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DFT Mechanistic Study of Methane Mono-Esterification by Hypervalent Iodine Alkane Oxidation Process

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ABSTRACT: Recent experiments report high yield (up to 40%) and selectivity (generally > 85%) for the direct partial oxidation of methane to methyl trifluoroacetate in trifluoroacetic acid solvent using hypervalent iodine as the oxidant and in the presence of substoichiometric amounts of chloride anion. We develop here the reaction mechanism for these results based on DFT calculations at the M06-2X/6-311G**++/aug-pVTZ-PP level of plausible intermediates and transition states. We find a mechanistic process that explains both reactivity as well as selectivity of the system. In this oxy-esterification (OxE) system **IO₂Cl₂⁻ and/or IOCl₄⁻ act as key transient intermediates**, leading to the generation of the high-energy radicals IO₂[·] and Cl[·] that mediate methane C–H bond cleavage. These studies suggest new experiments to validate the OxE mechanism.

INTRODUCTION

Natural gas is a naturally-occurring hydrocarbon mixture composed chiefly of methane that is generally found in the same places as petroleum.^[1] However, methane is a gas with a very low boiling point of –161.5°C, making it difficult to liquefy, and consequently expensive to store and transport.^[2] Because natural gas sells for a much lower price than petroleum on the world market, it is often uneconomical to harvest.^[3] And because it is also a potent greenhouse gas with 72 times the climate change potential of CO₂, release into the atmosphere can have significantly deleterious environmental effects.^[4] It has been estimated that 140 billion cubic meters of natural gas are flared annually.^[5]

Much effort has been expended towards partially oxidizing methane to methanol onsite.^[6] As a liquid under standard conditions and a common chemical feedstock, methanol is both easier to store and transport, and also more valuable than methane.^[7] A frequently used industrial process is called steam-methane reformation (SMR). A mixture of methane and steam is passed through a nickel catalyst at high temperatures and pressures to form synthesis gas (CO and H₂), which is then recombined in a second catalytic process to form methanol. Unfortunately, this process is both highly energy and capital intensive, and it is generally not feasible to be located near remote extraction sites.^[8] Another strategy for methane functionalization is methane oxychlorination, which involves the catalyzed reaction of methane with HCl and O₂ to form methyl chloride and water. The products can further react to produce methanol and regenerate HCl.^[9–13] Unfortunately, this process produces a large amount of over-oxidized byproducts such as methylene chloride, chloroform, and carbon tetrachloride. In fact, a common limitation of radical based mechanisms such as oxychlorination is the fact that the C–H

bond of methane, 104 kcal/mol, is stronger than that of methanol (96 kcal/mol) or methyl chloride (100 kcal/mol), leading to abundant over-oxidized side products.^[14]

In the 1960s, Shilov and coworkers discovered that platinum salts in aqueous HCl solution could activate methane under mild conditions, producing methyl chloride (and consequently methanol by hydrolysis) through an electrophilic two-electron C–H activation mechanism.^[15–17] In the ensuing decades, much work has been done to improve catalyst stability, find less expensive alternatives to platinum, and replace Pt(IV) with dioxygen as the stoichiometric terminal oxidant.^[18–19] One of the most promising developments is the Catalytica process developed by Periana and coworkers, in which methane in oleum solution (H₂SO₄/SO₃) is oxidized to methyl bisulfate via diverse late-transition metals such as Pt, Pd, Hg, and Au.^[20–24] In all of these cases, the reaction is selective for methyl bisulfate production, often with negligible over-oxidation. This has been attributed to the presence of the electron withdrawing group –OSO₃H which serves as a protecting group, removing electron density from the methyl C–H bond and slowing over-oxidation by electrophilic catalysts.^[25–26] Currently, the chief drawback of the Catalytica family of methane oxidation systems is the use of superacidic media such as oleum, which must be constantly replenished due to H₂O being produced by the reaction, rendering cost-effective product extraction very difficult. More recent work by Periana and coworkers include DFT studies that show that superacidic media can be avoided when using main-group elements.^[27] In particular, a trifluoroacetate complex of Sb(V) has been shown to activate methane and ethane.^[28] There is a variety of other recent literature showing methane partial oxidation to methanol, syngas, or other products.^[29–43]

Our work on the partial oxidation of methane has focused on the search for processes efficient under less acidic

environments, in particular trifluoroacetic acid (TFAH).^[44] For instance, we have characterized a number of rhodium complexes with C–H activation ability in TFAH.^[45–49] Recently, we have reported the ability of hypervalent iodine complexes to oxidize light alkanes (methane, ethane and propane) under mild conditions. Hypervalent iodine complexes were reported to activate C–H bonds in an electrophilic 2-electron oxidation.^[50–54] Since then, we have also seen that simple iodate and other iodine oxide salts oxidize methane and other light alkanes in the presence of catalytic amounts of chloride anion.^[55–56] In addition to 2-electron pathways, our work on the hypervalent iodine oxide reactions indicate that 1-electron radical pathways should be explored.

