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# A Continuous Flow Generator of Organic Hypochlorites for the Neutralization of Chemical Warfare Agent Simulants with Frugal Resources

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Herein is reported the development of a continuous flow generator that produces highly reactive organic hypochlorites for the chemical neutralization of sulfur-based chemical warfare agent (CWA) simulants. The generator relies on widely available, cheap and common chemicals that can be sourced from household products (such as bleach). This work relates to the development of cost-effective, low footprint and operator-friendly protocols for the oxidative neutralization of sulfur-based CWA “mustard gas” (aka Yperite or **HD**), a noxious compound belonging to the vesicant class of CWAs. A standard decontamination protocol relies on bleach (aqueous sodium hypochlorite) as a convenient oxidative neutralization measure, though the high lipophilicity of **HD** causes the formation of micelles and hence superficial and/or unselective detoxification. This work illustrates how aqueous bleach can be rapidly upgraded to more lipophilic organic hypochlorites (**MeOCl**, **EtOCl**, **iPrOCl** and **tBuOCl**) with low environmental footprint resources and equipment. The latter are demonstrated to readily oxidize simulants of **HD** (i.e. 2-chloroethyl ethyl sulfide (**CEES**) and 2-chloroethyl phenyl sulfide (**CEPS**)) to the corresponding sulfoxides (**CEESO** and **CEPSO**, respectively). With a fine tuning of the reaction conditions, the oxidation is nearly instantaneous and prevents the formation of toxic overoxidized sulfones, though organic hypochlorites also contribute to the innocuous chlorination of the neutralized sulfoxide. The assets of continuous flow technology enable to merge both the upstream hypochlorite generator and the downstream neutralization setup to provide a safe, compact and mobile setup that relies only on stable, widely available chemicals. Some aspects of the reactivity of organic hypochlorites with model sulfur compounds are also discussed by means of computational chemistry (DFT).

## Introduction

The wide diversity of chemical processes can be labelled as *constructive* processes and aim at increasing the molecular diversity and the added value of compounds, starting from widely available and affordable building blocks. For instance, the manufacture of pharmaceutical active ingredients clearly fits in such definition, where complex reaction sequences or costly catalysts and reagents are acceptable, as long as the added value of the final target leaves room for comfortable margins. [REF] *Destructive* processes are different in essence. Regardless of the end application, the latter aim at the physical or chemical destruction of molecular entities to annihilate safety concerns through a chemical modification. [REF] In the

and catalysts, but also on robust and straightforward process conditions that are amenable to chemical threats of high societal impact. [REF]

The design of affordable and robust conditions is not an easy task. [REF] The affordability of a process comes mostly from the chemicals (ideally off-the-convenience-store) and the operating conditions (ideally room temperature and low pressure), as well as from the process technology that is relied on. The robustness of a process results from the combination of a thorough understanding of the mechanisms at stakes with process technologies that enable steady process conditions. Besides, within the specific context of the neutralization of CWAs, additional important criteria include a potential mobility and high operational safety to make it deployable anywhere with minimal resources. [REF]

The development of new neutralization protocols on CWAs simulants (as well as on actual CWAs with military clearance) attracts an increasing attention from the Chemical and Chemical Engineering communities, as witnessed by an increasing number of reviews and original articles over the past 10 years. [REF] This is somehow paradoxical, yet easily justifiable with the current background threat of terror attacks against civilians in the Middle East as well as in the Western countries. Indeed, the inception of the Chemical Weapons Convention (CWC) bans since 1993 the possession, manufacture and use of CWAs and all of their precursors. A CWA is defined as “a chemical (gas, liquid or solid) which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals”. [REF] CWAs are considered as Weapons of Mass Destruction (WMDs) along with biological agents and nuclear weapons (Figure 1). [REF] The CWC was ratified in 1997 by over 193 countries, although large inventories of CWAs are still

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specific context of the chemical destruction of Chemical Warfare Agents (CWAs), added-value (in the sense of their production costs and not for their end application) molecular entities with an acute toxicity are neutralized through chemical modification of their backbone toward lower value, lower toxicity entities that can be next safely handled for disposal. [REF] It comes without saying that such processes inherently come with a reverse economical scheme. An ideal destructive process would therefore rely not only on affordable reagents

stockpiled across the world. For instance, the USA aimed at the complete destruction of its reminiscent inventory by 2023. Besides the CWC, the European Union (EU) adopted coercive measures in 2018 against the use of chemical weapons in a strong response to the use of CWAs against civilians in the Middle-East. Just in Syria, there have been no less than 336 reported incidents involving CWAs at least credibly substantiated between 2012-2018 according to the Global Policy Public Institute (GPPI). [REF] Besides, the emergence of a smaller scale, targeted use of CWAs such as in Salisbury (UK, 2018) or more recently with the poisoning of Aleksey Navalnyj in 2021, justifies the investment of resources and the development of research programs aiming at the detection and/or the chemical neutralization of CWAs [REF].

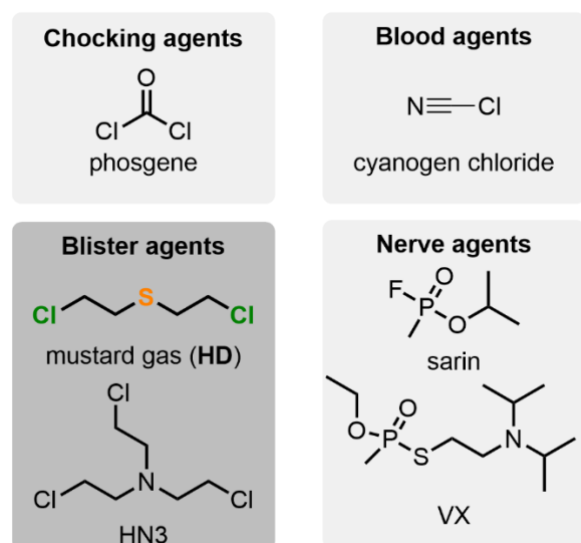


Fig. 1. Representative examples of CWAs. [REF]

Mustard gas (**HD**, 1-chloro-2-[(2-chloroethyl)sulfanyl]ethane, CAS 505-60-2) is a viscous liquid with vesicant (blistering) properties that causes severe, yet delayed, damages to the eyes, skin, and respiratory tract. Besides its vesicant properties, **HD** also damages cells as a strong alkylating agent and can also affect the nervous system upon acute exposure. While the most common destruction of **HD** is through incineration, 3 main chemical neutralization protocols are reported in the literature (oxidation, hydrolysis and dehydrohalogenation). Most labs involved in research programs aiming at neutralizing **HD** rely on simulants to mitigate the risk of exposure. Simulants share with the parent **HD** specific inherent features, *i.e.* the ability to form a strongly alkylating episulfonium species through the neighboring interaction of a donor  $n_s$  lone pair and an acceptor  $\sigma^*_{C-Cl}$  (Figure 2). The closest simulant of **HD** is hemi mustard **CEES** (2-chloroethyl ethyl sulfide, CAS 693-07-2), which is commercially available. **CEPS** (2-chloroethyl phenyl sulfide, CAS 5535-49-9) is also often relied on, despite not being strictly speaking a simulant of **HD**, yet it shares a common 2-chloroethyl limb and has the advantage of being UV active for LC monitoring. **CEES** and **CEPS** are not considered as CWAs, yet both are highly toxic and severe

vesicants. Other molecular structures can be used as less noxious simulants, as we reported in a recent article. [REF]

Among the neutralization methods, the oxidative neutralization of **HD** (or its simulants **CEES** or **CEPS**) toward the corresponding sulfoxide **HDO** (**CEESO** or **CEPSO**) is by far the most represented in the literature. Through a selective oxidation to a sulfoxide, the formation of the episulfonium species is disrupted, hence suppressing most of the toxicity profile of the corresponding structure. It is however critical to ensure a selective oxidation and to avoid an overoxidation to the corresponding sulfones (**HDO<sub>2</sub>**, **CEESO<sub>2</sub>** or **CEPSO<sub>2</sub>**), the latter having an acute toxicity as precursors of potentially strong Michael acceptors (vinyl sulfone derivatives **CEVSO<sub>2</sub>**, **EVSO<sub>2</sub>** or **PVSO<sub>2</sub>**) (Figure 2).

