Hydrogen bonding to hexafluoroisopropanol controls the oxidative strength of hypervalent iodine reagents

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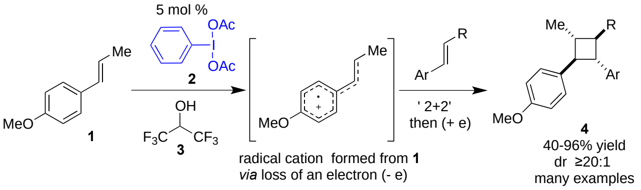
Supporting Information Placeholder

ABSTRACT: Hexafluoroisopropan-2-ol (HFIP) has been found to be an unusually beneficial solvent for undertaking hypervalent iodine initiated [2+2] cycloaddition of styrenes. For the initiator phenyliodine(III) diacetate (PIDA), voltammetric data demonstrates that the enhanced reactivity in HFIP is due to its greater oxidizing abilities in this fluorinated solvent. Such that in HFIP the reactivity of PIDA is comparable if not superior to its fluorinated analog phenyliodine(III) bis(trifluoroacetate) (PIFA). These results contrast with the often reported view that the role of the fluoroalcohol is to stabilize a radical cation formed by single electron transfer. Moreover, combined NMR and HRMS results reveal the formation of a strong H-bonded adduct between the solvent and oxidizing reagent which is the physical origin of the observed altered synthetic reactivity.

1. INTRODUCTION

Hypervalent iodine reagents exhibit diverse reactivity and find widespread use in organic synthesis.[1] Much of their chemistry is analogous to that found for transition metal complexes. As an extension of these properties, under suitable conditions they may be utilised as less toxic and safer replacements for heavy metal oxidants. Surveying the literature reveals the common and regular usage of fluorinated solvents in combination with this class of reagents.[2] Specifically in the case of single electron transfer (SET) reactions the requirement and benefit of the use of solvents such as hexafluoroisopropanol (HFIP) and trifluoroethanol are often attributed to their ability to stabilize radical cations.[3] As compared to many other solvents the properties of HFIP are extreme, it is highly polar, strongly hydrogen-bond donating and very weakly nucleophilic. The use of HFIP as a solvent or additive is known to kinetically enhance or alter the selectivity of a number of synthetically important reactions. Most notable is its use in combination with hydrogen peroxide for both epoxidations and Baeyer-Villiger oxidations,[4] as well as a H-bond donor to epoxides or carbonyl compounds, therefore increasing their electrophilicity.[5] It has been recently reported that hypervalent iodine reagents such as phenyliodine(III) diacetate (PIDA, **2**, Scheme 1) can initiate the dimerization of styrenes (see *trans*-anethole, **1**, Scheme 1) in hexafluoroisopropanol (HFIP, **3**, Scheme 1), leading to the synthesis of cyclobutanes **4**.[6] Approaching the stereoselective synthesis of substituted cyclobutanes is of great interest and represents a challenging topic in organic chemistry.[7] Despite the presence of the cyclobutane moiety in different natural products with antifungal, anticancer and many other biological activities,[8] the absence of reliable, efficient and benign methods for its synthesis and incorporation into complex molecules has hampered its widespread use.

Scheme 1. Hypervalent iodine initiated homo- and cross dimerization of styrenes in hexafluoroisopropanol



This synthetic [2+2] cycloaddition is used in the present work as an exemplar reaction by which the reactivity of the hypervalent iodine(III) reagents may be explored. The formation of the cyclobutane is considered to initially proceed via single electron oxidation of the alkene **1**, to form a radical cation intermediate that can react with another molecule of **1** (homodimerization) or with a different alkene (hetero- or cross dimerization). HFIP was found to be a unique solvent in which the hypervalent iodine reagents can act as single electron oxidants in the cyclobutane forming process.[9] Importantly, analogous [2+2] cycloadditions have been seen in other organic solvents (typically CH_2Cl_2 and acetonitrile (ACN)) when initiated using a triaryl amine radical cation, anodic oxidation or photoredox catalysis[10] (although we found that the sole use of PIDA in both dichloromethane or acetonitrile did not lead to the formation of the cyclobutane product). In light of the above-mentioned results this work provides a systematic investigation of the redox properties of the alkene and the oxidant in both ACN and HFIP. The voltammetric oxidation of a series of electron-rich styrenes demonstrates that the fluorinated solvent HFIP only *relatively* minimally alters the oxidative response of the alkene. Hence, the influence of the fluoroalcohol is reassessed and the significant role hydrogen bonding[11] with the fluorinated solvents has upon controlling the reactivity of the PIDA is illuminated.

