ChemComm
FEATURE ARTICLE

Making radical cations live longer

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By all measures, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP) appears as a solvent with properties at the extreme. Its combination of low nucleophilicity, high hydrogen bonding donor strength, low hydrogen bonding acceptor strength, high polarity and high ionizing power makes it an ideal solvent for radical cations. Applications of HFP as a solvent for EPR spectroscopy and mechanistic studies of radical cations as intermediates in electrophilic aromatic substitution, photochemistry and spin trapping are described.

Introduction

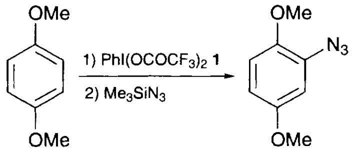
We are engaged in an effort to elucidate whether electrophilic aromatic substitution reactions can proceed *via* radical cation mediated mechanisms, as formulated in eqns. (1) and (2).[1]

$$ArH + E^+ \rightarrow ArH^{\bullet +} + E^\bullet \qquad (1)$$

$$ArH^{\bullet +} + E^\bullet \rightarrow Ar(H)E^+ \rightarrow Ar\text{-}E + H^+ \qquad (2)$$

During this work we have found 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP) to be an exceptionally useful solvent, enabling us to arrest certain electrophilic aromatic reactions at the radical cation stage and make them accessible for study by EPR and/or UV spectroscopy. Below we detail the properties of HFP–extreme in almost every respect–and its applications for studies of reaction mechanisms.

In 1991, Kita *et al.*[2a] performed the oxidative azidation of ArH by treatment with phenyliodine(III) bis(trifluoroacetate) **1**, followed by addition of trimethylsilyl azide [as exemplified in eqn. (3)]. For this reaction a non-nucleophilic solvent was essential, HFP being superior to all others tried. Later,[2b] it was shown by EPR and/or UV spectroscopy that radical cations might be intermediates in the reaction. Other reactive nucleophiles were trimethylsilyl acetate, β-dicarbonyl compounds and arenethiols.[2c]



Solvent	Yield (%)
HFP	68
CF_3CH_2OH	60
MeCN	7
CF_3CO_2H	0
CH_2Cl_2	0

(3)

Since the generation of ArH$^{\bullet +}$ for EPR spectroscopy can always capitalize on new oxidant/solvent combinations, we were prompted to study the properties of **1** for this purpose. In trifluoroacetic acid at −11 °C, **1** oxidized ArH with $E°(ArH^{\bullet +}/ArH)$ up to a limit of about 2.1 V *vs.* Ag/AgCl giving primary ArH$^{\bullet +}$ or various types of secondary ones, *e.g.* from dehydrodimers Ar–Ar$^{\bullet +}$. Trifluoroacetic acid was preferred over HFP because of its lower freezing point, but it was noticed that HFP had 'truly excellent properties' as a solvent for radical cations, comparable to or better than those of trifluoroacetic acid.[3] Since HFP is 10^9 times less acidic than trifluoroacetic acid, it also held promise for use with acid-sensitive ArH systems.

However, it was another problem which alerted us to the unique position of HFP as a solvent for radical cations. In order to explain the 1e$^-$ oxidizing properties of thallium(III) trifluoroacetate (denoted Tl^{III}) we had suggested that an organo-Tl^{III} bis(trifluoroacetate) ought to act as an oxidant towards ArH.[4] 4-Tolylthallium(III) bis(trifluoroacetate) (denoted tolyl-Tl^{III}) was selected as a model compound and was found to work well as a 1e$^-$ oxidant in trifluoroacetic acid for ArH with $E° \leq 2$ V *vs.* Ag/AgCl. To avoid the objection that Tl^{III} might be the active species, formed in the equilibrium of eqn. (4), control

$$\text{Tolyl-Tl}^{III} + CF_3COOH \rightleftharpoons \text{Tolyl-H} + Tl^{III} + CF_3COO^- \qquad (4)$$

experiments were performed with tolyl-Tl^{III} in HFP. It soon became evident that the tolyl-Tl^{III}–HFP reagent introduced a new dimension to radical cation stability in fluid solution; generally, half-lives increased by factors of 10–100 or more.[5] The mild conditions allowed for generation of radical cations of chemically sensitive systems and dispensed with the need for cooling or use of flow systems. This finding initiated a programme to utilize HFP for studies of possible electron transfer mechanisms of electrophilic aromatic substitution, such as nitration, nitrosation, halogenation and thalliation.

Solvent properties of HFP

Some physical properties of HFP, 2,2,2-trifluoroethanol and propan-2-ol are listed in Table 1. Early in solvent studies it was recognized that HFP and 2,2,2-trifluoroethanol are distinctly different from other hydrogen-bonding solvents in that they solvate anions extensively but cations poorly. A study of the conductance of tetralkylammonium salts in HFP showed that ionic association was 'incredibly small' for a solvent of such low dielectric constant, explicable by formation of tightly solvated complexes between anions and HFP. At contact distance with a tetraalkylammonium ion, the distance between the ions would still be large and ionic association facilitated.[6]

Table 1 shows that HFP has lower viscosity, boiling point and entropy of vaporization than the two other solvents, indicating

Table 1 Physical properties of HFP, 2,2,2-trifluoroethanol and propan-2-ol[6,42]

Property	HFP	2,2,2-Trifluoroethanol	Propan-2-ol
ρ^{25}	1.605	1.383	0.781
Melting point/°C	−5	−43.5	−89.5
Boiling point/°C	58.6	73.8	82.5
Dipole moment/D	2.05	2.03	1.68
η/cP	1.62	1.78	2.08
ε	16.7	26.7	19.4
pK_a in water	9.30	12.37	*ca.* 17
pK_a in Me_2SO	18.2	24.0	30.3
Entropy of vapourization/ Gibbs	26.2	28.0	28.3

that the degree of intermolecular hydrogen bonding in neat HFP is smaller. The dimerization constants [eqn. (5)] for ROH have

$$2\ \mathrm{ROH} \rightleftharpoons \mathrm{R{-}O{-}H \cdots O(R)H} \qquad (5)$$

been measured[7] in CCl_4, being for HFP 0.13, 2,2,2-trifluorethanol 0.65 and ethanol 0.89 $dm^3\ mol^{-1}$. The low value for HFP depends on its unsuitability as a hydrogen bond acceptor.