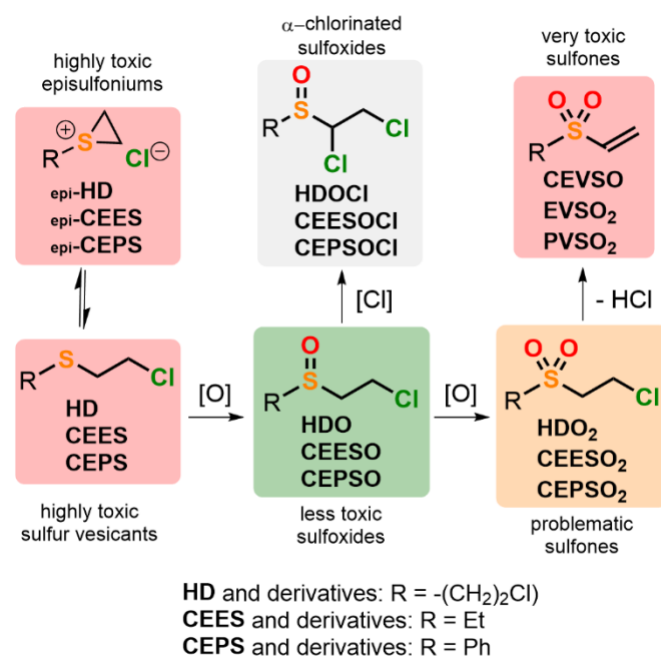
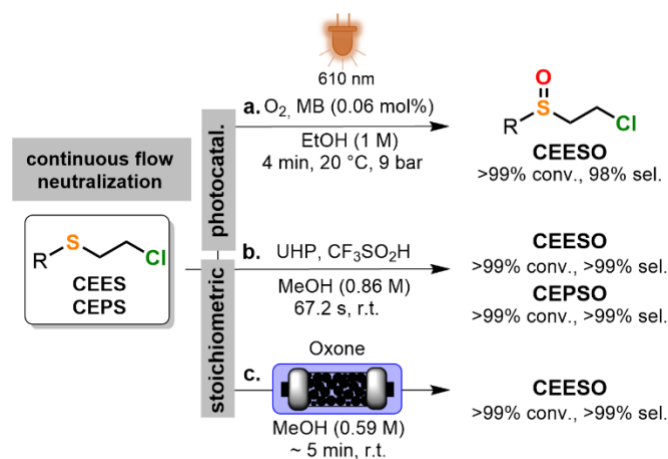


Fig. 2. Reactivity of **HD** and common simulants under oxidative neutralization conditions

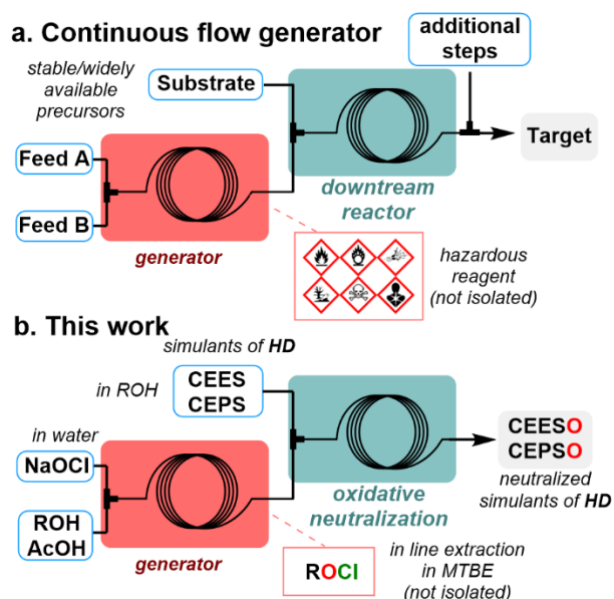
Among oxidative neutralization protocols, photocatalytic processes have attracted a lot of attention (Figure 3a). [REF] A large array of homogeneous and heterogeneous photosensitizers was developed, among which Zeolites, MOFs and organic photosensitizers (methylene blue, rose Bengal, porphyrins, riboflavin tetraacetate or BODIPY to name a few), for the generation of reactive oxygen species (ROS, such as singlet oxygen) from oxygen that would selectively oxidize mustard gas and/or its simulants to the corresponding sulfoxides. [REF] The synergistic combination of continuous flow process technology with photocatalysis is now well established, and efficient photocatalytic continuous flow processes for the neutralization of CWAs were therefore reported. [REF] Using our expertise in such processes, our group reported in 2020 a low footprint continuous flow setup that integrates a singlet oxygen photogenerator and exploits its oxidative power to selectively neutralize **CEES**. [REF]

Stoichiometric oxidizers are also reported in the literature (Figure 3a). Unlike ROS-based process, these processes inherently bear the disadvantage of not being catalytic, hence requiring a large supply of oxidizers and generating significant waste (Figure 3b). They, however, do not require the access to specific light sources and the complex setups that come along. The ideal case scenario for such processes relies on affordable, widely available and non-toxic oxidizers with a high atom economy. Among stoichiometric oxidizers, the most common decontamination protocol used by Emergency Responders or Armed Forces relies on aqueous solutions of hypochlorites (e.g. 3-5% commercial bleach as well as chlorinated lime). [REF] A military report from 1969 disclosed that the oxidation of **HD** with mineral hypochlorites in aqueous solutions leads to the formation of a mixture of the corresponding sulfoxide, sulfone, as well as a diversity of elimination and chlorination products mostly derived from the sulfoxide (**HDOCl**, **CEESOCI** or **CEPSOCI**). [REF] The aggressive nature of bleach solution also raises significant corrosion issues in the decontamination of metal-based hardware. The reaction of **HD** with bleach is also described as violently exothermic and very sensitive to concentration and pH. [REF] Above all these issues, the high lipophilicity of **HD** often leads to micelle formation and, hence, superficial oxidative neutralization of **HD** droplets. [REF] Other stoichiometric chlorine-based oxidants, including *N,N*-dichlorourethane and *N,N*-dichlorovaleramide, were reported by Mazumder for the sulfoxidation of **HD** in batch, yet they suffer from a poor atom-economy. [REF] The authors also reported the extensive formation of 2-chloro-1,2-dichloroethyl sulfoxide (**HDOCl**) through a competitive chlorination of **HDO**; **HDOCl** can therefore be also considered as a neutralized form of **HD**, as long as it does not lead to the formation of strong Michael acceptors. *N,N*-dichlorovaleramide was also reported as an effective oxidizer for the oxidative neutralization of **VX** and related simulants. [REF] In 2018, Smolkin and Colombus reported an electrophilic iodine reagent (*N*-iodosuccinimide, **NIS**) as a fast and selective oxidative neutralization cocktail for **HD** and simulants. [REF] *N*-methyl-1,4-diazabicyclo[2.2.2]octane fluoride (**Me-DABCOF**) was studied by Fridkin and Zafrani for the oxidative neutralization of **HD** and **VX**. [REF] Other more typical oxidizers were reported, in combination with innovative process technologies. For instance, Legros et al. reported a series of continuous flow processes using stoichiometric oxidizers under homogeneous or heterogeneous conditions (Figure 3b,c): (a) a first report in 2017 where the authors disclosed a continuous flow setup integrated with in-line low field NMR and relying on the hydrogen peroxide/urea complex (UHP) as oxidizer in methanol in the presence of methanesulfonic acid [REF] and (b) a more recent report in 2021 relying on Oxone ( $\text{KHSO}_5$ ) in a packed-bed flow setup. [REF] In both cases, the oxidation of **CEES** afforded selectively the corresponding sulfoxide **CEESO** with a complete conversion in less than 5 min. Despite its effectiveness, their procedure imposes the availability and transportation of explosive, corrosive or at least specialty reagents that can be difficult to source for rapid and large-scale neutralization.



**Fig. 3.** Typical oxidative continuous flow protocols for the chemical neutralization of **HD** and stimulants. (a) Photocatalytic oxidation with singlet oxygen. (b) Stoichiometric oxidizer under homogeneous conditions. (c) Stoichiometric oxidizer under heterogeneous conditions.

With the increase of restrictive safety and environmental guidelines, the use of unstable, toxic and explosive chemicals is now barely an option in either academic or industrial settings, at least using conventional batch processing. The latter indeed precludes large scale operations with such chemicals and is restricted to discrete amounts under strict safety protocols. Consequently, a range of highly reactive intermediates, yet very useful according to their reactivity profiles, becomes inaccessible to the Chemist. [REF] The emergence of continuous flow strategies in this context, and in particular the development of continuous flow Chemical Generators, has emerged over the last decade as a game changer when unstable chemicals are at stakes. The concept of Chemical Generator, which was extensively documented by Kappe and coworkers, [REF] is summarized in Figure 4a. A suitable chemical generator for the preparation of lower alkyl hypochlorous esters relies on stable, low toxicity and widely available chemicals that are reacted under continuous flow conditions to access dangerous chemicals of limited stability. As is, this generator does not mitigate the risk associated with the downstream handling of dangerous chemicals (here lower alkyl hypochlorous esters), since downstream collection would require batch processing, hence exposing the operator to high chemical hazards. Connecting the upstream generator to a downstream unit that immediately consumes organic hypochlorites (aka reaction concatenation/telescoping) contributes significantly to reducing operation and exposure hazards. Based on our recently published work on the electrophilic amination with  $\alpha$ -chloro nitrosocycloalkyl derivatives, the preparation and use of **tBuOCl** and other organic hypochlorites was investigated.



**Fig. 4.** (a) General concept of chemical generator under continuous flow conditions. (b) This work: development of an upstream chemical generator for the safe preparation of discrete amounts of lower alkyl hypochlorous esters.

A solution was sought for addressing the oxidative neutralization of **HD** simulants, including **CEES** and **CEPS**, as well as other relevant thioethers, using frugal and widely available resources with a compact and safe setup. The high lipophilicity of **CEES** and **CEPS** was circumvented through the use of lipophilic alkyl hypochlorites (**MeOCl**, **EtOCl**, **iPrOCl** and **tBuOCl**). Given the instability of the latter, the opportunity to exploit the assets of continuous flow process technology was investigated for the design of an upstream hypochlorite generator. The hypochlorite generator is fed with widely available, stable and low toxicity chemicals, including common lower alcohols (**MeOH**, **EtOH**, **iPrOH**, **tBuOH**), acetic acid and an aqueous solution of sodium hypochlorite. The corresponding lipophilic alkyl hypochlorites are then subjected to in-line extraction and liquid-liquid membrane separation, providing a neat organic stream (MTBE) of hypochlorites directly usable for the sulfoxidation of **HD** simulants and other thioethers. The upstream generator is directly concatenated with the downstream oxidation, also featuring in-line NMR analysis. Besides, this work documents a thorough mechanistic investigation, combining experiments and computational chemistry, as well as an advanced optimization of the process conditions. Once validated at the microfluidic scale, the process is transposed to a mesofluidic commercial setup to validate its utilization at larger scales. This work discloses a simple, yet elegant and robust protocol that provides consistent neutralization with high selectivity yet relying on simple, non-toxic, cheap and widely available chemicals. The setup is engineered to be functional with frugal technology requirements and has a low footprint, which makes it an ideal solution for rapid and efficient deployment.