3. RESULTS AND DISCUSSION

This work first studies the altered reactivity of PIDA towards *trans*-anethole. In HFIP, as opposed to ACN, this reaction is found to proceed and leads to the formation of the cyclobutane product. Having evidenced the physical origin of the altered reactivity the article continues by considering the reactivity of related substituted styrenes and iodinanes.

3.1 The electrochemical behavior of *trans*-anethole and phenyliodine(III) diacetate. The oxidation of *trans*-anethole **1** was recorded voltammetrically at a glassy carbon electrode in both HFIP (Figure 1 A) and acetonitrile (SI section 2.1). In both solvents a well-defined irreversible oxidative feature was observed (at +0.85 V and +1.02 V vs. Ferrocene, for HFIP and ACN respectively). In acetonitrile this electrochemical oxidation is known to correspond to the one electron oxidation of the *trans*-anethole species followed by an irreversible and fast dimerization (log k ($M\ s^{-1}$) = 8.6±0.4) of the formed radical cation.[12] In HFIP the oxidative voltammetric response was confirmed to correspond to the one electron oxidation of the *trans*-anethole. This assessment of the numbers of electrons transferred was achieved via recording of the voltammetric response at an ultramicroelectrode. Comparison of the steady-state and linear diffusive response enables direct assessment of the number of electrons transferred during the course of the electrochemical oxidation (SI section 2).

The oxidative peak potential of the *trans*-anethole at a macro electrode in HFIP and ACN (Figure 1 A and SI section 2.1) reflects both the thermodynamics and kinetics of the chemically irreversible redox process. By using ferrocene as an internal redox marker the potential difference between the oxidation of *trans*-anethole in the two solvents is measured to be -0.18 V, thus evidencing the oxidation of the alkene to be easier in HFIP. Relatively weak stabilizing effects of HFIP on extensively delocalized radical cations have been previously reported. For example the formal potential for the one-electron oxidation of durene (1,2,4,5-tetramethylbenzene) in HFIP was shifted by -0.14 V versus that recorded in dichloromethane.[13] Hence, the observed shift of -0.18 V between the two solvents is consistent with the greater radical cation stabilizing abilities of HFIP over ACN.

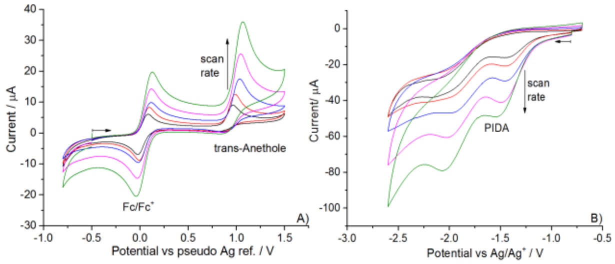


Figure 1: The voltammetric response of A) *trans*-anethole 1 mM (oxidation) and B) phenyliodine(III) diacetate 2 mM (reduction) in HFIP (0.1 M Bu_4NPF_6) recorded as a function of scan rate (0.025-0.4 V s^{-1}) at a glassy carbon electrode (radius = 1.5 mm). In A) the reversible voltammetric response of ferrocene is also shown, the ferrocene was used as an internal redox reference potential. In B) a silver/silver hexafluorophosphate reference electrode ($E_{ferrocene}$ = -0.988 V vs Ag/Ag^+) was used due to reaction between the ferrocene and PIDA. The horizontal arrow indicates voltammetric starting potential and initial scan direction.

