Short Communication

Rate of single electron reduction of Togni's reagent

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ABSTRACT

We report on the rate of reduction of a popular electrophilic trifluoromethylating agent, Togni's reagent (T-CF$_3$), with solvated electrons (e$_{aq}^-$) generated by pulse radiolysis. By means of competition experiments against methyl viologen (MV^{2+}) and direct observation of the decay of e$_{aq}^-$ we determined k (T-CF$_3$ + e$_{aq}^-$) $\approx 2 \times 10^{10}$ M^{-1} s^{-1}. To the best of our knowledge, this constitutes the first report on a reduction of T-CF$_3$ with an unambiguously clear *outer*-sphere mechanism. Furthermore, we studied the oxidation of 2-(2-iodophenyl)propan-2-ol (ROH) by peroxyl-radicals to a presumably cyclic iodanyl radical RI$^\bullet$. This species RI$^\bullet$ was not detected during the reduction of T-CF$_3$ with e$_{aq}^-$ and therefore, this reduction does not proceed via heterolytic I-CF$_3$ bond cleavage to CF$_3^-$ and RI$^\bullet$. More likely, a CF$_3$ radical is formed, as was observed in numerous synthesis studies reported to date.

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1. Introduction

The electrophilic trifluoromethlyating agents 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (T-CF$_3$) and 1-(trifluoromethyl)-1,2-benziodoxol-3-(1H)-one (A-CF$_3$), introduced in 2006 in a seminal report by *Togni* and co-workers [1], have since become the center point of a broad variety of CF$_3$-functionalization strategies [2]. Whilst molecular editing of the scaffolds can modulate the reactivity of these reagents [3], the activation of native T-CF$_3$ or A-CF$_3$ by relying on Brønsted or Lewis acids has proven more valuable [2]. Indeed, both structures are relatively basic and readily form complexes, as was highlighted for example by the successful isolations of an adduct of form [Zn(A-CF$_3$)$_2$(OR)$_2$(H$_2$O)$_2$](NTf$_2$)$_2$ or of the proton-bridged *pseudo*-dimer [(T-CF$_3$)···H···(T-CF$_3$)](BArF$_{24}$) [4,5]. Most recently, *Toste et al.* also demonstrated the direct protonation of T-CF$_3$ and A-CF$_3$ with gaseous HCl to afford the iodonium-type salts T-CF$_3$•HCl and A-CF$_3$•HCl in 96 and 57% yield, respectively. These structures retain their reactivity and do not require additional activation by Lewis acids. However, in many cases a phase-transfer catalyst in form of the weakly coordinating BArF$_{24}$ anion had to be employed [6].

The effect of protonation of T-CF$_3$ and A-CF$_3$ on the frontier molecular orbitals was investigated more thoroughly by

computational means [2,6]. In this regard a restructuring of the highest occupied and lowest unoccupied molecular orbitals (HOMO & LUMO) in T-CF$_3$ was uncovered. Whilst the LUMO in T-CF$_3$ is situated on the C$_{Ar}$-I bond, protonation results in a translocation of this orbital to the I-CF$_3$ bond concomitant to a significantly smaller HOMO-LUMO gap. This was interpreted as T-CF$_3$•H$^+$ likely constituting a more potent oxidant in comparison to native T-CF$_3$. Similar results were also obtained for A-CF$_3$. This restructuring of frontier molecular orbitals is particularly interesting with regard to single electron reductions of T-CF$_3$ and A-CF$_3$. Notably, a number of reports have indicated the generation of CF$_3$ radicals upon exposure of the reagents to suitable reductants, *e.g.* photoredox catalysts [2,7]. Most intriguingly, when A-CF$_3$ was treated with the sodium salt of the reduced form of free stable radical 2,2,6,6-tetramethyl-piperidinyloxyl (TEMPO), 2,2,6,6-tetramethylpiperidin-1-olate (TEMPONa), CF$_3^\bullet$ alongside TEMPO was produced. These reactive species could then be added across various double bonds [8]. Building on the same concept, the reaction of hydroxylamines with either T-CF$_3$ or A-CF$_3$ is perceived to occur in two steps: the protonation of the reagent scaffold is followed by single electron reduction to yield CF$_3^\bullet$ and R'R"NO$^\bullet$. Finally, radical recombination affords the desired *O*-trifluoromethylated species R'R"NOCF$_3$ [9]. However, whilst the formulation of an *outer*-sphere mechanism is appealing on paper, in most examples the nature of the reduction mechanism remains uncertain and the reaction could also proceed through a number of distinctive processes (Fig. 1). Importantly, the occurrence of