## Experimental section

### General information

Conversion, selectivity and yield were determined by Gas Chromatography coupled to Flame Ionization Detection (GC-FID) or Mass Spectrometry (GC-MS) or by High Performance Liquid Chromatography coupled to Diode-Array Detection (HPLC-DAD) or coupled with Mass Spectrometry (LC-MS). GC and HPLC conversions and yields were determined using external calibration curves established with commercial standards (2-chloroethylethyl sulfide, 2-chloroethylethyl sulfone, ethyl vinyl sulfide, ethyl vinyl sulfone, methyl vinyl sulfone, methyl phenyl sulfide, xxxxxxxx) or with synthesized reference samples following reported procedures (see Supporting Information, Section XXXX for experimental procedures). The selectivity toward the sulfoxide is defined as the ratio between the area% of the sulfoxide and the sum of the area% of all oxidation products. The neutralization selectivity is defined as the ratio between the sum of the area% of all sulfoxide derivatives (including the chlorinated sulfoxides) and sum of the area% of all oxidation products. The neutralization selectivity is defined only for the most favorable cases. Structural identity was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy (400 MHz Bruker Avance spectrometer), by LC-MS or GC-MS (Supporting Information, Section XXXX). Thioanisole (**1a**), methyl phenyl sulfoxide (**2a**), chloromethyl phenyl sulfoxide (**3a**), methyl phenyl sulfone (**5a**), chloromethyl phenyl sulfone (**6a**), diphenyl sulfide (**1b**), diphenyl sulfoxide (**2b**), diphenyl sulfone (**5b**), dibenzo[b,d]thiophene (**1c**), dibenzo[b,d]thiophene 5-oxide (**2c**), dibenzo[b,d]thiophene 5,5-dioxide (**5c**), dipropyl sulfide (**1d**), dipropyl sulfoxide (**2d**), dipropyl sulfone (**5d**), methanol, ethanol, 2-propanol, *tert*-butanol, MTBE, acetic acid, sodium hypochlorite pentahydrate were purchased from commercial sources and used without additional purification. **CEESO**, **CEPSO** and **CEPSOCl** were prepared according by adapting protocols from the literature. **CAUTION:** 1-chloro-2-(ethylsulfinyl)ethane (**CEES**) and 2-chloroethyl phenyl sulfide (**CEPS**) are highly toxic and severe vesicants. Organic hypochlorites are heat, light and shock sensitive materials. Methyl hypochlorite spontaneously and vigorously decomposes at room temperature. The isolation of **MeOCl**, **EtOCl** and **iPrOCl** should not be attempted. **tBuOCl** can be stored over  $\text{CaCl}_2$  at 4 °C in a brown glass container for several days. Reactor setups involving organic hypochlorites were covered in aluminum foil to prevent light exposure.

### Computations

Computations were performed at the B3LYP/6-311+G\*\* level of theory with empirical dispersion (gd3bj) using the Gaussian 09 package of programs (Revision D.01) with implicit solvation (SMD, methanol). Stationary points were optimized with gradient techniques (tight optimization convergence). Transition states were localized using the Newton-Raphson algorithm, and the nature of the stationary points was determined by analysis of the Hessian matrix. Intrinsic reaction coordinate (IRC) calculations were performed on representative transition states. Cartesian coordinates for representative



stationary points are available in the Supporting Information (section XXXX).

## Experimental setup

### Typical run

**Microfluidic setups.** Microfluidic setups were constructed from PFA tubing (1.58 mm outer diameter, 750  $\mu$ m internal diameter) equipped with PEEK/ETFE connectors and ferrules (IDEX/Upchurch Scientific). Feed and collection lines consisted of PFA (1.58 mm outer diameter, 750  $\mu$ m internal diameter) equipped with PEEK/ETFE connectors and ferrules (IDEX/Upchurch Scientific). Liquid feeds were handled with Chemyx Fusion 6000 syringe pumps (SS syringes equipped with Dupont Kalrez O-rings) or with HPLC pumps (Knauer Asurea equipped with a ceramic head). The temperature was regulated with a Heidolph MR Hei-Tec equipped with a Pt-1000 temperature sensor. Downstream pressure was regulated with back pressure regulators from Zaiput Flow Technologies (BPR-10) or from IDEX/Upchurch Scientific (BPR 75 psi). Liquid-liquid extraction was carried out with a Zaiput Flow Technologies membrane separator (SEP-10, equipped with a 1  $\mu$ m pore hydrophobic membrane). See Supporting Information, section XXXX for details of the microfluidic setups.

**Mesofluidic setup – lab scale.** Lab scale mesofluidic experiments were carried out in a Corning® Advanced-Flow™ Lab Reactor (2.5 mL internal volume glass fluidic modules). Feed and collection lines consisted of PFA tubing (1/8" o.d.) with PFA or SS Swagelok connectors and ferrules. Liquid feeds were handled with Syrris Asia pumps. The process temperature was regulated with a LAUDA Integral XT 280 thermostat. A Zaiput Flow Technologies membrane separator (SEP-10, equipped with a 1  $\mu$ m pore hydrophobic membrane) was utilized for downstream extraction and liquid-liquid separation. Downstream pressure was regulated with a backpressure regulator from Zaiput Flow Technologies (BPR-10). In-line analysis was performed on an in-line benchtop NMR (43 MHz Spinsolve™ 1H NMR spectrometer from Magritek® equipped with a flow-through cell). See Supporting Information, section XXXX for details of the mesofluidic setup.

## Results and Discussion

Various (in)organic hypochlorites were investigated for the oxidation of thioethers [REF] and sodium hypochlorite pentahydrate (NaOCl·5H<sub>2</sub>O) was recently featured for large scale oxidations on model thioethers and other model sulfur-based compounds under homogeneous conditions (CH<sub>3</sub>CN/H<sub>2</sub>O) or as a slurry. [REF] Under these conditions, the formation of the sulfone was reported to a certain extent, as well as  $\alpha$ -chlorinated sulfoxides, the occurrence of which was strongly solvent-, pH- and time-dependent. [REF] Organic lower alkyl hypochlorous esters, such as **tBuOCl** were also reported for accessing sulfoxides. The advantages of using such

hypochlorous esters include the selective formation of the corresponding sulfoxide with barely trace amounts of the sulfone, their lipophilicity as well as their convenient preparation from simple and common lower alcohols.

**MeOCl, EtOCl, *i*PrOCl and **tBuOCl**** are the smallest organic hypochlorites, the synthesis of which typically starts from the corresponding widely available lower alcohols. The first report by Sandmeyer on **MeOCl** dates back to 1885. [REF] **MeOCl** was prepared through the chlorination of a mixture of methanol and sodium hydroxide. A common feature from these lower esters of hypochlorous acid (HClO) is their relative insolubility in water that leads to spontaneous phase separation. Preliminary reports in the literature by Chattarway and Backeberg emphasized that primary and secondary hypochlorites, such as **MeOCl, EtOCl**, as well as the hypochlorous esters of all isomers of propyl alcohol were much less stable than tertiary hypochlorites such as **tBuOCl**. [REF] Sandmeyer original's protocol involved passing Cl<sub>2</sub> gas through a saturated solution of chalk or limestone, and then adding a lower alcohol to the corresponding filtrated solution. Further processing of the hypochlorous ester includes extraction with an organic solvent and sodium carbonate, as well as storage over CaCl<sub>2</sub> in the dark at low temperature. [REF]

Several reports indicate that spontaneous and vigorous decomposition occurs upon standing at room temperature for **MeOCl** and **EtOCl**, yielding the corresponding aldehydes. [REF] Such instability led to several explosions in research laboratories. It is also a significant safety concern at larger scales, where the oxidation of thioether compounds into their corresponding sulfoxides is implemented as a standard protocol for the treatment of waste effluents. An industrial accident that killed three people at the Midland Resource Recovery facility in West Virginia in 2017 was investigated by the US Chemical Safety Board. [REF] The explosion very likely involved the unexpected formation of **MeOCl** with sodium hypochlorite in conjunction with trace amounts of MeOH in a downstream odor neutralization step. Secondary hypochlorous esters are described as more stable. Tertiary hypochlorous esters such as **tBuOCl** are the most stable of the series, yet decomposition occurs upon exposure to intense day light or at higher temperature. Purification of **tBuOCl** can be carried out through careful vacuum distillation, although this is not recommended for safety reasons. Consequently, the relative stability and reactivity profile of **tBuOCl** has led to a diversity of applications in preparative organic chemistry. [REF] All organic hypochlorites share a pungent smell.