As a hydrogen bond donor, HFP is uniquely strong. Table 2 shows the strengths of hydrogen bonds from HFP to various neutral acceptors, 2,2,2-trifluorethanol, ethanol and phenol being included for comparison. The solvating power is so strong that the tetrahydrofuran–HFP complex distils as a discrete entity at 100 °C, far above the boiling point of the two components.[8] Thus HFP is the solvent *par preference* for polar compounds, as exemplified by the high solubility of protected peptides.[9]

The strong anion-solvating properties deduced from conductance studies were amply corroborated by gas-phase studies of anion–neutral molecule bonding. Bonding constants of different species to halide ions and cyanide ion are shown in Table 3.[10] HFP is the strongest hydrogen bond donor, *e.g.* for the chloride ion by >10 kcal mol^{-1} (1 cal = 4.184 J) greater bond strength in comparison to acetonitrile or dichloromethane.

Physical organic chemistry has many parameters describing solvent properties to be used in different situations. Table 4 lists values of the important parameters involved in the interpretation of solvolysis results, the ionizing power Y and the nucleophilicity parameter N.[11] The values of HFP are consistently towards the extreme: it has high ionizing power and is very weakly nucleophilic, in both respects somewhat less pronounced than for trifluoroacetic acid.

Table 5 lists other solvent parameters: the ^{59}Co chemical shift[12] and the acceptor number (AN), both measuring solvent electrophilicity,[13] the Reichardt E^N_T value, measuring solvent polarity,[14] and the Kamlet–Taft β, α and π* parameters,[15] measuring hydrogen bond acceptor, hydrogen bond donor and polar properties, respectively. Again HFP emerges as a solvent of low nucleophilicity, high polarity and strong hydrogen bond donating ability. With $E^N_T = 1.068$, it is the only solvent among 360 which falls outside the scale defined by tetramethylsilane at $E^N_T = 0.00$ and water at $E^N_T = 1.00$.

NMR spectral parameters used to classify HFP include ^{13}C NMR chemical shift differences between various sites of *N*,*N*-dimethyl- or *N*,*N*-diethyl-benzamide.[16] Fig. 1 shows one such correlation (filled symbols). Also, hyperfine splitting (hfs) constants from EPR spectra of spin adducts correlate well with solvent parameters, as shown in Fig. 1 (empty symbols) for the

Table 2 Strengths ($-\Delta H°$/kcal mol^{-1}) of hydrogen bonds between alcohols and acceptors, in carbon tetrachloride unless otherwise stated[43]

Alcohol/acceptor	CF_3CH_2OH	HFP	EtOH	PhOH
Acetone	3.7	5.9, 6.7, 6.4	2.9	3.7, 4.9, 5.2
Tetrahydrofuran	5.1	6.3		
Diethyl sulfide		5.1	4.6	
N,*N*-Dimethyl-acetamide	5.8	7.7, 8.5, 8.7		6.1, 6.8
Tetramethylurea	5.8	8.1, 8.4	4.2	6.0, 6.7
N-Methyl-pyrrolidinone	4.7[a]	*ca.* 5.3[a]	2.0[a]	5.3[a]
Acetonitrile		5.9, 6.2		4.7
Dimethyl sulfoxide	5.6	7.0, 8.7, 8.6		6.9, 6.9
Sulfolane	4.0	4.9		
Pyridine		8.4, 9.8[b]		8.0
Triethylamine		10.0, 11.5[b]		9.1

[a] In 1,1,1-trichloroethane. [b] In hexane.

Table 3 Gas phase anion-binding energies (kcal mol^{-1}) of some solvent molecules[10]

Solvent	F^-	Cl^-	Br^-	I^-	CN^-
MeCN	16.0	13.4	12.9	12.0	16.4
CH_2Cl_2		15.8			16.3
MeCOMe		14.1			14.7
H_2O	23.4	14.8	12.7	10.0	13.8
MeOH	29.6	16.8		11.2	16.5
HCO_2H	45.4	25.6		18.9	
$MeCO_2H$	44.2	23.9		17.0	
CF_3CH_2OH	39.1	~24.0		20.0	24.6
HFP	48.0	>26.5		23.9	25

Table 4 Ionizing power and nucleophilicity of fluorinated alcohols in relation to similar solvents[11]

Alcohol	Ionizing power, Y	Nucleophilicity, N
Ethanol–water (80:20 v/v)	0.00	0.00
2,2,2-Trifluoroethanol	1.74; 1.80	2.67; −3.0
HFP	3.82	
HFP–water (3% *m*/*m*)	3.53; 3.61	−4.91; −4.27
Formic acid	3.04	−2.35
Acetic acid	−0.61	−2.35
Trifluoroacetic acid	4.57	−4.74, −5.56

Table 5 Various parameters for solvent properties[12–15]