In this contribution, we use density functional theory (DFT) to determine the mechanism for the oxidation of methane to methyl trifluoroacetate in TFAH solution using hypervalent iodine oxide as the oxidant. Our results explain current observations for a range of iodine based oxidants. In particular, we provide a comprehensive characterization of the mechanism of iodate oxidation, and suggest how it may be extended to other iodine sources. In addition, our calculations are valid for TFAH and predict non-reactivity in acetic acid. We also present our experimental work conducted in parallel to our calculations that accounts for reactivity in acetic acid and supports our calculated results.^[57]

MATERIALS AND METHODS

General calculations

All quantum mechanical calculations were carried out using the Jaguar software version 8.4 developed by Schrödinger Inc.^[58] Geometry optimizations were carried out on initial guess structures, and vibrational frequencies were calculated to confirm the optimized geometries as intermediates (no negative curvatures) or transition states (one negative curvature) and to calculate the zero-point energy, entropy, and temperature corrections to obtain the free energy profile. Calculations were performed using the M06-2X density functional^[59] with the Grimme post-SCF D3 correction for van der Waals interactions.^[60] The double- ζ 6-31G** basis set^[61–62] was used for all elements except bromine and iodine (which used the Peterson pseudopotential along with a diffuse-augmented correlation-consistent triple- ζ basis set without f functions, i.e. aug-cc-PVTZ-PP(-f)^[63–65] for geometry optimization and frequency calculations. All calculations were performed using a temperature set to 498.15 K. A comparison of relevant calculated and experimental reaction enthalpies is given in Table S4.

Construction of the solvation energy

Solvation energies ΔE_{solv} were calculated using the PBF Poisson-Boltzmann implicit continuum solvation model^[66–67] using the triple- ζ 6-311G**++ basis set^[68–69] for all elements except bromine and iodine, which used the aug-cc-PVTZ-PP basis set with Peterson pseudopotential and f functions.^[63–65] This model treats any arbitrary solvent with two parameters: its dielectric constant ϵ and its probe radius r . The probe radius is calculated according to the formula $r = \sqrt[3]{3\Delta MW/4\pi N_A \rho}$, where r is the probe radius in Å, MW is the molecular weight, N_A is Avogadro's number, ρ is the density, and Δ is the liquid packing density and estimated at 0.5 (for comparison, $\Delta = 0.74$ for FCC and HCP crystals).^[70] Solvent energies were calculated

using a dielectric constant of 8.55 for TFAH.^[71] Using the above formula, the probe radius was thereby set to 2.451 Å.

Construction of the free energy

The state energies for each species in the gas phase were calculated using the formulae $U_{\text{gas}} = E_{\text{gas}} + \text{ZPE} + U_{\text{lib}}$, $H_{\text{gas}} = U_{\text{gas}} + pV$, and $G_{\text{gas}} = H_{\text{gas}} - TS$, where U_{lib} is the total contribution of temperature-dependent librational (translational, rotational, and vibrational) effects to the internal energy. For each species in the solution phase, the free energy was calculated as $G_{\text{sol}} = G_{\text{gas}} + \Delta E_{\text{solv}} + \Delta G_{\text{gas} \rightarrow \text{solv}}$, where ΔE_{solv} is the solvation energy as described above and $\Delta G_{\text{gas} \rightarrow \text{solv}} = kT \ln(24.5)$ represents the free energy change of compressing 1 mol of an ideal gas (volume 24.5 L at 25°C) to 1 L (for 1 M standard concentration). In the specific case of individual atoms or ions such as Br[•] or Cl[•], ZPE = 0 and $H_{\text{tot}} = 5/2kT$, and S is taken from Chase.^[72]

Experimental methods

All reactions were prepared in air. Glacial acetic acid (HOAc), acetic acid- d_4 , methyl acetate (MeOAc), ammonium iodate (NH₄IO₃), and potassium chloride (KCl) were purchased from commercial sources and used as received. Methane and argon were purchased from GTS-Welco and used as received. ¹H NMR spectra were recorded on a Varian Inova 500 MHz NMR spectrometer, using neat samples each with C₆D₆ in a sealed capillary as an internal lock reference. Chemical shifts are reported relative to standards of nitromethane (CH₃NO₂) (¹H NMR δ 4.30). GC-MS data were obtained on a Shimadzu GC-2010 instrument equipped with a Restek RT-Qbond 30 m $\times$ 8 mm fused silica PLOT column. Reactions were carried out in in-house-built high-pressure stainless steel VCO reactors using Swagelok parts. Each reactor had a Teflon liner and stir bar and was heated in an aluminum block.

RESULTS

The ability of simple iodate salts to oxidize methane was reported by Fortman et al.^[55] A wide variety of iodine containing species were investigated in that contribution, and the chemistry was subsequently extended to simple periodate salts in a follow-up contribution.^[56] Table 1 is a summary of the reactions methane undergoes in TFAH, when various iodine oxidants and other additives are added.