The use of electrochemical techniques for studying cathodic processes in HFIP is limited; this situation has plausibly arisen due to the reduction processes of interest being obscured by concomitant hydrogen evolution. However, the use of non-metallic electrodes such as boron-doped diamond or glassy carbon can effectively extend the potential window of study due to their associated sluggish electron transfer kinetics towards proton reduction.[14] The reduction of PIDA was studied in both HFIP (Figure 1 B) and ACN (SI section 2.3) using a glassy carbon macro-electrode. In HFIP the presence of both PIDA and ferrocene in solution led to rapid reaction and decomposition of the PIDA as evidenced by the change in the solution color. This is in contrast to solutions of PIDA and ferrocene in ACN which were found to be stable. Consequently, the voltammetry of PIDA in HFIP was recorded against a silver/silver hexafluorophosphate reference electrode. The ferrocene redox potential was determined to be -0.988 V vs Ag/Ag^+ in HFIP (see SI section 2.5), this measurement enabled direct comparison of the voltammetric data across the two solvents.

In both ACN and HFIP the reduction of PIDA exhibits two distinct voltammetric reduction waves. In both cases the analysis of the first reduction wave indicated the transfer of up to three electrons to the PIDA (SI section 2) over the course of the voltammetric reduction. On the basis of the molecular structure it may be anticipated for the hypervalent iodine to undergo two two-electron transfers with the formation of iodobenzene after the first reduction wave. However this aside, importantly, for the voltamemtric reduction in both solvents the transfer coefficients were measured to be 0.3 and 0.4 in ACN and HFIP respectively, indicating the first electron transfer to be rate determining in both cases. Most notably the reduction of PIDA occurs at a 0.85V less negative potential (versus ferrocene) in HFIP as compared to ACN. The voltammetric peak potentials for both the oxidation ($E_{p,a}$) of *trans*-anethole and the reduction ($E_{p,s}$) of PIDA in both HFIP and ACN are summarised in Table 1. Also given in Table 1 are the differences in the reduction and oxidation peak potentials ($\Delta E_{p\text{-}p}$) in these two solvents. From these data, two points should be highlighted. First, in both solvents the voltammetric reduction of the iodinane is at a significantly lower potential than the *trans*-anethole oxidation. This large difference in potentials likely indicates the electron transfer to PIDA from the *trans*-anethole is endergonic. This result is in agreement with previous work which has highlighted how for SET initiated cycloadditions the oxidant should be sufficiently weak so as to ensure only low concentrations of the radical cation are produced in-situ avoiding dimerisation and associated formation of the dication.[15] Second, the difference between the voltammetric oxidation and reduction peak potentials is almost a Volt less in HFIP as compared to ACN! This change in the peak potentials predominantly reflects the significantly easier reduction of PIDA in HFIP. These results evidence the strong enhancement of the oxidising abilities of PIDA in HFIP and yield insight into why the synthetic reaction is successful in HFIP but not ACN.

Table 1. The voltammetric peak potentials for two redox species measured versus Fc/Fc$^+$ as measured at 100 mV s^{-1}

	ACN	HFIP
***trans*-anethole 1 $E_{p,a}$**	1.02 V	0.85 V
PIDA 2 $E_{p,c}$	-1.32 V	-0.47 V
Δ $E_{p\text{-}p}$	**-2.35 V**	**-1.31 V**

3.2 Characterising the altered reactivity of PIDA in HFIP by MS and NMR. Although the voltammetric response reported above evidences a significant shift in the oxidising abilities of the PIDA in HFIP such techniques do not readily yield insight into the physical origin of this altered reactivity. Due to the irreversibly of the electrochemical process the shift in the voltammetric wave may reflect a change in the kinetics or the thermodynamics associated with first (rate determining) electron transfer. In light of the importance of ligand exchange as a dominant reaction route for many iodinane synthetic pathways one plausible explanation for the altered reactivity in HFIP is the substitution of the acetate groups by the solvent. Such a ligand exchange might be anticipated to be observed via High Resolution Mass Spectrometry (HRMS).