Solvent	δ ^{59}Co	AN	E^N_T	β	α	π*
Methanol	91.0	41.3	0.762	0.62	0.93	0.60
Ethanol	129.3	37.1	0.654	0.77	0.83	0.54
Water	28.1	54.8	1.00	0.18	1.17	1.09
2,2,2-Trifluoro-ethanol	18.6	53.3	0.898	0.00	1.51	0.73
HFP	−22.5	83.6	1.068	0.00	1.96	0.65
Formic acid	−7.28	83.6	0.728			
Acetic acid	13.4	52.9	0.648		1.17	1.09
Trifluoroacetic acid		105.3				0.50

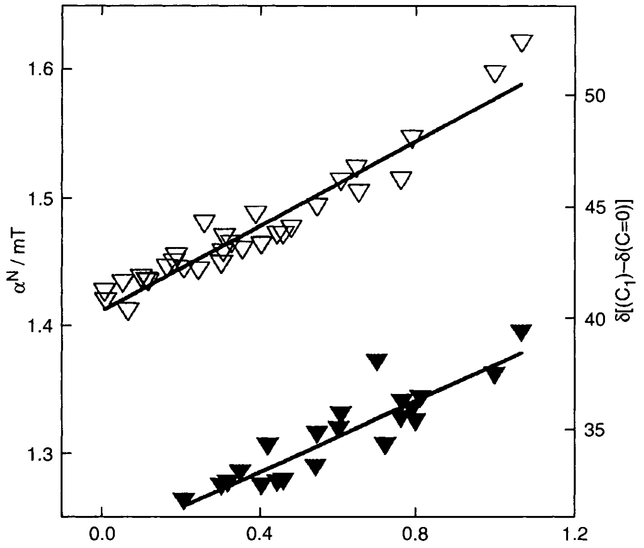
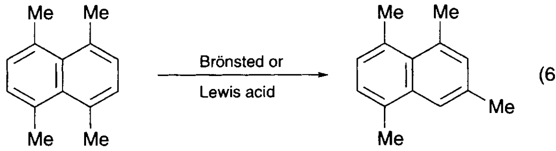


Fig. 1 Plots of the ^{13}C NMR spectral shift difference $\delta(C^1) - \delta(C{=}O)$ in *N*,*N*-diethylbenzamide (filled symbols) and of the hfs constant to nitrogen in the phenyl radical spin adduct **2** (empty symbols) for various solvents *vs.* the Reichardt E^T_N parameter (data from refs. 14 and 16–18)

nitrogen hfs constants in **2**, the Ph$^{\bullet}$ adduct to α-phenyl-*N*-*tert*-butylnitrone.[17,18] In both plots, HFP represents the most extreme point to the top right.

General comment about the EPR spectral observation of radical cations

For the generation of ArH$^{\bullet+}$ one must choose from a large number of oxidant–solvent combinations, in many cases with some Lewis or Brönsted acid present.[19] The latter either serves as the oxidant or suppressor of further reactions of the radical cation or both, but has the disadvantage of sometimes inducing side-reactions, *e.g.* rearrangements, of the neutral ArH. We developed a practical scale for the acidity of such media by measuring rate constants of the acid catalysed rearrangement of **3** into **4** [eqn. (6)]. Once formed, **3**$^{\bullet+}$ does not undergo rearrangement.[20] Table 6 shows the rate constant for the **3** → **4** reaction in systems commonly used in EPR spectroscopy. The scale covers a range of 10^6 in reactivity, aluminium chloride in nitromethane being the most reactive. The borderline for useful, *i.e.* non-rearranging, systems can be placed at trifluoromethanesulfonic acid (0.74 mol dm^{-3}) in nitromethane, meaning that only trifluoroacetic acid, antimony trichloride and BF$_3$–diethyl ether are acceptable as acid components from this aspect. Unfortunately, the method does not further distinguish between solvents at this low level of reactivity.

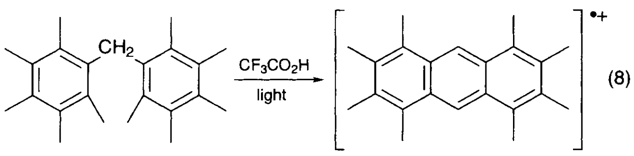


3 **4** (6)

Thus a non-acidic oxidant in trifluoroacetic acid should be favourable for the generation of primary radical cations from ArH. Such are available in Tl^{III} (thermally or *hν*), Hg^{II} trifluoroacetate (*hν*), phenyliodine(III) trifluoroacetate (thermally), and 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) (thermally or *hν*). Among these, DDQ had emerged as the reagent of choice around 1994.[19d] Although it is a relatively weak electron transfer oxidant [$E°$ = 0.57 V *vs.* Ag/AgCl], it can be used thermally for substrates with $E°$ up to *ca.* 1.4 V *vs.* Ag/AgCl due to fast protonation of DDQ$^{\bullet-}$ by the acid [eqn. (7)]; photochemically the borderline can be placed around 2.5 V. Protonation is thus an efficient way of preventing the back electron transfer step.

$$\mathrm{ArH + DDQ \rightleftharpoons ArH\cdots DDQ \overset{h\nu \text{ or } \Delta}{\rightleftharpoons} ArH^{\bullet+}\,DDQ^{\bullet-} \xrightarrow{H^+} ArH^{\bullet+}\,DDQH^{\bullet}} \qquad (7)$$

Even if trifluoroacetic acid is relatively weak, it can still cause or assist unwanted side-reactions which stem from its acidic or nucleophilic properties. A drastic example is the transformation of bis(pentamethylphenyl)methane **5** into the 1,2,3,4,5,6,7,8-octamethylanthracene radical cation **6**$^{\bullet+}$ merely by its dissolution in trifluoroacetic acid [eqn. (8)].[21] The reaction pathway from **5** to **6** involves a series of carbocationic rearrangements and hydride transfers whereas the final 1e$^-$ oxidation of **6** is light-promoted.