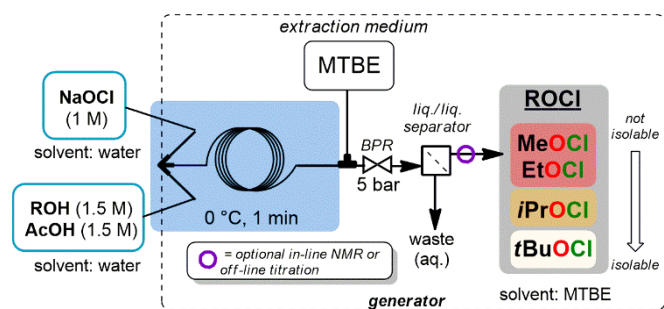
The original protocol from Mintz and Walling was adapted for the preparation of a small library of hypochlorous esters. This process involves the reaction of a lower (MeOH, EtOH, *i*PrOH and *t*BuOH) in the presence of sodium hypochlorite and acetic acid in water (Figure 5). [REF] Preliminary trials in batch confirmed the near instantaneous reaction of hypochlorous acid with MeOH, EtOH, *i*PrOH and *t*BuOH, yielding a yellowish lipophilic phase of lower density than the aqueous reaction mixture. The extraction efficiency can be improved with an organic solvent (typically MTBE). The reaction was carried out at 0 °C for 30 minutes in the dark to avoid degradation of the

corresponding hypochlorites (Supporting Information, section XXXX). A suitable organic solvent was then added; the resulting organic phase was washed with 10% Na<sub>2</sub>CO<sub>3</sub> (1 x) and brine (1 x) and finally dried over CaCl<sub>2</sub>. The protocol was first optimized under batch conditions, and rapidly transposed to flow conditions after witnessing the spontaneous and vigorous decomposition of **MeOCl** and **EtOCl** upon extraction. NMR analysis on the crude hypochlorites revealed that the formation of **tBuOCl** was very selective, while the formation of **MeOCl**, **EtOCl** and **iPrOCl** came with a variety of side products (Supporting Information, section XXXX).

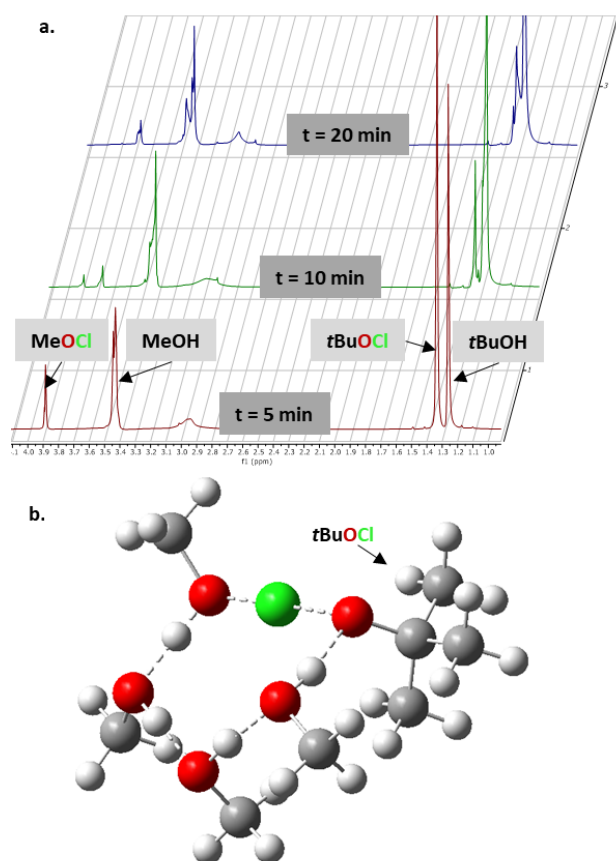
The absence of solids or issues related to an increased viscosity were also important preliminary observations that foresaw a straightforward implementation under continuous flow conditions. The hypochlorite generator was constructed from PFA coils and HPLC-type connectors (Supporting Information, section XXXX) under strict thermoregulation (Figure 5). In a typical procedure, a feed solution of NaOCl in water (1.5 M) and a feed solution of alcohol (1 M) and AcOH (1.5 M) in water were injected at 0.1 mL min<sup>-1</sup> through a static high performer arrowhead micromixer and reacted for 1 min at 0 °C in a PFA coil (I.D. = 750 µm). To avoid the collection of neat hypochlorites, the reactor effluent was connected to an additional T-mixer for a downstream extraction with an organic solvent. The flow rate of the extraction medium was adjusted to reach the desired concentration (typ. 0.5 M). The resulting segmented reaction mixture was next redirected to a membrane separator (hydrophobic PTFE membrane, 1 µm pore size); the organic stream was collected, and the aqueous stream was discarded. Extraction with chloroform enabled off-line <sup>1</sup>H NMR quantification, as well as qualitative in-line NMR monitoring (Supporting Information, section XXXX), yet the most reproducible results were obtained with MTBE and off-line back-titration with potassium iodide. MTBE was selected as a preferential extraction medium for further experiments since it does not react with hypochlorites and, as a common fuel additive, might be considered as a widely accessible chemical. The results of the iodide back titration emphasized the much lower stability of **MeOCl** compared to the 3 other organic hypochlorites. With theoretical concentrations of 1 M in MTBE, the titrations of **MeOCl**, **EtOCl**, **iPrOCl** and **tBuOCl** in MTBE gave 0.11, 0.96, 0.86 and 0.98 M, respectively (Supporting Information, section XXXX).

With the proof of concept of an upstream generator of organic hypochlorites in hands, the oxidation of model thioether compounds was next investigated. The selection of model thioethers included thioanisole (**1a**), diphenyl sulfide (**1b**), dibenzothiophene (**1c**) and dipropyl sulfide (**1d**). Compounds **1a-d** were used to calibrate the protocol and set boundaries, as well as to identify potential competitive reactions and side products. Compounds **1b,c** are known to be quite reluctant to well-described photocatalytic oxidations with singlet oxygen, while compounds **1a** and **1d** were validated as reliable, low toxicity simulants of **HD** in a recent publication. [REF] There is, however, an additional structural feature shared by compound **1a** and **1d**, which is lacking from **1b,c**, namely, a pseudo-enolizable position in α of the corresponding sulfoxides. Such pseudo-enolizable position opens up a very competitive path, that is, an α-electrophilic chlorination of the sulfoxide. With compound **1a**, the electrophilic chlorination can potentially yield the corresponding α-chlorinated, α,α-bis-chlorinated and α,α,α-tris-chlorinated sulfoxides **3a**, **4a** and **5a**, respectively (Scheme 1). [REF]

Since **tBuOCl** was the most stable of the series, a small inventory of 10 mL was prepared and stored over CaCl<sub>2</sub> in a brown glass bottle for preliminary trials in batch (Supporting Information, section XXXX). A fresh 1 M solution in MTBE was prepared and used to investigate the reaction with model compound **1a** (Scheme 1) under various scenarios. For the first set of reactions, the experiments involved reacting a 0.5 M solution of **1a** and a 0.5 M solution of **tBuOCl** both in MeOH (Scheme 1). However, the stock solution of **tBuOCl** in MeOH was not stable overtime. Iodide back titration after 30, 60, 90 and 120 min gave XX, XX, XX and XX M, respectively. An additional NMR study clearly showed the hypochlorite exchange between **tBuOCl** and MeOH, hence leading to the near-instantaneous of **MeOCl** that further decomposed (Figure 6) (Supporting Information, section XXXX). Preliminary trials in batch were therefore attempted in MTBE. Compounds **1-3a** and **5-7a** were purchased from commercial sources either as starting material or as reference, while compound **4a** was prepared according to an adapted protocol from the literature (Supporting Information, section XXXX). [REF]



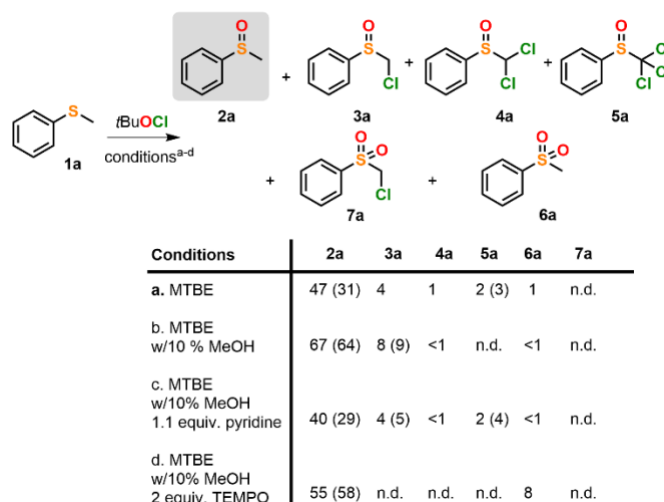
**Fig. 5** Continuous flow generator of hypochlorous esters at the microfluidic scale. (Supporting Information, section XXXX). [REF]



**Fig. 6** Exchange of hypochlorites. (a)  $^1\text{H}$  NMR monitoring of the hypochlorite exchange between **tBuOCl** and MeOH (in  $\text{CDCl}_3$ ). The first spectrum is recorded 5 min after the addition of **tBuOCl** and shows the formation of **MeOCl** and **tBuOH**; after 10 min, **MeOCl** has almost completely decomposed and the amount of **tBuOCl** has decreased significantly; (b) Tentative transition state for the hypochlorite exchange between **tBuOCl** and MeOH with a small cluster of MeOH (B3LYP/6-311+G\*\*) (Supporting Information, section XXXX).