The HRMS of PIDA (**2**) was recorded and the pattern of ionization peaks found to be in agreement with the literature (See SI section 3 for more details).[16] The main species detected are the Na$^+$ (344.9588) and K$^+$ (360.9326) adducts, as well as [PhIO-AcOIPh]$^+$ (482.8936), [PhI]$^{\cdot+}$ (203.9428) and [PhIOAc]$^+$ (262.9559). Similarly, the HRMS for HFIP (**3**) resulted in the observation of the anion derived from the loss of H$^+$ [(CF$_3$)$_2$CHO]$^-$ (166.9934). Importantly, the HRMS for a 1:1 mixture of PIDA:HFIP (**5**) gave the same mass spectra as obtained for PIDA (**2**), without the observation of any new formed species (within the sensitivity of the HRMS). This null result, although not conclusive, tentatively allows ligand exchange as a cause for the altered reactivity to be ruled out. This apparent lack of exchange with the HFIP is consistent with the low nucleophilicity of the solvent.

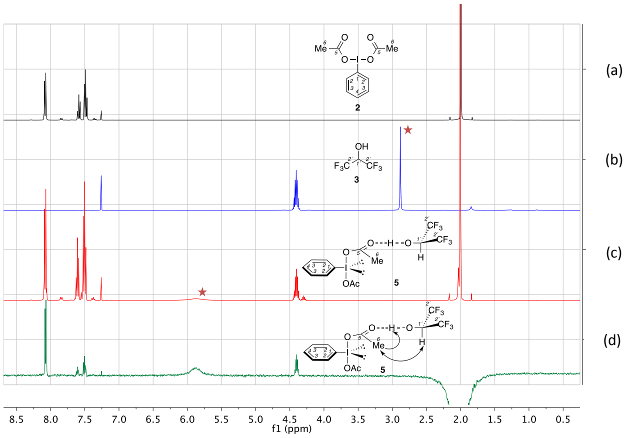


Figure 2. ^{1}H NMR of (a) PIDA (2), (b) HFIP (3), (c) 1:1 mixture of PIDA:HFIP (5) and (d) 1-D gradient nOe with T_{mix} of 800msec for the 1:1 mixture of PIDA:HFIP (5) when irradiating 6-H$_3$ (Me), showing a plausible structure of an adduct; the key nOe with arrows (See supporting information for a complete study of nOe and NOESY-2D). Red star indicates the position of the deshielded $^-$OH signal of interest.

As an alternate explanation, the enhanced reactivity of PIDA in HFIP, may relate to the protic nature of the solvent, notably HFIP has a pK$_a$ in water of 9.3 (as compared ~17 for iso-propanol).[13a] Nuclear Magnetic Resonance (NMR) was utilised to gain insight into this question. First, using ^{1}H NMR and ^{13}C NMR (See SI section 4 for full characterization and further details) the spectra of the species separately and in mixture were recorded. Figure 2 shows the ^{1}H NMR for PIDA (**2**), HFIP (**3**) and a 1:1 mixture of PIDA:HFIP (**5**) in CDCl$_3$.[17] The ^{1}H NMR spectra of the 1:1 complex of PIDA with HFIP (**5**, Figure 2c) is predominantly simply the sum of the two individual spectra. However, we observed a deshielded shift of the OH signal in HFIP (**3**, Figure 2b) from 2.88 ppm to 5.88 ppm in the 1:1 adduct (**5**, Figure 2c), accompanied by broadening of the linewidth. Such a shift in the OH signal is consistent with the formation of a H-bonded adduct between the HFIP and PIDA.[18, 19] To further evidence the presence of a H-bonded adduct nuclear Overhauser effect (nOe) and diffusion-ordered spectroscopy (DOSY)[20] experiments were performed. NOe experiments provide evidence of dipolar spatial interactions between protons, nearby in space 2.5-4.5Å. On irradiating the PIDA Me signal of the equimolecular mixture of PIDA:HFIP (**5**) at 2.01 ppm (Figure 2d) significant nOes were observed with the HFIPA broad OH signal at 5.88 ppm as well as with the HFIP 1´-H at 4.40 ppm (See supporting information for a complete study of the nOe and NOESY-2D).