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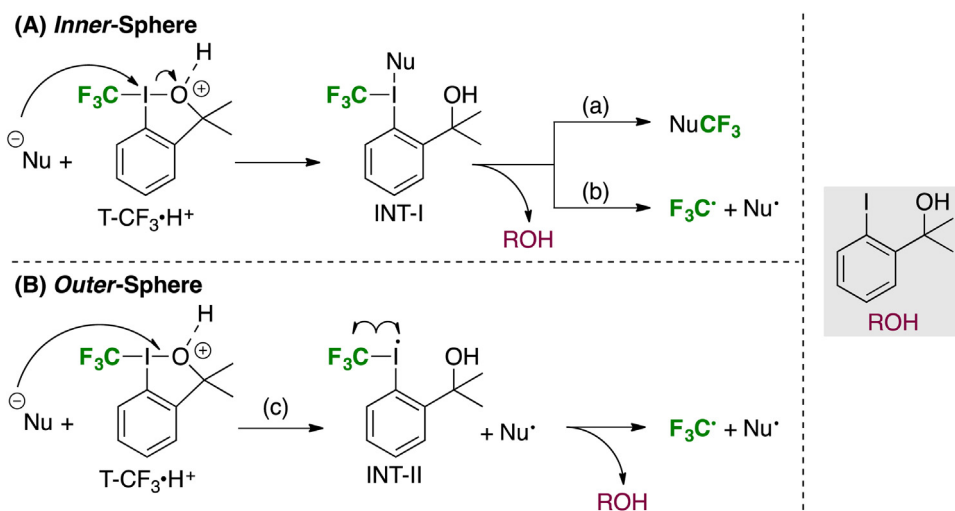
Fig. 1. The mechanism of the reaction of T-CF$_3$•H$^+$ with a nucleophile Nu$^-$ is complex. Formation of intermediate INT-I may either be followed by reductive elimination to the product NuCF$_3$ (a) or by a dissociative electron transfer (DET, b) to radical intermediates; both pathways constitute *inner*-sphere (associative) reduction mechanisms. *Outer*-sphere reduction of T-CF$_3$•H$^+$ to INT-II (c) followed by fragmentation also affords radical intermediates.

radical intermediates such as F$_3$C$^•$ does not necessitate an *outer*-sphere mechanism. An illustrative example is the functionalization of thiols [10]. Proton transfer from PhSH to T-CF$_3$ occurs simultaneously to the coordination of the sulfur center to the iodine core leading to a covalently bound intermediate (Fig. 1, INT-I). The subsequent dissociative electron transfer (DET) affords the experimentally observed radical intermediates, which recombine to the final product, PhSCF$_3$. An analogous reaction for hydroxyl-amines appears plausible. We are not aware of any experiment demonstrating the unambiguous involvement of an initiating *outer*-sphere reduction with these popular reagents.

2. Results and discussion

We selected T-CF$_3$ as the reagent of choice based on a series of favorable properties: T-CF$_3$ typically features increased solubility in comparison to A-CF$_3$ and the alcohol-derived ligand is more basic than the carboxylate. Also note that the determination of the rate of an *outer*-sphere reduction is contingent on the availability of a species that cannot form adducts with the substrate, *i.e.* coordination to the iodine core has to be prohibited. The simplest such species is the solvated electron e$_{solv}^-$. This intriguing species may, for example, be generated by dissolving alkali metals in liquid ammonia (Birch conditions)[11] or, alternatively, by photolysis or radiolysis [12,13]. We chose pulse radiolysis as the method to access the hydrated electron, e$_{aq}^-$, and determined the kinetics of the reduction of T-CF$_3$ by means of time-resolved UV/VIS spectroscopy. Upon exposure of bulk water to ionizing radiation HO$^•$, H$^•$, e$_{aq}^-$ and H$^+$ are produced with approximate radiochemical yields (G-values) of 2.60, 0.55, 2.60 and 2.60, respectively [13]. These yields translate into effective concentrations of 27, 6, 27 and 27 μM per 100 Gy radiation dose. In bulk water we also expect T-CF$_3$ to be hydrogen-bonded and after irradiation to resemble T-CF$_3$•H$^+$ (drop in pH value due to generation of H$^+$). The argon-saturated sample solutions were prepared in MilliQ water (18.2 Ω) containing 10 vol-% tBuOH (1.1 M) with the latter serving two purposes: tBuOH acts as a scavenger for the HO$^•$ radical and solubilizes T-CF$_3$.