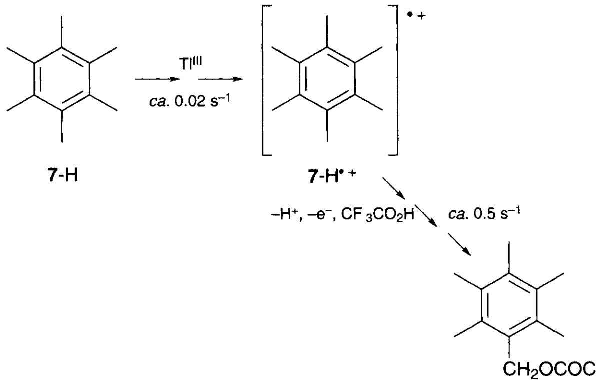


5 **6**$^{\bullet+}$ (8)

HFP as a solvent for the EPR spectral observation of radical cations

The fact that the oxidation of ArH by phenyliodine(III) bis(trifluoroacetate) in HFP gave high-quality EPR spectra of the corresponding ArH$^{\bullet+}$ was not combined with any significant increase in their half-life as compared to trifluoroacetic acid.[3] However, with thallium(III) based reagents a large increase of half-life ($\tau_{1/2}$) was noted, sometimes by factors of $>10^2$. Table 7 shows a comparison of $\tau_{1/2}$ of a number of ArH$^{\bullet+}$ in HFP and TFA, respectively.

Why do we see this difference? A study[4] of the kinetic behaviour of the hexamethylbenzene (**7**-H)–Tl^{III} system in TFA sheds some light on this question. The pertinent rate constants for formation and disappearance of the hexamethylbenzene radical cation (**7**-H$^{\bullet+}$) are as given in eqn. (9). The key feature is the rate-determining, slow formation of the radical cation, leading to a low, stable and long-lasting concentration of **7**-H$^{\bullet+}$ which is readily monitored by EPR spectroscopy. The fact that the formation of **7**-H$^{\bullet+}$ was subject to a kinetic isotope effect of k_H/k_D maximally *ca.* 7, suggested that the slow step might be thalliation of **7**-H.[22] The organothallium compound then must have a pathway available to give the radical cation, assumed to be an electron transfer step with ArH as the second reactant according to eqn. (10). Alternatively, one can envisage a



7-H **7-H**$^{\bullet+}$ **7-OCOCF$_3$** (9)

$$\mathbf{7}\text{-Tl}^{III}(OCOCF_3)_2 + \mathbf{7}\text{-H} \rightarrow \mathbf{7}\text{-Tl}^{II}(OCOCF_3)_2^- + \mathbf{7}\text{-H}^{\bullet+} \qquad (10)$$

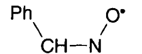


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Table 6 Rate constant (k) for the rearrangement of **3** into **4** in various acidic systems at 22 °C[20]

Acid (conc./mol dm^{-3})	Solvent	k/min^{-1}	log k_{rel}
Trifluoroacetic acid (8.7)	Dichloromethane	$<10^{-6\,a}$	<-3.7
Trifluoroacetic acid (6.5) + triflic acid (0.057)	Dichloromethane	0.42	1.8
Triflic acid (0.74)	Nitromethane	0.0063	0.0
Sulfuric acid, 96% (2.8)	Nitromethane	0.073	1.1
AlCl$_3$ (0.31)	Nitromethane	1.5	−2.4
SbCl$_3$ (0.56; 3.8)	Nitromethane	$<10^{-6\,a}$	<-3.7
SbCl$_3$ (3.8), AlCl$_3$ (0.31)	Nitromethane	1.6	2.4
SbCl$_5$ (0.31)	Dichloromethane	—[b]	
SbCl$_5$ (0.030), SbCl$_3$ (0.30)	Nitromethane	—[c]	
BF$_3$–diethyl ether (0.6)	Nitromethane	$<10^{-6\,a}$	<-3.7

[a] The practical limit was defined as < 1% conversion in 168 h. [b] No isomerization occurred within 6 h. Instead, fast chlorination of **1** took place. [c] Slow monochlorination of **1** occurred.

homolytic bond cleavage of the C–Tl bond, leading to a strongly oxidizing $\mathrm{Tl^{II}}$ species [eqns. (11) and (12)].

$$\mathbf{7}\text{-}\mathrm{Tl^{III}(OCOCF_3)_2} \rightarrow \mathbf{7}^{\bullet+} + \mathrm{Tl^{II}(OCOCF_3)_2} \quad (11)$$

$$\mathrm{Tl^{II}(OCOCF_3)_2} + \mathbf{7}\text{-H} \rightarrow \mathrm{Tl^{I}(OCOCF_3)_2^-} + \mathbf{7}\text{-H}^{\bullet+} \quad (12)$$

The advantage of a slow rate of formation of the radical cation can be seen in Fig. 2, where the reaction between **7**-H and $\mathrm{Tl^{III}}$ is modelled kinetically [eqn. (9)]. The solid line shows the time development of [**7**-H$^{\bullet+}$], passing through a maximum after about 7 s and decreasing slowly over a period of 200 s. In this time span [**7**-H$^{\bullet+}$] is readily monitored by EPR spectroscopy, in spite of the large decay rate constant of 0.5 $\mathrm{s^{-1}}$. If on the other hand the reaction between the oxidant and **7**-H is fast, as for example is the case with **1** as the oxidant,[3] [**7**-H$^{\bullet+}$] appears in much higher concentration but decays within 50 s.