Table 1. Summary of experimentally determined methane oxidation reactions in TFAH with various iodine oxidants and other additives.^a

Entry	Species	Additive	Yield MeTFA; MeX
1	I ₂	–	–
2	I ₂	KCl	–
3	I ₂	NH ₄ IO ₃	2%
4	ICl	–	–

5	ICl ₃	—	5%; 43% MeCl
6	I(TFA) ₃	—	7%
7	I(TFA) ₃	KCl	43%
8	NH ₄ IO ₃	KCl	21%; <1% MeCl
9	(IO ₂) ₂ S ₂ O ₇	—	<1%
10	(IO ₂) ₂ S ₂ O ₇	KCl	48%
11	I ₂ O ₄	—	2%; 15% MeI
12	I ₂ O ₄	KCl	30%; 17% MeI
13	(IO) ₂ SO ₄	—	5.3%
14	(IO) ₂ SO ₄	KCl	31%
15	KIO ₄	KCl	41%; 1% MeCl

^aYields for all entries except for **8** and **15** are reported relative to the amount of iodine source, which was 0.4 mmol. Yields for entries **8** (NH₄IO₃) and **15** (KIO₄) are relative to methane (8.4 mmol for NH₄IO₃ and 2.9 mmol for KIO₄). The experiment with KIO₄ (entry 15) was performed at 200 °C, whereas all other experiments were performed at 180 °C.

In the following sections, we will address the individual observations in each entry of Table 1.

Entries 1-2. The lack of reaction with elemental iodine is of little surprise, as iodine radicals are generally thought of as being too weak to break the C–H bonds of methane. This is confirmed by our calculations (equations 1-3). From equation 2, we see that abstracting a hydrogen atom from methane by an iodine radical is endergonic by 25.8 kcal/mol. More importantly, by combining equations 2 and 3 we see that conversion of methane and iodine to methyl iodide and hydrogen iodide is both endothermic and endergonic.

^aValues based on experimental BDEs.^[73] All numbers in kcal/mol.

Entry 3. Although I₂ and KIO₃ have been reported to oxidize methane in oleum,^[74-77] the same reaction was not observed in the more weakly acidic TFAH. The oleum reaction is proposed to involve I⁺ as a reactive intermediate, but we find that this species is too unstable to be accessible in TFAH (equation 4). TFAI may be seen as a lower-energy analogue (equation 5); however, the O–I bond dissociation energy is still too high (equation 6).

Entry 4. ICl has a BDE of 51 kcal/mol, and breaking the bond is too endergonic to occur to any significant extent under reaction conditions (equation 7). However, if we assume that it could break into chlorine and iodine radicals, we see from equation 8 that the chlorine radicals are able to break the C–H bonds of methane. The resulting methyl radicals would react with additional ICl to form iodine radicals (equation 9), which may be able to regenerate additional chlorine radicals (equations 10). Hence our DFT shows that ICl cannot initiate methane oxidation, although it may be able to sustain a reaction that has already been initiated by a different radical source.

^aValues based on experimental BDEs.^[73] All numbers in kcal/mol.

Entry 5. ICl₃ actually exists in the solid form as the dimer I₂Cl₆,^[78] although under reaction conditions it is monomeric (equation 11). It is known to be a powerful oxidizer and chlorine source. In our mechanism, ICl₃ generates chlorine atoms (equation 12), which abstract the hydrogen from methane to generate methyl radicals. The methyl radical abstracts chlorine from another equivalent of ICl₃ to generate the product, methyl chloride (equation 13). Finally, radical propagation is achieved through the decomposition of ICl₂·, which generates additional chlorine radicals (equation 14).

^aValues based on experimental BDEs.^[73] All numbers in kcal/mol.

This is our first entry in which methane is oxidized to a significant extent, although the main product is methyl chloride. Equations 11 and 12 show that dissociation to the monomer ICl₃ is favorable and I–Cl bond homolysis is accessible. According to experimental observations,^[55] methyl chloride does not convert to methyl trifluoroacetate under reaction conditions. However, methyl iodide is rapidly converted via S_N2 attack to methyl trifluoroacetate, even at room temperature, but only under basic conditions such as for the NH₄IO₃/KCl case (entry **8**) or the KIO₄/KCl case (entry **17**).

Entries 6-7. In 2014, Konnick et al. reported the ability of the hypervalent I(III) compound (C₆F₅)I(TFA)₂ to oxidize methane to MeTFA in TFAH solution.^[79] Their mechanism, supported by DFT calculations, involved the electrophilic 2-electron activation of methane to form an organoiodine(III)

intermediate, which is then attacked via S_N2 to form MeTFA. However, our calculations which examine I(TFA)₃ instead find that the analogous closed-shell transition state is too high in energy (Scheme 1). Hence, we believe an alternative mechanism is needed to explain the reactivity in entries 6 and 7.

Scheme 1. Closed shell mechanism of methane oxidation by I(TFA)₃.

Instead, we propose a radical mechanism initiated by the homolysis of an I–TFA bond (Scheme 2). Both radical fragments TFA· and I(TFA)₂· can then either activate methane (red) or decompose (blue). Finally, the methyl radical can react with another equivalent of I(TFA)₃ to form the product MeTFA and propagate the reaction (equation 15).

Scheme 2. Open shell mechanism of methane activation by I(TFA)₃^a.

^aMethane activation in red; decomposition in blue. ^bValues based on experimental BDEs.^[73] All numbers in kcal/mol.

