phys. Chem.* 2008, **112**, 15034-15044.

[2] R. H. Schuler, L. K. Patterson, E. Janata *J. Phys. Chem.* 1980, **84**, 2088-2089.

[3] 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.