The oxidation of aromatic compounds by tolyl-$\mathrm{Tl^{III}}$ in HFP is limited to ArH with $E^\circ < 1.6$ V *vs.* Ag/AgCl in dichloromethane. The addition of 1–5% TFA extends the borderline upwards by about 0.1 V, probably because of the increase of the active reagent according to eqn. (13) similar to $\mathrm{Tl^{III}}$ itself.[22]

$$\text{Tolyl-}\mathrm{Tl^{III}(OCOCF_3)_2} + \mathrm{CF_3COOH} \rightleftharpoons \text{Tolyl-}\mathrm{Tl^{III}(OCOCF_3)^+} + \mathrm{(CF_3COO)_2H^-} \quad (13)$$

Table 7 Comparison between persistencies of radical cations, generated by tolyl-$\mathrm{Tl^{III}}$ in HFP or trifluoroacetic acid (TFA) at 22 °C[23]

Radical cation from	$\tau_{1/2}$/h in HFP	$\tau_{1/2}$/h in TFA	HFP:TFA
2,2′,4,4′-Tetramethyl-1,1′-binaphthalene	16	*ca.* 0.1	*ca.* 160
Benzo-1,3-dioxole (5% TFA)	2.5	0.017	147
Anthracene	0.61	0.017	36
3,3′,4,4′-Tetramethyl-1,1′-binaphthalene	15.3	0.17	90
4,4′,6,6′-Tetramethyl-1,1′-binaphthalene	*ca.* 5	*ca.* 0.05	*ca.* 100
4,4′,5,5′-Tetramethyl-1,1′-binaphthalene	*ca.* 5	*ca.* 0.05	*ca.* 100
Biphenylene	> 100	3.5	> 29
1,4,5,8-Tetramethylnaphthalene	28	0.67	42
1,2,4,5-Tetrahydroxybenzene, diacetonide	141	18	8

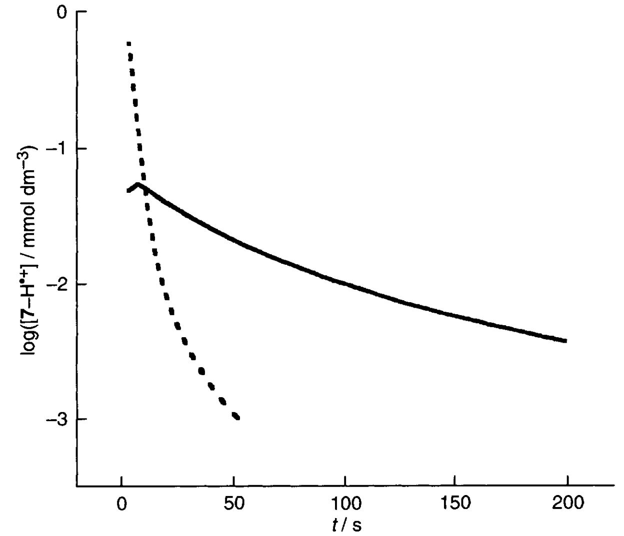
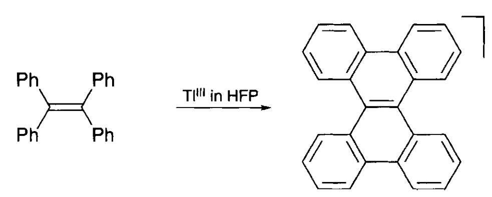


Fig. 2 Simulations of log([**7**-H$^{\bullet+}$]/mmol dm^{-3}) *vs.* *t*/s for the reaction between $\mathrm{Tl^{III}}$ ($[\mathrm{Tl^{III}}]_0$ = 2 mmol dm^{-3}) and hexamethylbenzene ($[\mathbf{7}\text{-H}]_0$ = 2 mmol dm^{-3}) using the kinetic scheme of eqn. (9) and rate constants 8 dm^3 mol^{-1} s^{-1} and 0.5 s^{-1} (solid line) and rate constants 800 dm^3 mol^{-1} s^{-1} and 0.5 s^{-1} (dashed line)

In general, well resolved EPR spectra of radical cations of high persistence are obtained (see Fig. 3). Compared to $\mathrm{Tl^{III}}$, the incidence of side-reactions is low, being mainly confined to the formation of dehydro-dimers, *e.g.* from 1-methoxynaphthalene. Anthracene, tetraphenylethylene and 1,3-benzodioxole cleanly give their radical cations, no side-reactions being observed (see below). Thus tolyl-$\mathrm{Tl^{III}}$ in HFP presently must be considered as the mildest available reagent for the generation of radical cations from sensitive compounds.[5,23a] Its use only appears to be limited by the redox potential requirement above; amine and phosphine functional groups in aromatics and sulfur in heteroaromatic compounds of thiophene, thianthrene, dibenzothiophene and phenothiazine type are well tolerated.[23b]

With $\mathrm{Tl^{III}}$ as the oxidant, the full potential of the stabilizing effect of HFP upon radical cations can be realized. A number of reactive radical cations, such as those of 4,4′-difluorobiphenyl, 4-fluoroanisole, 4-chloroanisole, 4-methylanisole, triptycene, phenanthrene, 1,1′-binaphthalene and biphenyl, earlier only detectable at lowered temperatures or in flow systems, can be generated and monitored by EPR spectroscopy at room temperature.[23a] The upper limit of redox reactivity now can be placed at about 2.3 V *vs.* Ag/AgCl in dichloromethane, 2,3,5,6-tetrafluoro-4-methylanisole representing a successful case near this borderline. As expected, the more reactive $\mathrm{Tl^{III}}$ induced side-reactions, such as trifluoroacetoxylation of anthracene [eqn. (14)], cyclization of tetraphenylethylene [eqn. (15)] and dehydrodimerization-ring opening of benzo-1,3-dioxole [eqn. (16)].