From a close examination of Scheme 2, we see that a number of decomposition pathways may affect the yield of CH₃· radical generation, hence explaining the low yield observed for entry 6. Our case is bolstered by the experimental observation of fluoroform formation as a side product as reported by Konnick et al.,^[79] indicating that their hypervalent iodine reaction may have a radical component as well. Also, evidence of radical CF₃ formation is found for the conversion of methane and iodate/chloride in TFAH.^[55-56]

In comparing entries 6 to 7, we see that the addition of chloride greatly improves yield from 7% to 43%. We first consider the possibility of I(TFA)₃ and Cl⁻ forming adducts (equations 16-18), and we see that substitution of TFA by Cl is favorable for all three reactions. However, we consider that only the formation of I(TFA)₂Cl is feasible since only substoichiometric amounts of KCl are added.

From I(TFA)₂Cl, we may expect thermal homolysis to break either the I–TFA (equation 19) or I–Cl (equation 20) bond. Either way, radicals are formed that can activate methane as in Scheme 2.

The resulting methyl radicals can react with additional I(TFA)₂Cl to form MeTFA (equation 21) in preference to MeCl (equation 22), which provides an explanation for why only MeTFA is observed as an oxidized product.

Non-radical paths for CH₄ activation using potential I(III) intermediates were sought, but no thermally accessible transition states were found (see Supporting Information, Scheme S1).

Entry 8. The reaction of methane and iodate salts in the presence of catalytic amounts of chloride is the chief focus of the report by Fortman et al.^[55] and may be considered the “canonical” hypervalent iodine oxidation reaction. Hence, we devote the bulk of our analysis to this reaction and its variations.

We begin by noting that while iodate is quite basic in TFAH solution under reaction conditions (equation 23) and thus protonated to HIO₃, chloride, iodide, and water are all weak bases (equations 24-26, respectively) and remain unprotonated.

Furthermore, we note that if elemental iodine is in the system (as it is the eventual fate of iodate in the reaction^[55-56]), it can complex to chloride and iodide (equations 27-28, respectively). This would further decrease the thermodynamic activity of these halides and thus make their protonation even less likely.

Having established that iodate is initially protonated to HIO_3 , we wish to ascertain if the TFAH environment may result in TFA/aqua/chloro adducts being formed. In order to approach this rigorously, we begin by noting that HIO_3 is an I(V) complex with only oxo and hydroxo ligands. In water, an oxo ligand can interconvert with two hydroxo ligands. In TFAH, an oxo can interconvert with two TFA ligands. And in the presence of a chloride salt, hydroxo and TFA ligands may interconvert with chloro ligands. Thus, we would expect HIO_3 in wet TFAH with chloride to exist as a multitude of iodine complexes with a combination of oxo, hydroxo, chloro, and TFA substituents such that the overall oxidation state of the iodine is +5.

A complete accounting of I(V) species in TFAH/ H_2O with optional chloro ligands, along with their relative energies, is given in Table S1. From this table, we can extract the lowest energy I(V) species containing at least one I–Cl bond (Scheme S2). By calculating the difference in energy between each species and the corresponding species with the I–Cl bond broken, we can find the BDEs and free energies for homolytically cleaving each I–Cl bond (see Supporting Information, Scheme S2, in red). These values are in excellent agreement with the previous coupled-cluster work by Dixon and coworkers.^[80] However, we did not find a species with a readily homolyzible bond. The lowest energy species are IO_2Cl_2^- and IOCl_4^- , but breaking the I–Cl bond of these species is endergonic by 44.1 and 37.7 kcal/mol, respectively, which is too unfavorable to be considered as contributing processes. By contrast, the species IOCl_3 and ICl_5 can have their I–Cl bonds broken at a free energy cost of 23.8 and 17.1 kcal/mol, respectively, but they are significantly less stable than IO_2Cl_2^- (G_{rel} of 10.3 and 20.1 compared to –6.5 for IO_2Cl_2^-) and hence not likely to be present in solution.

In considering how the reaction might proceed, we decided to investigate more closely the role of elemental iodine. We have observed experimentally that elemental iodine is formed as a final product in our reaction.^[55] Elemental iodine is well known to be a radical inhibitor, due to the relative inertness (as far as radicals go) of I^- .^[81] Hence, we decided to add the assumption that the system at steady state would include a significant concentration of I^- , either produced from 1), the reaction of other radicals with I_2 , or 2), the autolysis of I_2 itself, which according to equation 1 is endergonic by a relatively accessible 32.2 kcal/mol. A steady state approximation for the reaction kinetics should also affect our calculation for the overall reaction barrier, given later in this section.

We thus look at the reaction of several I(V) species with I^- (Figure S1), and we are gratified to find that the abstraction of Cl is generally facile. In particular, we see that our low energy anionic species IO_2Cl_2^- and IOCl_4^- also have the lowest barriers for reacting with I^- , generating ICl and IO_2Cl^- (which spontaneously decomposes to $\text{IO}_2\cdot$ and Cl^-) or $\text{IOCl}_3\cdot$, respectively (equations 29–30).

Both ICl and $\text{IOCl}_3\cdot$ can generate Cl radicals: ICl through reaction with I^- , and $\text{IOCl}_3\cdot$ through auto-dissociation (equations 31–32).

^aValues based on experimental BDEs.^[73] All numbers in kcal/mol.