In order to determine the rate of reduction k(T-CF$_3$ + e$_{aq}^-$), we initially concentrated on competition experiments with methyl viologen (MV^{2+}), whose rate of reduction is well documented: k(MV^{2+} + e$_{aq}^-$) = 5.4–9.0 × 10^{10} M^{-1} s^{-1} [14]. To this end, the

concentration [T-CF$_3$] was varied from 0.1–1.0 mM, whilst keeping [MV^{2+}] constant at 0.1 mM. This resulted in a decreasing absorbance A with increasing concentration [T-CF$_3$]. As reference in Fig. 2 we use experiments carried out with only MV^{2+},A_0. Since [e$_{aq}^-$] << [T-CF$_3$] and [MV^{2+}] for the applied doses of 10 Gy, the change in relative absorbance A_{rel} = A/A_0 results from two competing *pseudo*-first order processes. Therefore, the linear relationship [T-CF$_3$]/[MV^{2+}] = r × (1 − A_{rel})/A_{rel} may be used to derive the ratio r = k(MV^{2+} + e$_{aq}^-$)/k(T-CF$_3$ + e$_{aq}^-$). This consideration affords k(T-CF$_3$ + e$_{aq}^-$) = 1.3–2.2 × 10^{10} M^{-1} s^{-1}, based on r = 4.02 ± 0.08 with R^2 = 0.999 (Fig. 2, inset).

In analogy, competition experiments with K$_3$Fe^{III}(CN)$_6$ (k (Fe^{III} + e$_{aq}^-$) = 2.4–3.7 × 10^9 M^{-1} s^{-1}) were carried out [15]. However, the system did not behave ideally and the data could not be linearized satisfactorily. We presume the cause to lie in the kinetic instability of [Fe^{III}(CN)$_6$]$^{3-}$ which, in contrast to the ferrous species, hydrolyses readily. This exposes the ferric iron for reactions with suitable ligands. Complexation of T-CF$_3$ by transition metals is well known (*vide supra*) and, therefore, may compromise the measurement. We cannot fully exclude that the
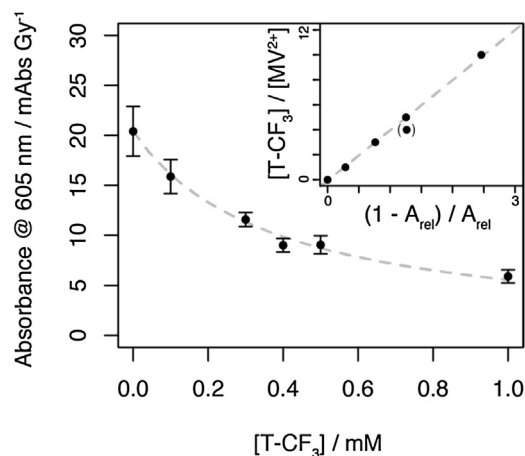
Fig. 2. Competition for e$_{aq}^-$ between T-CF$_3$ (0.0–1.0 mM) and MV^{2+} (0.1 mM) was studied by observation of MV$^{•+}$ at 605 nm. Error bars represent two standard deviations. Inset: linearization affords the ratio k(MV^{2+} + e$_{aq}^-$)/k(T-CF$_3$ + e$_{aq}^-$) = 4.02 ± 0.08, R^2 = 0.999 (value in brackets was neglected).