(14)



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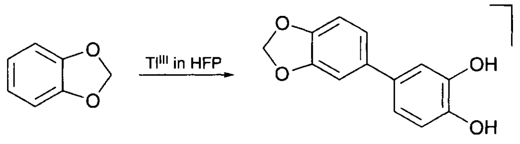


(16)

The irradiation of charge transfer (CT) complexes of ArH with $\mathrm{Hg^{II}}$ trifluoroacetate[24] is a useful method for the oxidation of unreactive ArH. In HFP radical cations of tri- and tetraphenylene and a few pentamethylbenzyl derivatives were detectable by this method;[23] one substrate, 4-*tert*-butylanisole, otherwise prone to undergo dehydrodimerization, gave the radical cation of a mercuriated derivative, a side-reaction sometimes encountered.[25]

Attempts to use DDQ as the oxidant were not encouraging. Thermally, a substrate such as 3,3′,4,4′-tetramethyl-1,1′-binaphthalene gives a weak EPR spectrum in HFP but it disappears upon irradiation and is replaced by the spectrum of DDQ$^{\bullet-}$. Thus the protonating ability of HFP (pK_a = 9.3) is not sufficient to protonate DDQ$^{\bullet-}$. Addition of 5% trifluoroacetic acid removed the DDQ$^{\bullet-}$ signal and allowed for the recording of a strong signal of the radical cation. However, its half-life was much shorter than with the tolyl-$\mathrm{Tl^{III}}$ reagent.[23]

HFP as a solvent for anodic electrochemistry

Little systematic work has been done to utilize HFP for electrochemical studies. Its ability to stabilize radical cations makes it a medium of choice for certain types of problems, such as the determination of reversible potentials[23,26] or studies of electropolymerization. HFP dissolves quaternary ammonium salts in sufficient concentrations, and the conductivities of such solutions are good. Less favourably, the solubility of nonpolar compounds is low. Table 8 shows reversible redox potentials of a few aromatic systems in HFP–Bu_4NPF_6. Where comparisons were made, the sweep rate v at which reversibility is reached in HFP is 500–1000 times smaller than in dichloromethane. The potentials, referred to the Ag/AgCl electrode, are 0.4–0.5 V lower than in dichloromethane.

The anodic polymerization of a few ArH in HFP was explored briefly.[26] In comparison with the solvents usually employed, *e.g.* dichloromethane or acetonitrile, electropolymerization seems to be slower in HFP. Attempts to measure electrochemically the kinetics of reactions between radical cations and added nucleophiles were not successful due to the fact that HFP drastically curtails nucleophilic reactivity.[27] This effect is shown by the rates of the reaction between tris(4-bromophenyl)aminium ion and nucleophiles in HFP,[18] as compared to those obtained in acetonitrile (Table 9). The rate ratio observed for chloride ion, *ca.* 10^7, is compatible with the gas phase H-bond strength difference, >13 kcal mol^{-1} (Table 3).

Spin trapping in HFP

Spin trapping is a commonly used technique for identifying transient radicals. A spin trap (ST) is a compound capable for reacting with a radical $R^\bullet$ with the formation of a spin adduct [eqn. (17)]. The latter is a persistent radical which can be

$$ST + \underset{\text{transient}}{R^\bullet} \longrightarrow \underset{\text{persistent}}{R\text{-}ST^\bullet} \qquad (17)$$

recorded EPR spectroscopically and identified by its hfs constants, thus defining the nature of the added radical $R^\bullet$. Common spin traps are nitrones or nitroso compounds, such as **8** and **9**. A difficult problem appears when mixtures of ST and a nucleophilic Nu^- (halide ion, cyanide ion, carboxylate ions, pyridines) are treated by strong oxidants, including excited states formed by $h\nu$, and spin adducts $Nu\text{-}ST^\bullet$ are identified: Does proper spin trapping [eqn. (18)] or 'inverted

$$Nu^- \xrightarrow{\text{oxidant}} Nu^\bullet \xrightarrow{ST} Nu\text{-}ST^\bullet \qquad (18)$$

spin trapping' [eqn. (19)][28] take place? The latter mechanism

$$ST \xrightarrow{\text{oxidant}} ST^{\bullet+} \xrightarrow{Nu^-} Nu\text{-}ST^\bullet \qquad (19)$$

gives the same spin adduct as in proper spin trapping, but $Nu^\bullet$ is not an intermediate. In the solvents normally used inverted spin trapping is a common phenomenon and thus can make interpretations of results from ST/Nu^- oxidation uncertain or impossible. Such difficulties were encountered in the trapping of imidyl radicals formed in the thermal or photochemical reactions of *N*-halogenosuccinimides,[28d] but with HFP as solvent the identification of unambiguous cases was possible. Due to the decreased reactivity of nucleophiles in HFP (Table 9), inverted spin trapping could be ruled out.[18]

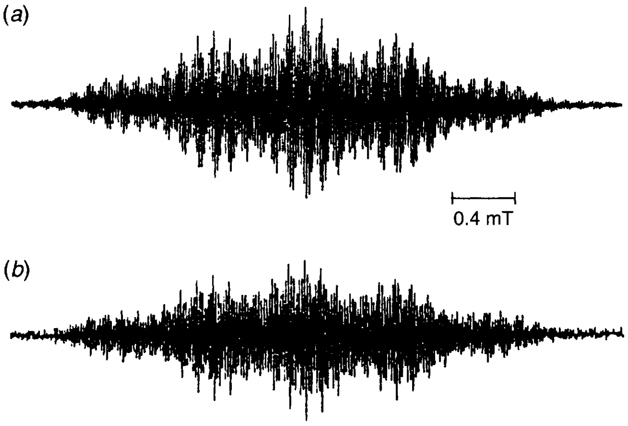


Fig. 3 EPR spectrum of a solution of 3,3′,4,4′-tetramethylnaphthalene and tolyl-Tl^{III} in HFP at 22 °C, recorded (*a*) 1 h and (*b*) 43 h after mixing. The ratio of the spectral intensities is *ca.* 5 ($\tau_{1/2}$ = 15.3 h). In trifluoroacetic acid, $\tau_{1/2}$ of the same radical cation under otherwise identical conditions is *ca.* 10 min.