Both $\text{IO}_2\cdot$ and Cl^- radicals are able to initiate hydrogen abstraction from methane (equations 32 and 8, respectively). The HCl produced by equation 8 is then deprotonated and absorbed by I_2 (equations 24 and 27), while the HIO_2 produced by equation 32 disproportionates to HIO_3 and HOI (equation 33), which can then convert to additional ICl (equation 34). A more detailed treatment of HIO_2 and other I(III) species can be found below in the section for entries 11–14.

^aValues based on experimental BDEs.^[73] All numbers in kcal/mol.

Due to the presence of elemental iodine in the reaction, the methyl radicals produced will most likely react with I_2 to produce CH_3I (equation 35), which is converted to the product CH_3TFA under reaction conditions (equation 36). Finally, the iodine radicals can recombine to form additional I_2 (equation 37), and the iodide produced in equation 36 can comproportionate with HIO to produce additional elemental iodine (equation 38).

^aValues based on experimental BDEs.^[73] All numbers in kcal/mol.

Scheme 3 shows the synthesis of the above equations into a full mechanism for the conversion of methane to methyl trifluoroacetate for the iodate-based OxE process. The mechanism proceeds through typical phases of initiation, propagation, and termination. During initiation, the lowest energy I(V)–Cl species are formed, and I^- radical is generated. Propagation begins with the I^- radical reacting with the I(V) species to create the more reactive radicals $\text{IO}_2\cdot$ and Cl^- (reactive radical activation). The radicals $\text{IO}_2\cdot$ and Cl^- then abstract hydrogen atoms from methane, which rebounds on elemental iodine to form methyl iodide and regenerate I^- (methane activation and iodine radical regeneration). Finally,

methyl iodide can undergo S_N2 attack by TFA^- to produce the methyl TFA product, and the iodide and HIO_2 can disproportionate and comproportionate to form additional iodate and elemental iodine (iodate regeneration).

In order to estimate the overall kinetic barrier for Scheme 3, we consider a steady-state approximation for $[I\cdot]$, using the method in Carey and Sundberg's *Advanced Organic Chemistry* page 683.^[82] We approximate that the rate of formation and destruction of $I\cdot$ to be equal, i.e. $k_1[I_2] = k_{-1}[I\cdot]^2$, where $k_1[I_2]$ is the rate of initiation (equation 1) and $k_{-1}[I\cdot]^2$ the rate of termination. Then, $[I\cdot] = \sqrt{k_1/k_{-1}}[I_2]^{1/2}$. We can also say that the rate of the reaction is the rate of a propagation step, for example equation 29: $\text{rate} = k_{29}[I\cdot][IO_2Cl_2^-] = k_{29}\sqrt{k_1/k_{-1}}$

$[I_2]^{1/2}[IO_2Cl_2^-]$. Hence, the rate constant is $k = k_{29}\sqrt{k_1/k_{-1}}$.

Using the Eyring-Polanyi equation $k = \frac{k_B T}{h} \exp\left(-\frac{\Delta G^\ddagger}{RT}\right)$,^[83-84] we see that overall activation barrier is then $\Delta G^\ddagger = -RT \ln\left(\frac{h}{k_B T} k_{29} \sqrt{k_1/k_{-1}}\right) = \Delta G_{29}^\ddagger - \frac{1}{2} RT \ln(k_1/k_{-1}) = \Delta G_{29}^\ddagger + \frac{1}{2} \Delta G_1^\ddagger - \frac{1}{2} \Delta G_{-1}^\ddagger$. If we assume that the dissociation and reformation of I_2 has minimal barrier, we can approximate $\Delta G_1^\ddagger \approx \Delta G_{-1}^\ddagger$ and $\Delta G_{-1}^\ddagger \approx 0$. Since we have calculated $\Delta G_{29}^\ddagger$ as 4.5 kcal/mol (Scheme 3) and ΔG_1 as 32.2 kcal/mol (equation 1), we estimate the effective barrier to be about 20.6 kcal/mol.

Scheme 3. Overall summary of the mechanism for the iodate-based OxE process for methane oxidation. All numbers in kcal/mol. *Values based on experimental BDEs.^[73]

Initiation:

Propagation:

Reactive radical activation

Methane activation

Iodine radical and iodate regeneration

Termination and product formation

Equation 39 shows the overall reaction of the iodate/chloride oxidation.

Entry 8, acetic acid variation. Previously, we showed that the reaction of methane and iodate/chloride in acetic acid produces methyl acetate (MeOAc).^[55] However, on further evaluation, it was found that MeOAc formed under these conditions is the result of the reaction with acetic acid only and that the majority of the MeOAc is not derived from methane oxidation. Control

reactions in the absence of methane gave statistically identical MeOAc yields as reactions that include methane, approximately 30% yield with respect to oxidant using 0.67 mmol KCl and 7.7 (39) mmol of NH_4IO_3 in acetic acid. Furthermore, GC-MS analysis of the reaction of perprotio-methane in acetic acid- d_4 indicated that the fully deuterated derivative $CD_3CO_2CD_3$ accounts for > 90% of methyl acetate production, while the product that would arise from methane functionalization, $CD_3CO_2CH_3$, accounts for < 2% of the methyl acetate product.