A preliminary test reaction involving the batch oxidation of thioanisole (**1a**, in MTBE) under biphasic conditions with aqueous  $\text{NaOCl} \cdot 5\text{H}_2\text{O}$  at  $0^\circ\text{C}$  led to a conversion of 58% and 87% selectivity to sulfoxide **2a** along with the formation of significant amount of sulfone **6a** (10%) after 1 min of reaction. Next, the oxidation under homogeneous conditions with **tBuOCl** was investigated (Scheme 1). Adding dropwise neat **tBuOCl** (over 10 s, 1.1 equiv.) to a 15 mL solution of **1a** in MTBE (0.5 M) gave a near instantaneous conversion at  $0^\circ\text{C}$  that plateaued at 69% after 4 min with a selectivity of 69% toward sulfoxide **2a** (Scheme 1a). Besides trace amounts of  $\alpha$ -monochlorinated sulfoxide **3a** (4%),  $\alpha,\alpha$ -bis-chlorinated sulfoxide **4a** (1%) and  $\alpha,\alpha,\alpha$ -tris-chlorinated sulfoxide **5a** (2%) and sulfone **6a** (1%), a large fraction of unidentified products (14%) was detected as well. The reaction was monitored over additional 40 min: the selectivity significantly decreased to 49%. The decrease in selectivity was mostly associated with a competitive reaction that further consumed **2a** (31% after 40 min vs 47% after 4 min) and led to the formation of unidentified decomposition products (up to 25%). The amounts of mono and di-chlorinated sulfoxides **3,4a** remained mostly unaffected, while **5a** increased up to 3% (Supporting Information, section XXXX). The next set

of experiments aimed at identifying the effect of MeOH on the oxidation reaction; a solution of model substrate **1a** (0.5 M, 15 mL) was prepared in MTBE with 10% MeOH and treated likewise with neat **tBuOCl** at  $0^\circ\text{C}$  (Scheme 1b). The reaction was again monitored over 40 min and the results differed quite significantly from the previous batch experiment. After complete addition of **tBuOCl**, the conversion plateaued at 77% with a selectivity of 88% toward sulfoxide **2a** with small amounts of **3a** (8%) and traces of **4a** (<1%) and of sulfone **6a** (<1%); compound **5a** was not detected. The reaction was monitored over 40 min and this time both conversion and selectivity remained constant. This preliminary set of observations thus suggested a very quick and selective oxidation of substrate **1a** with **tBuOCl** in the presence of MeOH and, most importantly, the formation of only trace amounts of sulfone **6a**. Besides, in conjunction with the rapid hypochlorite exchange reaction observed upon studying a solution of **tBuOCl** in MeOH (see above), the higher conversion and cleaner reaction profile for the oxidation of **1a** in MTBE/MeOH strongly incriminated **MeOCl** as the terminal oxidizer. These observations were supported with the computed activation barriers (see below).



**Scheme 1.** Preliminary optimization in batch for the oxidation of thioanisole (**1a**) as a model compound (Supporting Information, section XXXX) with the distribution of products from the direct oxidation of **1a** with **tBuOCl** in MTBE or MTBE with MeOH (10%). The reaction was monitored by LC analysis at 200 nm; values are expressed in %area for after 4 min of reaction (values in parentheses are for data collected after 40 min of reaction). n.d. = not detected. Conditions: (a) addition of neat **tBuOCl** (1.1 equiv.) over 10 s to 0.5 M solution of **1a** (in MTBE),  $0^\circ\text{C}$  with reaction monitoring over 40 min, after which up to 25% of unidentified products were detected by LC; (b) addition of neat **tBuOCl** (1.1 equiv.) over 10 s to 0.5 M solution of **1a** (in MTBE with 10% MeOH),  $0^\circ\text{C}$  with reaction monitoring over 40 min; (c) addition of neat **tBuOCl** over 10 s to 0.5 M solution of **1a** (in MTBE with 10% MeOH) and pyridine (1.1 equiv.),  $0^\circ\text{C}$  with reaction monitoring over 40 min, after which up to 42% of unidentified products were detected by LC; (d) addition of neat **tBuOCl** over 10 s to 0.5 M solution of **1a** (in MTBE with 10% MeOH) and TEMPO (2 equiv.),  $0^\circ\text{C}$  with reaction monitoring over 40 min, after which up to 16% of unidentified products were detected by LC.

An additional set of experiments was scheduled to gather more information on the mechanism and the species involved in the oxidation of **1a** (Supporting Information, section XXXX).

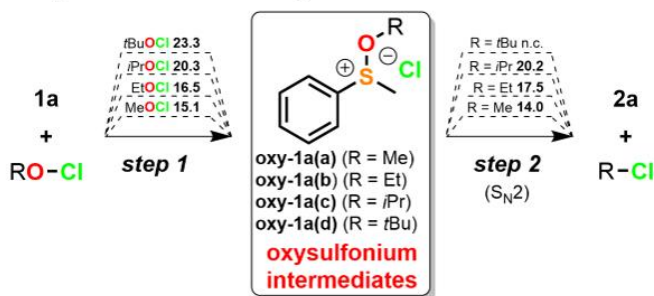


The formation of mono-chlorinated sulfoxides such as **3a** under similar conditions was documented in the literature, [REF] yet it involved the presence of a base (Scheme 1c). However, when the reaction was performed in the presence of pyridine (1.1 equiv.) with **1a** in MTBE/MeOH (0.5 M, 10% MeOH), the conversion reached 80% with a 51% selectivity towards **2a** after 4 min (36% after 40 min) with the significant formation of unidentified products (32% after 3min, 42% after 40 min); surprisingly, the formation of  $\alpha$ -chlorinated sulfoxides **3,4a** did not increase significantly (4 and <1%, respectively) in the presence of pyridine and remained stable over time; the formation of tris-chlorinated sulfoxide **5a** increased slightly over time (up to 4% after 40 min). [REF] The likelihood of a homolytic mechanism [REF] was investigated by performing the oxidation of **1a** (0.5 M in MTBE with 10% MeOH) with **tBuOCl** in the presence of TEMPO, a well-described radical-scavenger (Scheme 1d) (Supporting Information, section XXXX). Under these conditions, the conversion toward **2a** plateaued at 80% with a selectivity of which remained steady over 40 min for reaction monitoring. Interestingly, the formation of all chlorinated sulfoxides **3-5a** was suppressed, while the overoxidation sulfone **6a** became the main side-product (8%). Neither decomposition products from a potential sulfohaloform [REF] reaction nor from the Pummerer reaction [REF] were detected in these preliminary experiences. These results suggest that the formation of chlorinated sulfoxides **3-5a** most likely form according to a competitive radical-based mechanism. In the presence of TEMPO, the suppression of such competitive path leaves a slight excess of **tBuOCl**, which triggers the overoxidation of **1a** toward **6a** to a minor extent. An additional “competition” experiment with the oxidation of an equimolar mixture of **1a**, **2a** and **6a** further confirmed these hypotheses (Supporting Information, section XXXX).

While many aspects of the reaction of **tBuOCl** and other related hypochlorous esters with organosulfur derivatives lead to conclude they behave as electrophilic  $\text{Cl}^+$  donors and proceed through the formation of an intermediate chlorosulfonium cation, [REF] very much alike *N*-chlorosuccinimide (NCS) or 1-chlorobenzotriazole, [REF] the mechanism actually involves the formation of an oxysulfonium cationic intermediate (Figure 7). [REF] The mechanism of sulfoxide formation was thoroughly discussed by Ruff in 2011, including the exchange of hypochlorites with water and alcohols. [REF] Computations were performed at the B3LYP/6-31+G\*\* level of theory with the SMD model for the implicit inclusion of solvent for the reaction of **1a** with **MeOCl**, **EtOCl**, **iPrOCl** and **tBuOCl** (Supporting Information, section XXXX). The direct addition of the sulfur atom of **1a** onto the supposedly electrophilic Cl atom of the hypochlorites only gave an increasing enthalpy barrier without a transition state, while the addition on the O atom gave a transition state leading to the formation of an oxysulfonium cation intermediate **oxy-1a(a-d)** (Figure 7). The activation barrier towards **oxy-1a** increased with the steric hindrance of the starting hypochlorous esters: **oxy-1a(a)** (R = Me)  $\Delta G^\ddagger$  15.1 kcal mol<sup>-1</sup> < **oxy-1a(b)** (R = Et) 16.5 kcal mol<sup>-1</sup> < **oxy-1a(c)** (R = *i*Pr) 20.3 kcal mol<sup>-1</sup> < **oxy-1a(d)** (R = *t*Bu) 23.3 kcal mol<sup>-1</sup>. The first

step appeared exergonic ( $-18.4 \text{ kcal mol}^{-1} < \Delta G^\circ < -21.2 \text{ kcal mol}^{-1}$ ).