Table 8 Redox potentials of ArH in HFP–Bu_4NPF_6 (0.15 mol dm^{-3})[23,26]

Compound	Reversible at $v \geq$/V s^{-1}	E_{rev}/V *vs.* Ag/AgCl
Durene	2	1.35
Hexamethylbenzene	1	1.17
Anthracene	0.2	0.92
Phenanthrene	5	1.28
Benzo-1,3-dioxole	0.05	1.15
1-Methoxynaphthalene	0.2	1.00
4,4′-Dimethoxy-1,1′-binaphthalene	0.05	0.71
Dibenzofuran	40	1.51
Dibenzothiophene	20	1.26
Ferrocene		0.02–0.05

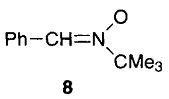
Reaction between radical cations and trinitromethanide ion

The photochemical addition of tetranitromethane to aromatic compounds by excitation of the ArH–tetranitromethane CT complex by light matching the wavelength of the CT band occurs by recombination of a triad consisting of $ArH^{\bullet+}$, trinitromethanide ion and nitrogen dioxide (eqn. (20)].[1a,b] The

$$\underset{\text{CT complex}}{ArH\cdots C(NO_2)_4} \xrightarrow{h\nu\ >\ 430\,\text{nm}} \underset{\text{triad}}{ArH^{\bullet+}\ (O_2N)_3C^-\ NO_2} \qquad (20)$$

Table 9 Rate constants for the reaction between $TBPA^{\bullet+}$ and various nucleophiles in HFP at 20 °C[18]

	log(k/dm^3 mol^{-1} s^{-1}) in		
Nucleophile	HFP	Acetonitrile	Difference
Chloride ion	−4.4	2.7	7.1
Bromide ion	−3.5	4.5	8.0
Hydrogendiacetate ion	−4.1	4.8	8.9
Trinitromethanide ion	−3.1	0.4	3.5
Pyridine	−3.4	—	—
3,5-Lutidine	−2.7	—	—
Iodide ion	>3	>6	—
Benzotriazolate ion	−2.8	—	—
Triethyl phosphite	−0.2	—	—



$$Ph\text{-}CH{=}N(O)CMe_3$$

8

Me_3CNO

9

first chemical step from the triad is reaction between $ArH^{\cdot+}$ and the trinitromethanide ion [eqn. (21)] to give a carbon-centred

$$ArH^{\cdot+} + (O_2N)_3C^- \longrightarrow Ar(H)C(NO_2)_3^{\cdot} \qquad (21)$$

radical which reacts with nitrogen dioxide to give nitro- and nitrito-trinitromethyl adducts [eqn. (22)]. The adducts exhibit

$$Ar(H)C(NO_2)_3^{\cdot} + NO_2 \longrightarrow \text{adducts} \qquad (22)$$

great variation in stability, their main pathways of decomposition being elimination of nitroform to give $ArNO_2$ and/or nitrous acid to give $ArC(NO_2)_3$ **10**.

Normally, the radical cation of eqn. (20) is not detectable by EPR spectroscopy in dichloromethane at −60 °C because of the rapid follow-up reaction of eqn. (21). The addition of a low concentration of trifluoroacetic acid leads to fast protonation of the trinitromethanide ion, similarly to the case of $DDQ^{\cdot-}$ [eqn. (7)]; consequently, in many cases the radical cation can be observed by EPR spectroscopy.[29] The major follow-up reaction now becomes the slower reaction between the radical cation and NO_2 [eqn. (23)], or sometimes dimerization of the radical

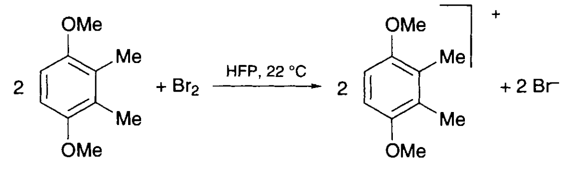
$$ArH^{\cdot+} + NO_2 \longrightarrow Ar(H)NO_2^+ \longrightarrow Ar\text{-}NO_2 + H^+ \qquad (23)$$

cation. A preparative consequence of the addition of trifluoroacetic acid was a switch from the formation of trinitromethanide ion dependent adducts [eqns. (20)–(22)] to the formation of nitro compounds (Table 10).

The use of HFP as solvent gave similar results. The reactivity of trinitromethanide ion was strongly decreased compared to dichloromethane.[30] Table 10 shows the effect of the two ways of reducing the reactivity of trinitromethanide ion. Both in dichloromethane–trifluoroacetic acid and HFP the trinitromethyl-containing products are strongly reduced or eliminated.

Electrophilic aromatic substitution; is a radical cation intermediate involved?