Using NMR, molecular association via H-bonding can be monitored via the differences in the diffusion coefficients (as partially reflecting molecular size) of the species involved. DOSY experiments allow quantitative study, via NMR, of the species diffusion coefficients as measured relative to an internal reference (here TMS, chosen for its non-interacting properties and low chemical shift).[20b] The ratio of the diffusion between the species of study and the reference compound (D/D_{ref}) is relatively independent of solution viscosity. Consequently, any change in this ratio for the H-bonded adduct compared to the separate H-donor and/or the H-acceptor components may be attributed to the association of the components.

Table 2. Diffusion coefficients of PIDA (2), HFIP (3) and the 1:1 mixture of PIDA:HFIP (5) in CDCl$_3$ as measured via DOSY

Compound	***D* (10^{-9} m^2 s^{-1})**	***D* / *D*^{TMS}**
TMS	2.13	1.00
2	1.09	0.52
3	2.49	1.10
5	PIDA 1.09	0.51
5	**HFIP 1.35**	**0.63**

The results of the DOSY experiments (see SI section 4 for the complete account of experiments) and the measured diffusion coefficients (Table 2) confirm the existence of a H-bonded species upon mixing both H-donor HFIP (**3**) and H-acceptor PIDA (**2**). While for PIDA (**2**) the change in the diffusion ratio (D/D_{TMS} from 0.52 to 0.51) upon mixing is small; however for HFIP (**3**) the variation in the diffusion ratio (D/D_{TMS} from 1.10 to 0.63) is considerable. This shows HFIP (**3**) is diffusing more slowly in the presence of PIDA (**2**). Therefore both the nOe and DOSY results suggest the association of the HFIP with the PIDA, presumably via H-bonding. A similar set of NMR experiments were performed with a mixture of PIDA and 2-propanol, and these did not show a significant change in OH chemical shift upon mixing, nor significant changes in the diffusion ratios (DOSY), confirming the unique nature of HFIP. Although the PIDA has been shown to form a H-bonded adduct with the HFIP, a question remains as to whether this interaction serves to predominantly alter the thermodynamics or kinetics of the redox process.[21]

3.3 Exploring the scope of styrene reactivity. Although the use of HFIP as a solvent enables the homo- and hetero dimerisation of a number of styrenes a notable structural motif in the successful reactions is the presence of a *para*-methoxy group. Figure 3 provides a survey of the voltammetric oxidation peak potentials for a variety of substituted *trans*-β-methylstyrenes in both ACN and HFIP (voltammograms from which the data was obtained are shown in the SI section 2.6). As can be seen there is a general correlation between the peak potentials recorded in ACN and HFIP. For all but two of the tested alkenes the voltammetric oxidation is found to occur at a lower potential in HFIP as compared to ACN, specifically the average shift in the oxidative peak potential was recorded to be ~140 mV, as measured against the ferrocene redox indicator. It is concluded that these generally lower peak potentials in HFIP likely reflect the weakly stabilizing nature of the solvent towards the formed cation.