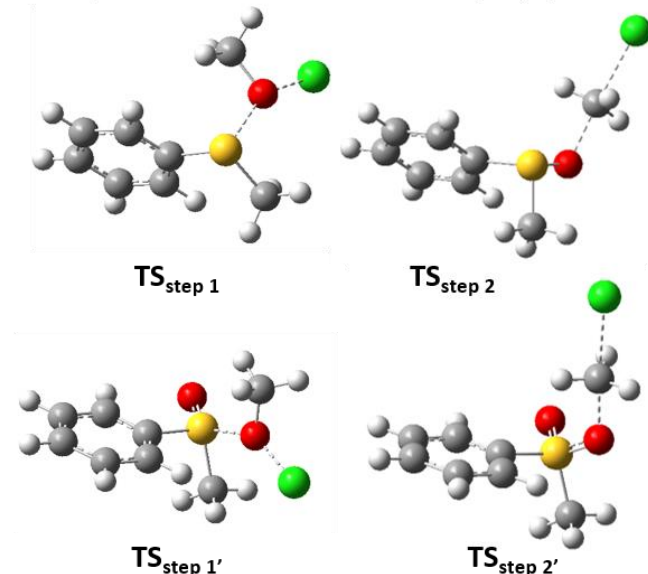
a. Hypochlorite-mediated oxydation of **1a**



b. Overoxidation of **2a** toward **6a** (with MeOCl)



c. Snapshots of the TSs associated with steps 1, 1', 2 and 2'



**Fig. 7** Computational study for the oxidation and overoxidation of thioether with organic hypochlorites. (a) Computed reaction and activation enthalpies for selected model reactions (B3LYP/6-311+G\*\*). Values are given in kcal mol<sup>-1</sup> and computed in MeOH (n.c. = not computed). The oxidation toward sulfoxide **2a** and sulfone **6a** proceed through a two-step mechanism: the preliminary formation of oxysulfonium cationic intermediates (**oxy-1a,2a**) is followed with a  $\text{S}_\text{N}2$ -type displacement with a chloride anion. (Supporting Information, section XXXX). (b) Snapshots of the transitions states corresponding to steps 1, 2 (oxidation to sulfoxide **2a**) and to steps 1', 2' (overoxidation to sulfone **6a**). [REF]

The second step involved the nucleophilic displacement of the electrophilic alkyl moiety of **oxy-1a(a-d)** with the chloride anion that was previously expelled. While a  $\text{S}_\text{N}2$  mechanism is foreseen for **oxy-1a(a,b)**, a competition may occur for **oxy-1a(c)** and a  $\text{S}_\text{N}1$  process is expected for **oxy-1a(d)**. It goes without saying the corresponding enthalpy barriers are expected to follow the same order, the smallest one being associated with

the  $S_N2$  reaction on **oxy-1a(a)** (14.0 kcal mol<sup>-1</sup>), yielding sulfoxide **2a** and methyl chloride (Figure 7). Step 2 appeared mostly isoenergetic to step 1 regarding the activation barriers. The overoxidation toward the formation of sulfone **6a** is expected to follow the same pattern, with the intermediate formation of an oxysulfonium intermediate **oxy-2a**, followed with a  $S_N2$  displacement. [REF] The overoxidation path was computed likewise for **2a** with **MeOCl** only. The formation of **oxy-2a** from sulfoxide **2a** was associated with an activation barrier of  $\Delta G^\ddagger = 21.6$  kcal mol<sup>-1</sup> and a comparable exergonicity as for the formation of **oxy-1a** ( $\Delta G^\circ = -20.1$  kcal mol<sup>-1</sup>). The second step, namely, the  $S_N2$  displacement with chloride anion was associated with a much smaller activation barrier ( $\Delta G^\ddagger = 9.3$  kcal mol<sup>-1</sup>) and a strong exergonicity ( $\Delta G^\circ = -22.7$  kcal mol<sup>-1</sup>) that both reflect the much higher electrophilicity of **oxy-2a** vs **oxy-1a** and its better leaving group ability (Figure 7). These results emphasize that it is unclear whether step 1 or step 2 are rate determining for the formation of the sulfoxide, while for the overoxidation toward **6a**, it is clear that step 1' to oxysulfonium intermediate **oxy-2a(a)** is rate-determining. The computations however emphasized that step 1' leading to the overoxidation intermediate **oxy-2a(a)** comes with a much higher activation barrier than step 1 leading to **oxy-1a(a)** ( $\Delta\Delta G^\ddagger = 6.5$  kcal mol<sup>-1</sup>) (Figure 7).

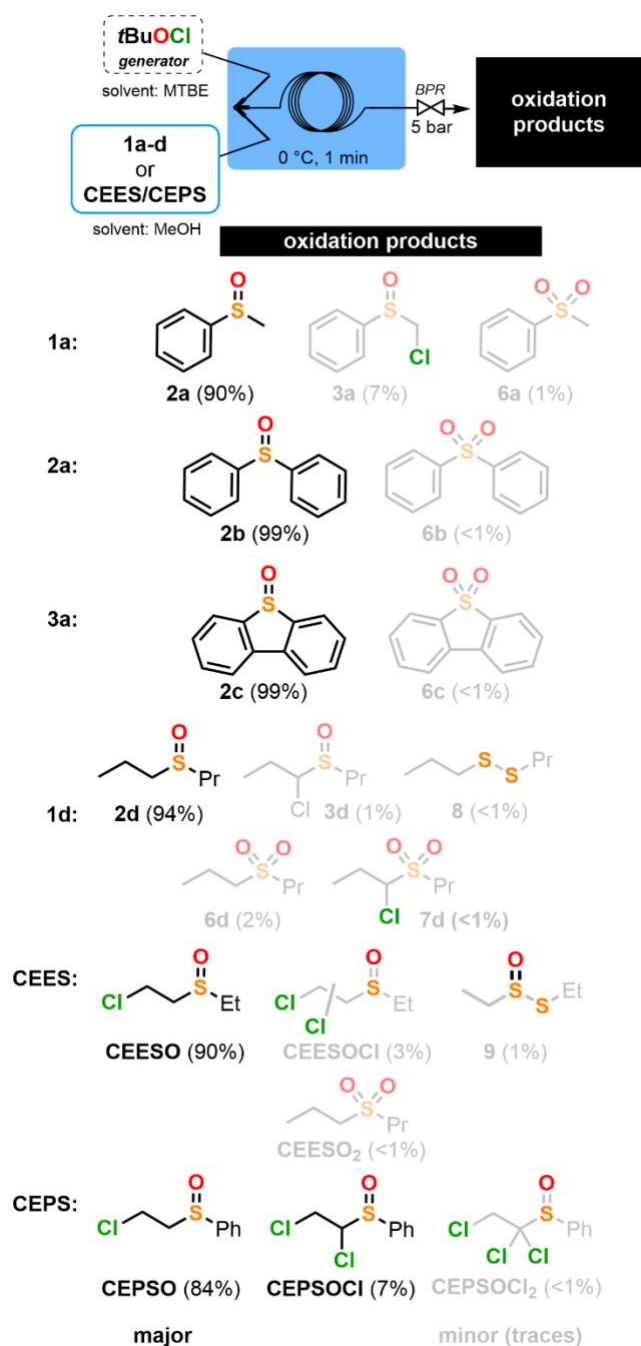
Regarding the sulfoxidation step, the much lower activation barrier for the rate-determining step is obtained with **MeOCl** (15.1 kcal mol<sup>-1</sup>), hence pointing toward its selection of as a potent oxidizer. The observed instability for **MeOCl**, however, precludes its generation upstream despite its potential as a sulfoxidation reagent. The computed activation barriers agree with the hypothetical formation of much more reactive **MeOCl** upon mixing a stock solution of **1a** in MeOH and of **tBuOCl** in MTBE (see above). This opportunity was therefore envisioned as a robust and straightforward compromise between the stability combined with a lower sulfoxidation activity for **tBuOCl** and the instability of **MeOCl** with its superior ability to produce sulfoxides. The computations, however, clearly indicate the likelihood of overoxidation towards **6a** should be minimized under these conditions.

With the combined insights from the preliminary batch trials and the computations, the oxidation of model **1a** was next attempted under continuous conditions (Figure 8): (a) a high-performance micromixer was selected to reach rapid homogenization and hence potentially control the formation of competitive radical-based chlorination mechanisms and (b) **tBuOCl** was selected as a primary hypochlorous ester and was solubilized in MTBE to avoid decomposition in the feed, in conjunction with substrate **1a** in MeOH for taking advantage of the *in situ* formation of more reactive **MeOCl**. The flow rates were set to have a 1:1.1 **1a/tBuOCl** ratio. The crude reactor effluents were collected, quenched by dilution in acetonitrile and then analyzed by HPLC (200 nm). The conditions were further optimized to assess the effects of the residence time, the mixing efficiency, the temperature, the excess **tBuOCl**, the concentration and the nature of the alcohol additive (MeOH, EtOH, *i*PrOH and *t*BuOH) (Supporting Information, section XXXX).

The temperature was the first parameter evaluated, starting with standard operating conditions with 60 s residence time and a 1:1.1 **1a/tBuOCl**. At -78 °C, the conversion dropped significantly to 45% (98% selectivity); rising progressively the temperature to 20 °C increased the conversion to 80% with a selectivity of 98%, hence pointing 0 °C as the best compromise ensuring short residence time with high conversion (93%) and selectivity (99%) toward **2a**. The effects of both the excess **tBuOCl** and the concentration were next addressed. As expected, a substoichiometric amount (0.75 equiv.) of the oxidizer led to a much lower conversion (62%) while maintaining an excellent selectivity (98%); by contrast, a larger excess (2.1 equiv.) of oxidizer gave a quantitative conversion but a very low selectivity (30%) with the emergence of sulfone **6a**, the  $\alpha$ -chlorinated sulfoxide **3a** and  $\alpha,\alpha$ -bis-chlorinated sulfoxide **4a** in significant amounts (6, 25 and 38%, respectively). Despite a lower selectivity toward **2a**, the neutralization selectivity, which includes all sulfoxide products, was still excellent (94%). The concentration had also a significant impact. With 0.5 M for both feeds, a conversion of 99% was reached within 60 s at 0 °C (91% selectivity, 99% neutralization selectivity). Increasing progressively the concentration to 2 M for both feeds led to a decreased conversion (81%) and selectivity (49%) with the formation of significant amounts of sulfone **6a**,  $\alpha$ -chlorinated and  $\alpha,\alpha$ -bis-chlorinated sulfoxides **3,4a** in significant amounts (2, 15 and 15%, respectively). Despite a lower output, the concentration was therefore set at 0.5 M for the subsequent optimizations.