HFP offers a unique possibility to study the electron transfer mechanism of electrophilic aromatic substitution [eqns. (1) and (2)], as shown for the halogenation of ArH by bromine, chlorine or iodine chloride.[31] In many of these reactions, radical cations can be monitored by EPR spectroscopy at 22 °C because of the extreme retardation of chloride and bromide ion reactivity (Table 9). Thus the oxidation of 1,4-dimethoxybenzene (representing an upper limit of reactivity with E_{rev} 1.50 V *vs.* Ag/AgCl in dichloromethane) by iodine chloride in HFP gave a high concentration of its radical cation which decayed with a half-life of *ca.* 0.5 h. As an example of bromination, the addition of bromine to a solution of 1,4-dimethoxy-2,3-dimethylbenzene **11** in HFP gives radical cation $\mathbf{11}^{\cdot+}$ in high concentration [eqn. (24)] which slowly (k = 0.17 $dm^3\,mol^{-1}\,s^{-1}$) reacts further with the bromide ion formed simultaneously to give exclusively 2-bromo-1,4-dimethoxy-2,3-dimethylbenzene. In dichloromethane, spectral observation of radical cations from ICl reactions was only possible at −70 °C.[32]



11 $\mathbf{11}^{\cdot+}$ (24)

Another reaction of current interest is nitration by nitrogen dioxide, presumably occurring by an electron transfer mechanism involving nitrosonium ion CT complexed to ArH [eqns. (25)–(27)].[33] This mechanism is analogous to that of

$$N_2O_4 \rightleftharpoons O_2NO\text{-}NO \rightleftharpoons NO_3^- + NO^+ \qquad (25)$$

$$NO^+ + ArH \rightleftharpoons NO^+\cdots ArH \rightleftharpoons NO + ArH^{\cdot+} \qquad (26)$$

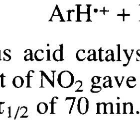
$$ArH^{\cdot+} + NO_2\ (\text{in excess}) \longrightarrow ArNO_2 + H^+ \qquad (27)$$

nitrous acid catalysed nitration.[34] The reaction of **11** with a deficit of NO_2 gave a high concentration of $\mathbf{11}^{\cdot+}$ which decayed with $\tau_{1/2}$ of 70 min. In the presence of excess NO_2, the radical cation decayed rapidly giving the 5-nitro derivative of **11**.[30b]

HFP as a medium for carbocations

The low nucleophilicity and high ionizing power of HFP (Table 4) makes it useful for promoting neighbouring group participation in solvolysis reactions, even when it is weakly developed. The two systems **12** and **13** are solvolysed in HFP with ≥99.5% π participation, whereas **14** only shows 1.5% participation.[35] The acid generated during solvolysis is unusually reactive, causing further reactions of the solvolysis products.[36]

Carbocations have been described as being 'remarkably long-lived' in HFP.[37a] Thus photochemically generated 9-fluorenyl cation (Fl^+) decayed in HFP[37a] with k = 3.4 × 10^4 s^{-1} while in 9:1 water–MeOH k was >5 × 10^{10} s^{-1}. In fact benzene can compete as a reactant toward Fl^+ in HFP. The phenyl-1-cyclohexenyl cation decayed in HFP[37b] with k = 5 × 10^2 $dm^3\,mol^{-1}\,s^{-1}$ and in methanol with k = 2.2 × 10^6



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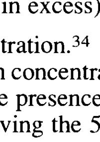

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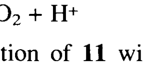

14

Ts = toluene-*p*-sulfonate; Ns = nitrobenzene-*p*-sulfonate

Table 10 Competition between 'addition' [adducts + $ArC(NO_2)_3$] and substitution (nitration) in the photochemical reaction between ArH and tetranitromethane[29,30,44]

	In CH_2Cl_2		In CH_2Cl_2–CF_3COOH		In HFP	
Compound	'Addition'	Nitration	'Addition'	Nitration	'Addition'	Nitration
Naphthalene	89	11	16	84		
1,4-Dimethylnaphthalene	68	32	0	100	0	100
1-Methoxynaphthalene	59	38	0	Trace[a]	0	28[b]
Dibenzofuran	77	17			0	100
1,2,3,4-Tetramethylbenzene	85	3	20	42	16	72
4-Fluoroanisole	90	10	43	48	0	100

[a] The dehydrodimer was formed in almost quantitative yield. [b] The dehydrodimer was formed in 72% yield.

dm^3 mol^{-1} s^{-1}. Various benzylic cations could be studied in HFP with similar results.[37c] Even 4-substituted aryl cations, formed by photolysis of the corresponding diazonium ions, are stable enough for observation in HFP ($\tau_{1/2}$ < 15 ps).[37d] It can be used as a detritylating agent for trityl protected, acid-sensitive deoxynucleosides.[38]

Another useful property of HFP is its ability to protonate excited states of certain ArH, like mesitylene, hexamethylbenzene and methoxybenzenes.[39] This reaction leads to transient cyclohexadienyl cations, the reactivity of which towards nucleophiles could be studied.

HFP has been found to promote rearrangements taking place *via* zwitterions.[40] This study indicated that commercial HFP may contain HF as an impurity, but nevertheless purified HFP was far more effective than solvents like methanol, dichloromethane or acetonitrile. HFP can be used to catalyse Diels–Alder reactions in cases where Lewis acid sensitive reagents are employed.[41]

Acknowledgements

Financial support from the Swedish Natural Science Research Council and the Knut and Alice Wallenberg Foundation is gratefully acknowledged.

Footnote

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Michael P. Hartshorn obtained his BSc with First Class Honours at Imperial College, London in 1957 and his D.Phil. in organic chemistry in 1960 at University College, Oxford. He became lecturer in chemistry at the University of Canterbury, New Zealand in 1960, Reader in 1968, and Professor in 1972. He was Fulbright Visiting Professor at Cornell University during the academic year 1966–67. His recent research interests deal with problems in electrophilic and electron transfer mediated aromatic nitration.

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Received, 29th April 1996; 6/02985J