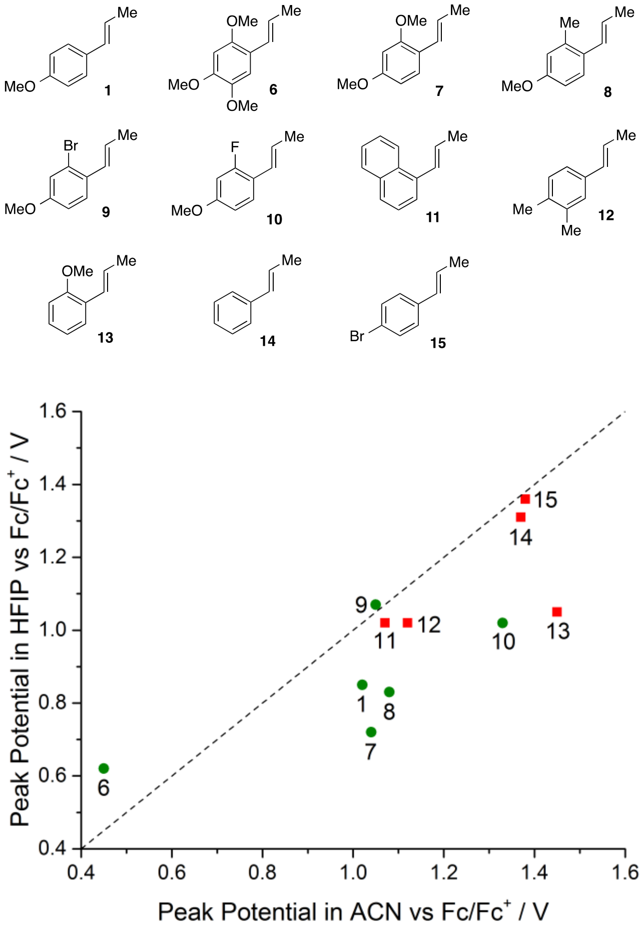


Figure 3. Voltammetric oxidative peak potentials (vs Fc/Fc$^+$ measured at 100 mVs^{-1}) for a series of substituted *trans*-β-methylstyrenes measured in both ACN and HFIP. Dotted line indicates equi-potential between ACN and HFIP. Points in green represent styrenes able to undergo PIDA intitated [2+2] cycloaddtions in HFIP.

None of the listed styrenes have been found to, in the presence of PIDA, react in ACN to form their associated cyclobutane products. However, the styrenes highlighted in green (Figure 3) are able found to undergo reaction in HFIP. Broadly the styrenes exhibiting oxidative peak potentials below ~+1.0V vs Fc/Fc$^+$ in HFIP lead to formation of the [2+2] cycloaddition product. Given that, as has already been discussed, the reduction peak potential of PIDA is found to occur at -0.47 V (vs Fc/Fc+) in HFIP the initiation reaction leading to the formation of the aryl radical cation is likely endergonic in nature. Consequently, for the styrenes with the higher voltammetric oxidation potentials the cycloaddition reaction likely does not proceed due to the initiation being *comparatively* even less thermodynamically favorable for these more electron deficient styrenes. In general the presence of a *para*-methoxy group serves to very effectively activate the styrene, such that all of the most voltammetrically oxidisable styrenes studied contain this functionality. This is true to the extent that even the presence of an *ortho*-methoxy group (**13**) is found to be insufficiently activating to enable the synthetic reaction to proceed.

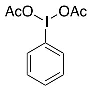
The general correlation between the synthetic and voltammetric data is notable. However, it should be commented that the synthetic reaction will be sensitive to not just the thermodynamics and kinetics of the initiation processes but is also predicated upon the efficiency of the following propagation reactions. Moreover, the position of the oxidative voltammetric wave is, as also previously discussed, sensitive to the involvement of possible further homogeneous chemical reactions.

3.4 Controlling the reactivity of hypervalent iodines with HFIP. This section starts by highlighting the feasibility of using HFIP as an additive with PIDA. Next it looks to evidence the influence of HFIP on two alternate and commonly used iodine (III) reagents, specifically phenyliodine(III) bis(trifluoroacetate) (PIFA) and hydroxy(tosloxy)iodobenzene (HTIB or Koser's reagent). [22]

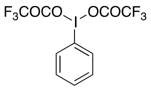
The NMR characterization presented in section 3.2 was performed in deuterated chloroform with 1:1 mixture of the HFIP and PIDA. The strong evidence for the formation of hydrogen bonded adduct leads to the question of the ability to use HFIP not as a solvent but as an additive. Indeed *trans*-anethole in the presence of 5.0 equiv. of HFIP and 10 mol% of PIDA in deuterated chloroform is found to successfully result in the formation of the associated cyclobutane product albeit with a lower yield than obtained when utilizing HFIP as the solvent (35% yield). First, this observation further evidences adduct formation between the oxidant and the fluoroalcohol. Note, conversely, use of HFIP as an adduct in ACN does not lead to significant product formation (<5% yield). Presumably, his arises due to the ACN solvent being a more available hydrogen bond acceptor than PIDA. NMR spectra of HFIP in d_3-ACN exhibited a downfield shift in the alcohol proton of 2.55 ppm, which is interpreted as H-bonding between the solvent and the fluoroalcohol. Second, the lower yields experimentally found with the use of 5.0 equiv. of HFIP as additive in $CDCl_3$ tentatively implies the importance of the hydrogen bonding network in the pure fluoroalcohol in further enhancing the reactivity of the hypervalent iodine.