The next experiments addressed the effect of the residence and the mixing efficiency. The effect of the residence time was assessed at constant flow rates for both feeds by adjusting the internal volume of the coil reactor, and 3 residence times (10, 30 and 60 s) were considered at 0 °C. The shortest residence time provided a conversion of 93% with a 99% selectivity towards sulfoxide **2a** with trace amounts of sulfone **6a** (<1%) and of the  $\alpha$ -chlorinated sulfoxide **3a** (1%). Increasing the residence to 30 s pushed the conversion to >99%, while the selectivity toward **2a** slightly decreased to 91%. In the latter, sulfone **6a** remained barely detectable (<1%), while the amount of **3a** increased significantly (8%). For the longest residence time (60 s), both conversion and selectivity remained unaffected. These preliminary microfluidic results emphasized once more the near-instantaneous and selective oxidation of **1a** toward **2a** and the control of the residence appeared as an important parameter to minimize the competitive radical chlorination of **2a** and the overoxidation to **6a**. In the next set of experiments, the impact of the mixing efficiency was evaluated through experiments carried out in the same PFA coil with decreasing flow rates for both feeds with a constant 1:1.1 **1a/tBuOCl** ratio at 0 °C. Residence times of 10, 30 and 60 s were achieved with decreasing mixing efficiencies, *i.e.* keeping the same internal reactor volume and decreasing the overall flow rate. With the reference reaction at 10 s of residence time in mind (93% conversion, >99% selectivity), progressively degrading the mixing efficiency had a deleterious impact on both the conversion and the selectivity: 82% conversion and 98% selectivity were achieved within 30 s of residence time, while

the experiment at 60 s gave 72% conversion and 84% selectivity (99% neutralization selectivity).



**Fig. 8** Microfluidic setup for the hypochlorite-mediated oxidation of model thioethers **1-4a**, **CEES** and **CEPS** with the upstream generator of  $t\text{BuOCl}$ . Data from LC analysis (200 nm, for the oxidation on compounds **1a-c** and **CEPS**) or from GC-MS analysis (oxidation on compounds **1d** and **CEES**) on the crude reactor effluents using optimized conditions: 60 s of residence time, 0 °C with a 1:1.1  $1\text{a}/t\text{BuOCl}$  unless otherwise stated in the main text. Feed solutions of **1a-c**, **CEES** and **CEPS** were prepared in MeOH (0.5 M). Feed solution of **1d** was prepared in 50:50 MeOH/ $\text{CH}_2\text{Cl}_2$  (0.25 M).

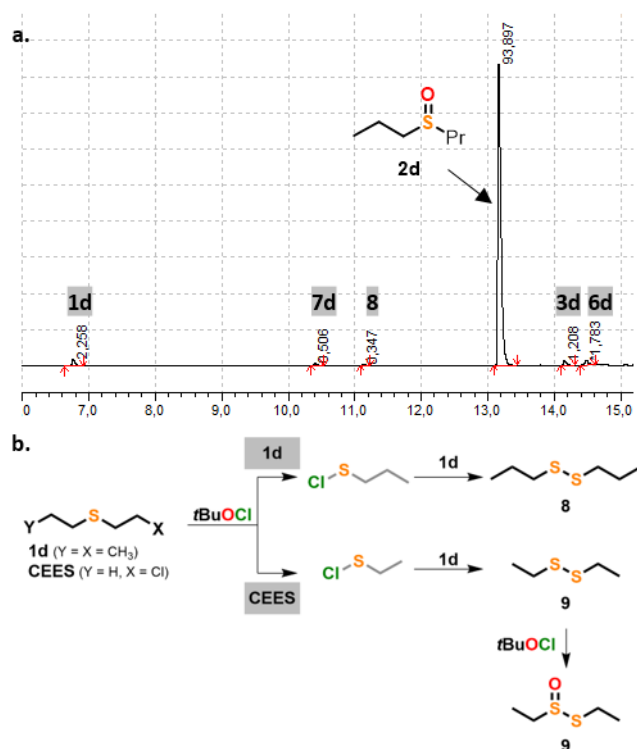
In conjunction with the preliminary batch trials, these results emphasize that poor mixing efficiency affects the output of the oxidation reaction; it is expected that longer residence times (not tested) associated with a poor mixing efficiency

would lead to increasing impurities associated with a local excess of  $t\text{BuOCl}$  (presumably chlorinated derivatives sulfoxides **3-5a** and sulfone **6a**). The last parameter that required some further preliminary trials concerned the selection of the alcohol used as solvent for substrate **1a**. Though the main idea was to combined both the stability of  $t\text{BuOCl}$  with the high reactivity of  $\text{MeOCl}$  through an *in situ* generation of the latter from MeOH and the former, 3 additional experiments were designed with incremental lower alcohols as solvents for **1a**. Under comparable conditions as for the MeOH/MTBE system (1.1 equiv.  $t\text{BuOCl}$ , 0 °C, 60 s), a lower conversion of 63% (39% selectivity) was obtained with EtOH as solvent for **1a**. With isopropanol, the selectivity went back to the upper 80s (87%) with 74% selectivity (84% neutralization selectivity). Lastly, the least system with  $t\text{BuOH}$  led to 65% conversion and 62% selectivity (83% neutralization selectivity). In all 3 cases, sulfone **6a** was formed in about 5%, **3,4a** ranged from 10 to 27% and from 1 to 6%, respectively. Compound **5a** was detected in the last experiment with  $t\text{BuOH}$  (1%). To conclude this section, the best compromise to balance conversion and selectivity, while forming minimal amounts of sulfoxide **6a** involves reacting 0.5 M feed solutions (thioanisole in MeOH and  $t\text{BuOCl}$  in MTBE), with a 1:1.1 stoichiometric ratio at 0 °C within 60 s of residence time with a high-performance arrow-head micromixer to reach complete conversion and very high selectivity (91%) and excellent neutralization selectivity (99%). Under these conditions,  $\alpha$ -chlorinated sulfoxide **3a** becomes the major side product (7%) and sulfone **6a** remains barely detectable (1%). Several of these experiments were run in triplicate to validate the reproducibility of the protocol (Supporting Information, section XXXX). Extrapolating these data for a potential application to neutralize **HD** simulants foresees a selective sulfoxidation along with the formation of  $\alpha$ -chlorinated sulfoxide, which still is considered as a neutralized form of the parent simulant, as a minor contaminant and only trace amounts of the corresponding sulfone.

The feed of thioether was next changed to diphenylsulfide (**1b**) and dibenzothiophene (**1c**), both in solution in MeOH (Figure 8).  $t\text{BuOCl}$  was generated upstream as a 0.5 M solution in MTBE. The crude reactions were collected and diluted in acetonitrile, and then analyzed by HPLC at a 200 nm. With substrates **1b,c**, which lack a pseudo-enolizable position, the formation of chlorinated sulfoxides does not compete anymore with the oxidation or the overoxidation. With **1b**, total conversion was obtained at under the same conditions. The corresponding sulfone **6b** was barely detected (<1%). With **1b**, the concentration had a limited impact on the reaction, since complete conversion was maintained with 1 M concentration for each feed solution (99% selectivity). Decreasing the residence time to 30 s had a minor effect on the conversion (97%), while the selectivity remained unchanged (99%). Dibenzothiophene (**1c**) was poorly soluble in MeOH, and the corresponding feed solution was prepared in a 50:50 MeOH/ $\text{CH}_2\text{Cl}_2$  blend (0.25 M). **1c** is notoriously difficult to oxidize; it was therefore not surprising that a larger excess of  $t\text{BuOCl}$  was required to reach complete conversion. A slight

increase of the excess oxidant (1.2 equiv.) gave 99% conversion with a 98% selectivity.

The optimized conditions were next transposed to dipropyl sulfide (**1d**) (Figures 8 and 9). The lack of chromophores on **1d** imposed a GC-MS monitoring for the oxidation reaction (Supporting Information, section XXXX). Transposition on **1d** gave 98% conversion with 96% selectivity toward **2d** (97% neutralization selectivity), with small amount of the corresponding sulfone (**6d**, 2%), traces of the corresponding  $\alpha$ -chlorinated sulfone **7d** (<1%) and of the  $\alpha$ -chlorinated sulfoxide **3d** (1%). 1,2-Dipropyldisulfane (**8**) was also detected in traces (<1%). A tentative mechanism of formation for **8**, based on the study of Barnwell *et al*, [REF] is proposed in Figure 9b. Slightly increasing the excess of **tBuOCl** to 1.2 equiv. slightly improved the conversion (98%), yet it produced more sulfone **6d** (5%) and its chlorinated analog **7d** (1%) with an overall neutralization selectivity of 94%.