Using DFT, it is readily apparent that the same mechanism proposed for the iodate-based OxE process in TFAH when translated to acetic acid solvent will not work. The biggest difference between acetic acid and TFAH is the much milder acidity of acetic acid. In equation 23, we see that iodate is quite

basic in TFAH and is expected to be fully protonated. However, by comparison we can see from equation 40 that iodate is a weak base in HOAc and is expected to remain in the anionic form. Chloride is expected to remain anionic in both cases (equations 24 and 41); however, in HOAc it is not expected to be absorbed by elemental iodine (compare equation 42 to 27).

^aValues calculated for HOAc solution All numbers in kcal/mol.

The calculated energies of various I(V)–Cl species compared to this new $\text{IO}_3^-/\text{Cl}^-$ baseline reveal that they are much higher in energy (Figure S2). We are simply unable to form the same quantities of the I(V)–Cl intermediates necessary to generate high energy radicals. We also note that the H–O bond in acetic acid is much weaker (BDE 112 kcal/mol) than that in TFAH (124.5 kcal/mol); hence, radicals that are generated are much more likely to react with the acetic acid solvent, abstracting H atoms to form species such as $\cdot\text{CH}_2\text{CO}_2\text{H}$ and $\text{CH}_3\text{CO}_2\cdot$, which may decompose to liberate CO_2 and form other radicals such as $\text{CH}_3\cdot$ that ultimately become MeOAc.

Entries 9-10. The mechanism for IO_3^- and Cl^- as described for entry 8 can easily hold if the iodate source is replaced by $(\text{IO}_2)_2\text{S}_2\text{O}_7$. We would expect any water in the system to hydrolyze $(\text{IO}_2)_2\text{S}_2\text{O}_7$ to HIO_3 and H_2SO_4 (equations 43-44). Hence, it is expected the same mechanism with improved yield due perhaps to the improved acidity of the system.

Note that HS_2O_7^- and HSO_4^- , like Cl^- and I^- , are weak bases in TFAH, but $\text{S}_2\text{O}_7^{2-}$ and SO_4^{2-} are favorable in reacting with TFAH and are thus protonated (equations 45-48).

Also note that H_3O^+ is a weak acid in TFAH (equation 49), and since the reaction generates H_2O as a byproduct, we would expect H_3O^+ and not TFAH_2^+ to be the active Brønsted acid in acidic wet TFAH solution. Although $\text{H}_2\text{S}_2\text{O}_7$, H_2SO_4 , HCl , and HI are all considered strong acids in aqueous solution, due to the much lower dielectric constant of TFAH, none of them are likely to protonate H_2O in TFAH solution (equations 50-53).

We also note that with the conversion of $(\text{IO}_2)_2\text{S}_2\text{O}_7$ to HIO_3 and H_2SO_4 , the system is still not acidic enough to remove chloride from its sequestration by elemental iodine (equations 54-55).

Although in basic solution the energies of I(V) species can be referenced to the species HIO_3 , I_2Cl^- , I_2 , H_2O , TFAH, and TFA^- , in acidic solution they should be referenced to the species HIO_3 , I_2Cl^- , I_2 , H_2O , TFAH, H_2SO_4 , and HSO_4^- . The columns in Table S1 that are marked “acid” show the energies of the I(V) species recalculated to this new reference. As in the basic case of the $\text{IO}_3^-/\text{Cl}^-$ system, the lowest energy species formed are still IO_2Cl_2^- and IOCl_4^- , with the only difference being that IOCl_4^- is now favored over IO_2Cl_2^- . Scheme S3 shows the new initiation steps for the methane oxidation in acidic condition (i.e., $(\text{IO}_2)_2\text{S}_2\text{O}_7$), whereas the propagation and termination steps remain the same as for Scheme 3.

Entries 11-14. I_2O_4 and $(\text{IO})_2\text{SO}_4$ can be analyzed as ionic species, consisting of a linear polymeric cationic $(\text{IO})_n^{n+}$ chain with either IO_3^- or SO_4^{2-} as the counterion.^[85-86] The iodine atoms in $(\text{IO})_n^{n+}$ have a formal positive charge, and the counterions may be coordinated to them (strongly so in the solid and in low dielectric solvents; more weakly in high dielectric solvents such as ethanol and dimethylformamide).^[86] We see that the $(\text{IO})_n^{n+}$ chain itself must be active in effecting methane oxidation, since entry 14 shows that the reaction works with an inert sulfate counterion. In general, it is known that I(V) salts are more stable than I(III), and indeed, both I_2O_4 and $(\text{IO})_2\text{SO}_4$ are known to disproportionate to HIO_3 and I_2 in hot water and sulfuric acid, respectively.^[85] We would thus expect HIO_3 to be likely formed in hot TFAH as well.

Our computational studies initially indicated that $(\text{IO})_n^{n+}$ chains in TFAH are unstable with respect to dissociation into $\text{I}=\text{O}^+$ monomers (equation 56).^[87-88] However, iodate or sulfate is the counterion, and both are very basic (equations 23 and 48), leading to the formation of TFA^- , which can very favorably react with IO^+ to form $\text{TFA}-\text{I}=\text{O}$ (equation 57). The $\text{TFA}-\text{I}=\text{O}$ produced can further add a water or TFAH molecule across the $\text{I}=\text{O}$ double bond (equations 58-59), or polymerize (equations 60-61). Table S2 shows a comprehensive listing of all monomeric I(III) species that may be formed in TFAH solution. The lowest energy monomeric species is ICl_3 in both basic and acidic systems. Since the polymerization of $\text{I}(\text{OH})\text{TFA}_2$ is approximately thermoneutral (equation 61), and since ICl_3 is significantly lower in energy than $\text{I}(\text{OH})\text{TFA}_2$ (equation 62), we can restrict our mechanistic considerations to monomeric I(III) species only.