Beyond PIDA, PIFA and HTIB are two other commonly utilized and commercially available iodine (III) reagents. Importantly, for the present reaction of study the use of PIFA in HFIP as the oxidant does lead to some formation of the cyclobutane product, however the side reactions are extensive resulting in a significantly lower yield (20%). In contrast the use of HTIB does not result in any product formation in either ACN or HFIP. Table 3 shows the experimentally determined voltammetric reduction potentials of these two other iodine (III) reagents in both HFIP and ACN.

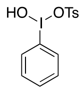
The electronegative nature of the fluoro groups on PIFA serve to significantly enhance the oxidative strength of the reagent in ACN as compared to PIDA (see Table 3 for comparison). Conversely the PIFA voltammetric reduction potential is only 110 mV (vs Fc/Fc$^+$) lower in HFIP. This shift is far smaller than found for PIDA, hence it seems credible that the trifluoroacetate ligands significantly decrease the PIFAs hydrogen bond accepting abilities. This conclusion is corroborated by the associated NMR spectra where for a 1:1 mixture of PIFA and HFIP, **16**, in deuterated chloroform (Figure 4c) the HFIP alcoholic proton signal is only downfield shifted 0.6 ppm as compared to the analogous downfield shift of 3.0 ppm for PIDA.



PIDA



PIFA



HTIB

Table 3. The voltammetric peak potentials for the iodine (III) compounds PIFA and HTIB measured versus Fc/Fc$^+$ as measured at 100 mV s^{-1}

	ACN	HFIP
PIDA $E_{p,c}$	-1.32 V	-0.47 V
PIFA $E_{p,c}$	-0.56 V	-0.45 V
HTIB $E_{p,c}$	-0.42 V	-0.64 V

Extra information supporting the weak interaction between PIFA and HFIP is evidenced using a heteronuclear Overhauser effect experiment, ^{1}H-^{19}F HOESY (See supporting information for a complete study), providing evidence of dipolar spatial interactions between fluorine and protons, nearby in space. On irradiating the PIFA ^{19}F signal of the equimolecular mixture of PIFA:HFIP, **16**, at –73.5 ppm significant effects were observed with the HFIP broad OH signal at 3.70 ppm as well as with the HFIP 1´-H at 4.40 ppm.

These results are in stark contrast to those recorded for Koser's reagent (HTIB) where the iodine (III) specie is on the basis of the voltammetric data found to be a *weaker* oxidant in the fluoroalcohol. Again the NMR data (Figure 4e) does not evidence the hydrogen bonding between the HFIP and HTIB to be particularly strong. Interestingly, in this case the ^{1}H NMR shows a broad signal at 3.90 ppm corresponding to both HTIB-OH and HFIP-OH (Figure 4e); it seems likely that the two protons have become equivalent (a proposed and time-averaged structure is shown in Figure 4e). This would imply HFIP-OH has been downfield shifted by 1.0 ppm, whereas the HTIB-OH by 2.3 ppm, suggesting that HTIB-OH has assumed an H-bond donor role in the proposed system. This type of interaction is possibly the origin of the 'deactivation' of the reagent in HFIP, where the deactivation is evidenced both voltammetrically and synthetically. Finally, complementary DOSY experiments (see SI section 4 for the complete account of experiments) and the measured diffusion coefficients (see SI, Tables 2 and 3) using PIFA and HTIB do not show the existence of very strong H-bonded species upon mixing H-donor HFIP (**3**) and PIFA or HTIB, judged by the small changes on the D/D_{TMS} ratio. This NMR data further corroborates the conclusion that for these two iodine(III) reagents the hydrogen bonding influence is less dominant than found for PIDA.