**Fig. 9** (a) Typical GC chromatogram for the oxidation of **1d** (dipropyl sulfide), featuring the distribution of side-products. The attribution of picks was carried out with the injection of commercial or synthesized reference samples (**1d**, **2d** and **6d**) or by GC-MS with NIST identification (**3d**, **7d** and **8**). (b) Tentative mechanism for the formation of impurities **8** and **9**. [REF]

With the data gathered on model substrates and a refined understanding of the mechanism and competitive reactions, the hypochlorite oxidation was attempted on **CEES** and **CEPS** (Figure 8). The conditions with 1.1 equiv. **tBuOCl** with **CEES** provided excellent conversion of 94% with a selectivity of 95% toward **CEESO** (neutralization selectivity of 97%) after 60 s of residence at 0 °C. Sulfone **CEESO**<sub>2</sub> and its chlorinated derivatives were barely detected (<1%). Other minor impurities included  $\alpha$ -chlorinated sulfoxide **CEESOCI** (4%) and diethylsulfinate **9** (<1%). [REF] A tentative mechanism of formation for **9**, based

on the study of Barnwell *et al*, [REF] is proposed in Figure 9b. Increasing the excess of **tBuOCl** to 1.2 equiv. led to 98% conversion with 92% selectivity toward **CEESO** (neutralization selectivity of 99%). Despite the slight excess of **tBuOCl** in the last trial, both **CEESO**<sub>2</sub> and its chlorinated analog **CEESO**<sub>2</sub>Cl remained barely detected, while diethylsulfinate **9** slightly increased (1%). With **CEPS**, 93% conversion was achieved with 90% selectivity towards **CEPSO** (98% neutralization selectivity). Sulfone **CEPSO**<sub>2</sub> was not detected. Increasing the excess **tBuOCl** to 2 equiv. pushed the conversion to 98% but the selectivity towards **CEPSO** dropped to 16%, with major side-products including the mono- and bis-chlorinated sulfoxides **CEPSOCl** and **CEPSOCl**<sub>2</sub> in 73 and 10%, respectively. Sulfone **CEPSO**<sub>2</sub> remained undetected, despite the larger excess **tBuOCl**.

The conditions for the neutralization of **CEES** and **CEPS** were next transposed to a commercial mesofluidic glass reactor setup (Corning® Advanced-Flow™ LF/G1 skid Reactor equipped with 2 glass fluidic modules connected in series (2.7 mL internal volume each, Figure 10a). For simplifying the setup, the upstream generator was disconnected from the downstream oxidation module. A fresh solution of **tBuOCl**, the molarity of which was controlled by back-titration, was used for the trials on **CEES** and **CEPS**. Full concatenation of a similar process was demonstrated elsewhere. [REF] With a 60 s residence time at 0 °C, the oxidation of **CEES** reached 99% conversion with a 96% selectivity toward **CEESO**. The major impurity became monochlorinated sulfoxide **CEESOCI**, while sulfone **CEESO**<sub>2</sub> remained undetected, hence providing a neutralization selectivity of 99%. With **CEPS**, the conversion with 1.2 equiv. **tBuOCl** reached 97% with 97% selectivity % toward **CEPSO**; increasing the excess **tBuOCl** to 1.4 equiv. pushed the conversion up to 98% with 79% selectivity toward **CEPSO**, the major impurity becoming its monochlorinated sulfoxide **CEPSOCl** (up to 20%), yet the overall neutralization selectivity was excellent (>99%).

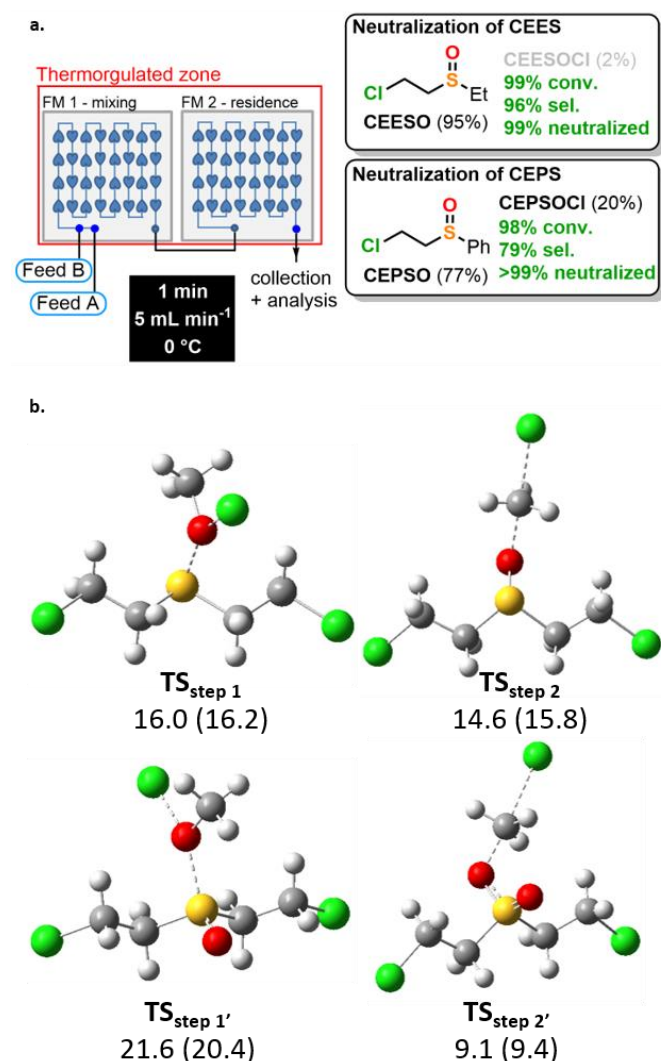
Lastly, the oxidation of **HD** with **MeOCl** was computed and compared to the computational results associated with **CEES** to further validate *in silico* the potential transposition of this oxidative neutralization protocol to an actual CWA (Figure 10b). Both the simulat and the actual **HD** came up with very close reaction profiles and activation barriers for the various steps leading to the corresponding sulfoxides and sulfones, hence suggesting that the experimental results for the neutralization of **CEES** are representative of the behavior of **HD** under similar experimental oxidative conditions (Supporting Information, section XXXX).

## Conclusion

This work reports on a scalable and robust continuous flow process for the oxidative neutralization of organosulfur CWA simulants. The process proposes an original solution to both produce and mitigate the high reactivity of lower alkyl hypochlorites from aqueous solutions of sodium hypochlorite. An upstream generator of organic hypochlorites produces a homogenous stream of organic hypochlorites in MTBE that is further used downstream for the selective oxidation of



thioethers. Despite the higher computed reactivity of **MeOCl** for the oxidation of thioethers in the corresponding sulfoxides, its inherent instability precludes its formation in the upstream generator, extraction in MTBE and direct use for oxidative neutralization. Instead, the upstream generation of **tBuOCl**, which is much more stable than **MeOCl**, but also much less reactive, is advantageously exploited to feed the downstream oxidation module. The latter is fed with the thioether substrate in MeOH, which provokes a near-instantaneous hypochlorite exchange with MeOH hence producing “on-the-spot” **MeOCl**.



**Fig. 10** (a) Mesofluidic reactor setup for the scalability trials featuring a Corning® Advanced-Flow™ LF/G1 skid Reactor equipped with 2 glass fluidic modules connected in series. Data from GC-MS (**CEES**) or LC-DAD/MS (**CEPS**); (b) Transition state structures (B3LYP/6-311+G\*\*) and activation energies (in kcal mol<sup>-1</sup>) for the *in silico* oxidation of **HD**. Values in parentheses are calculated for **CEES** (Supporting Information, section XXXX). See also Figure 7 for details on the various steps.

Such strategy exploits the higher reactivity of **MeOCl** without the safety and reproducibility issues related to its instability. It provides convenient and fast oxidative conditions for the transformation of thioethers into their corresponding sulfoxides. There are, however, several competitive reactions: (a) a radical-based chlorination of the sulfoxide, typically

leading to their corresponding  $\alpha$ -chlorinated derivatives (sometimes multiple chlorinations are observed); (b) the formation of disulfides or sulfinates through an intermediate sulfenyl chloride intermediates and (c) an overoxidation to the corresponding sulfone. While competitive paths (a) and (b) are not concerning when it comes to efficiency of the oxidative neutralization (since they may be considered as neutralized species), the emergence of a complete overoxidation is more concerning. Fortunately, in all trials executed in this study, the formation of the overoxidation sulfone is barely detected and is usually <1%. The use of organic hypochlorites alleviates the formation of micelles and superficial chemical neutralization of sulfur mustards with aqueous hypochlorites. The preliminary transformation of aqueous sodium hypochlorite into corresponding lower alkyl hypochlorous esters remains accessible according to a straightforward protocol that accommodates either batch (for the most stable hypochlorites such as **tBuOCl**) or flow procedures. The conditions were optimized on model thioethers and then adapted for the neutralization of **CEES** and **CEPS**, both under microfluidic and mesofluidic conditions, with excellent conversion and neutralization selectivity. Preliminary results indicated that “off-the-convenience-store” chemicals can be used for the preparation of organic hypochlorites and used likewise. The process relies on widely accessible and affordable chemicals and is amenable to larger scales for the chemical neutralization of large inventories of sulfur mustard vesicants to low-toxicity sulfoxides, which can thereafter be safely transported to incineration facilities. Besides the pragmatic aspects of this process, the assets of computational chemistry are further illustrated here as a convenient protocol for the validation of neutralization protocols developed on simulants, hence providing indication of transposability toward actual sulfur CWAs without military clearance and without extremely restrictive safety protocols.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references





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