We now see that the species involved here form the same collection of species in the reactions of entry 5 (ICl_3) and entry 7 ($ITFA_3/Cl^-$). As in the case of entry 7, MeTFA and not MeCl is formed due to the catalytic amounts of Cl^- preventing the build-up of ICl_3 itself. We can also consider a disproportionation route to form I(V) that can enter that mechanistic route. In one such example, monomeric $I(O)TFA$ favorably disproportionates to IO_2TFA (equation 63), which can then convert to HIO_3 (equation 64). The I(V) mechanism as for the iodate reaction (entry 8) then applies. The TFAI byproduct can convert to ICl (equation 65) and enter the I(V) mechanism from there.

Entry 15. Periodate can actually refer to two different ions: metaperiodate (IO_4^-) and the water adduct orthoperiodate ($H_4IO_6^-$).^[85] Whereas orthoperiodate is generally known to be the preferred species in aqueous solution, we wanted to ascertain if metaperiodate persists under our reaction conditions (potentially wet TFAH). Scheme S4 shows that both addition of water and protonation to IO_4^- is unfavorable; hence, we can begin our analysis with the IO_4^- species itself.

In the presence of elemental iodine, comproportionation to iodate is favorable (equation 66). In the absence of I_2 , chloride may serve as a reducing agent instead (equations 67-68).

As shown in Scheme 3, in the presence of chloride the iodate can oxidize methane to CH_3TFA and generate HIO_2 (equation 32), which then disproportionates to regenerate HIO_3 through several other iodine oxyacids (equations 33-34). The hypochlorous acid produced in equations 67-68 can react with these iodine oxyacids, aiding in the regeneration of HIO_3 (equations 69-70).

Because IO_3^- is generated from IO_4^- (equation 66), our mechanism for IO_3^- (entry 8) should also be valid for IO_4^- . However, since IO_4^- can be expected to make a much richer set of chloro, TFA, oxo, and hydroxo complexes than IO_3^- , we have only demonstrated the feasibility of one possible reaction pathway (IO_4^- to methane oxidation via IO_3^-) without discounting the possibility of other pathways. Equation 71 shows the overall reaction of the periodate/chloride oxidation, which is even more downhill than iodate/chloride oxidation (compare to equation 39).

DISCUSSION

As mentioned above, a common limitation of radical mechanisms is the difficulty of preventing over-oxidation. For example, free radical chlorination of methane at reasonable conversions often yields a mixture of methyl chloride, methylene chloride, chloroform, and/or carbon tetrachloride.^[91] Methane oxidation by electrophilic C-H activation can be selective for CH_3X ($X = TFA, SO_3H$, etc.) due to the electron-withdrawing nature of X acting as a protecting group.^[25-26] In the iodate/chloride OxE process, methane and ethane were oxidized to CH_3TFA and $EtTFA$ respectively, with conversions greater than 20% and with formation of minimal over-oxidized products.^[55] Is it possible that TFA could serve as a protecting group against radical oxidation?

Consider the immediate result of a radical H-atom abstraction on CH_3TFA : the formation of the radical $\cdot CH_2TFA$. A case could be made that a lone pair on the O atom of TFA directly bound to the CH_2 can stabilize the radical via the formation of a two-centered, three-electron bond.^[82] This would make radical attack on CH_3TFA and thus over-oxidation more likely, similar to observations for methane oxychlorination. A case could also be made that in the transition state $[TFACH_2\cdots H\cdots Cl]^\ddagger$, the C has partial cationic character due to the electronegative nature of the Cl atom. The presence of the electron-withdrawing TFA group thus destabilizes the transition state in what is termed a radical polar effect, and hence inhibits over-oxidation.^[92]

In order to investigate the competing trends of lone pair stabilization and polar effect destabilization, we examine several radical abstraction reactions and compare them to equation 8 (equations 72-76). Our insights from the comparisons are summarized in Table 2.

Table 2. Comparison of radical H-abstractions to isolate polar and lone pair effects.

Comparison	$\Delta\Delta G^\ddagger$	$\Delta\Delta G$
CH₄ v. CH₃TFA + Cl$\cdot$ (eqs. 8 v. 73)	2.9	-0.7
CH₄ v. CH₃TFA + Br$\cdot$ (eqs. 72 v. 74)	4.1	-0.7
CH₄ v. CH₃Cl + Cl$\cdot$ (eqs. 8 v. 75)	0.4	-2.0
CH₃Cl v. CH₂Cl₂ + Cl$\cdot$ (eqs. 75 v. 76)	0.7	-1.3

As shown in the final column of Table 2, the calculated $\Delta\Delta G$ s confirm the lone pair stabilization effect: In all cases, ΔG for the reaction $\text{Y}\cdot + \text{CX}_n\text{H}_{4-n} \rightarrow \text{HY} + \text{CX}_n\text{H}_{3-n}\cdot$ is lower if X is a substituent such as Cl or TFA as opposed to H.