For the above two hypervalent reagents it is interesting to comment that the influence of the solvent upon their redox behavior is comparable in magnitude to that found for the alkenes. Hence, the lack of reactivity observed with the HTIB in HFIP is due to the deactivation being significant enough to overcome any gains in the 'activation' of the alkenes associated with the use of the fluorinated solvent.

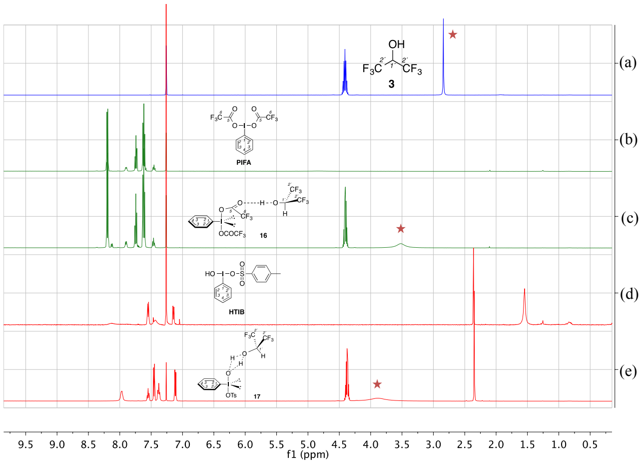


Figure 4. ^{1}H NMR of (a) HFIP (2), (b) PIFA (3), (c) 1:1 mixture of PIFA:HFIP (16), (d) HTIB and (e) 1:1 mixture of HTIB:HFIP (a putative and time averaged structure of an adduct 17 is shown). Red stars indicates the position of the deshielded OH signal of interest.

CONCLUSIONS

On average the voltammetric oxidation for the electron-rich styrenes studied within this work are found in HFIP to occur at a lower potential as measured against the ferrocene/ferrocenium redox couple potential as compared to ACN (average shift of ~140 mV as measured from 11 alkenes). This shift in the oxidative wave is attributed to the stabilization of the formed cation. Moreover, the recorded oxidative peak potentials of the styrenes are found to correlate well with the observed synthetic reactivity, such that those that oxidise voltammetrically at a higher potential are found to not synthetically undergo a [2+2] cycloadditon when initiated using hypervalent iodine reagents. Although not insignificant this shift in potential is small in contrast to the reduction of PIDA in HFIP as compared to ACN, where the reduction wave is observed to shift cf. 850 mV. Hence, the difference between the voltammetric oxidation of *trans*-anethole and the hypervalent reagent PIDA is over a volt less in HFIP than in ACN. NMR data strongly evidences this altered reactivity to be due to the strong hydrogen bonding and adduct formation between the HFIP and PIDA.

Two other iodine(III) reagents PIFA and HTIB (Koser's reagent) are studied and the influence of the solvent HFIP is shown to have markedly differing effects for these two species. Namely the electron withdrawing nature of the trifluoroacetate groups present on the PIFA serve to enhance the oxidative ability of the reagent in ACN as compared to PIDA. However, the presence of the fluorine on the PIFA also serve to decrease the hydrogen bonding abilities of the ligands, such that the influence of hydrogen bonding is significantly less. Consequently, in HFIP both PIFA and PIDA are very comparable in their oxidative strengths. Conversely for HTIB the use of HFIP as a solvent *decreases* the reactivity of the reagent, such that, with its reduction peak occurring at -0.64 V (vs Fc), the reagent is experimentally found to be unable to initiate the cycloaddition. Physically, this weaker H-bonding interaction of the fluoroalochol with the PIFA and HTIB is confirmed via NMR. Hence, this work has demonstrated how the choice of hypervalent iodine reagent and solvent used can dramatically alter the reactivity of this group of highly versatile synthetic reagents. Moreover, physical insight into the common usage of fluoroalcohol solvents with this class of reagents is provided.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, further electrochemical and NMR data and compound characterization (HRMS and NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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NOTES

The authors declare no competing financial interest.

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TOC graphic