From examining the $\Delta\Delta G^\ddagger$ column instead, we see that the transition state for H atom abstraction for $\text{CH}_3\text{TFA} + \text{Y}\cdot$ ($\text{Y} = \text{Cl}$ or Br) is about 3–4 kcal/mol higher than the corresponding transition state for $\text{CH}_4 + \text{Y}\cdot$. This is the polar effect, and it can be confirmed by Mulliken charges (Table S3). The charge on carbon in CH_4 is -0.60 due to the relative electronegativity of carbon versus hydrogen. For CH_3TFA and CH_3Cl , this increases to -0.33 and -0.40, respectively; due to the electron withdrawing TFA or Cl groups, which have Mulliken charges -0.27 and -0.12, respectively. In the transition states $[\text{CH}_3\cdots\text{H}\cdots\text{Cl}]^\ddagger$ and $[\text{CH}_3\cdots\text{H}\cdots\text{Br}]^\ddagger$, the charge on C is increased to -0.52 and -0.51, respectively; an illustration of the polar effect due to the electronegative Cl and Br atoms. In the comparison of CH_3TFA to the transition states $[\text{TFACH}_2\cdots\text{H}\cdots\text{Cl}]^\ddagger$ and $[\text{TFACH}_2\cdots\text{H}\cdots\text{Br}]^\ddagger$, the charge on TFA is increased from -0.27 to -0.16 and -0.07, which is quite destabilizing due to the electron-withdrawing nature of the TFA substituent. The charge on Cl for CH_3Cl and $[\text{ClCH}_2\cdots\text{H}\cdots\text{Cl}]^\ddagger$ similarly increases from -0.12 to 0.10, but this is less destabilizing due to the greater polarizability of Cl. As for CH_2Cl_2 and $[\text{Cl}_2\text{CH}\cdots\text{H}\cdots\text{Cl}]^\ddagger$, the average charge on the Cl's increases from -0.01 to 0.16. Thus, we see the relative lack of over-oxidation protection for CH_3Cl and CH_2Cl_2 .

This analysis explains the reason for the increased $\Delta G^\ddagger$ of CH_3TFA activation, and thus the origin of protection against over-oxidation.

CONCLUSION

We have examined existing experimental data regarding the oxidation of methane to methyl trifluoroacetate using a wide variety of hypervalent iodine complexes, and used DFT to model viable mechanistic pathways for each reaction. Although there is a wide variety of iodine reagents capable of effecting the reaction, the tendency of iodine complexes to disproportionate into I_2 and I(V) serves as a “funnel” that unites the sundry iodine precursors into the same mechanism based on iodic acid. In our common iodate/OxE mechanism, iodic acid is converted to IO_2Cl_2^- or IOCl_4^- as the key intermediate, which

reacts with iodine radicals present in the system to form $\text{IO}_2\cdot$ and $\text{Cl}\cdot$ radicals. These radicals are able to mediate the C–H bond cleavage of methane, leading to CH_3I and ultimately the final product, CH_3TFA , which is protected from further oxidation by the polar effect.

We thus report a simple and unifying solution to the mechanism of the iodate/OxE process, a problem that initially appears to involve an intractable soup of chemical species. These insights may serve as a starting point for further investigations into this class of oxidation reactions.

ASSOCIATED CONTENT

Supporting Information. Additional schemes and tables and a spreadsheet containing raw data for all chemical species studied. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

All calculations were carried out by RF, with strategies suggested by RF, RJN, and WAG. Experimental work was carried out by NSL under mentorship by TBG. Critical guidance was provided by JTG and TBG. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

BDE, bond dissociation energy; DFT, density functional theory; OxE, oxy-esterification; OAc, acetate; PBF, Poisson-Boltzmann Finite element method; SCF, self-consistent field; SMR, steam-methane reformation; TFA, trifluoroacetate.

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87. For $(\text{IO})_n^{n+}$ specifically, we optimized the geometry in solution phase, since a gas phase optimization would inevitably fail due to the large amount of positive charge.
88. $n = 2$: $\Delta H = 19.9$, $\Delta G = 30.0$; $n = 3$: $\Delta H = 16.9$, $\Delta G = 29.9$; $n = 4$: $\Delta H = 18.1$, $\Delta G = 32.8$.
89. $n = 0$: $\Delta H = -24.8$, $\Delta G = -6.1$; $n = 1$: $\Delta H = -23.9$, $\Delta G = -4.2$; $n = 2$: $\Delta H = -28.8$, $\Delta G = -7.5$; $n = 3$: $\Delta H = -27.9$, $\Delta G = -5.8$; $n = 5$: $\Delta H = -28.7$, $\Delta G = -8.3$.
90. $n = 0$: $\Delta H = 0$, $\Delta G = 0$; $n = 1$: $\Delta H = 0.9$, $\Delta G = 1.9$; $n = 2$: $\Delta H = -4.1$, $\Delta G = -1.4$; $n = 3$: $\Delta H = -3.2$, $\Delta G = 0.3$; $n = 5$: $\Delta H = -3.9$, $\Delta G = -2.2$.
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Methane oxidation by hypervalent iodine!

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