# Fluorine Substitution Enhances the Reactivity of Substituted Phenyl Radicals toward Organic Hydrogen Atom Donors

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**Abstract:** Phenyl radicals with different positively charged, chemically inert substituents in the para position were generated by collision-activated dissociation of para-substituted iodobenzene ions in the gas phase inside a Fourier-transform ion cyclotron resonance mass spectrometer. The reactivity of the radicals was examined toward organic hydrogen atom donors. The findings parallel those made by others for neutral radicals in solution. For example, the efficiency of hydrogen atom abstraction increases in the expected order phenol < thiophenol < benzeneselenol. Inspite of great exothermicity, hydrogen atom abstraction by the charged phenyl radicals occurs at a small fraction of the gas-phase collision rate, suggesting the presence of a significant barrier on the reaction coordinate. Fluorine substitution on the phenyl ring was found to drastically enhance the reaction rate for all the substrates studied. For example, hydrogen abstraction from thiophenol by the (2,3,5,6-tetrafluoro-4-dehydrophenyl)trimethylphosphonium ion occurs at 21% of the collision rate while the (4-dehydrophenyl)trimethylphosphonium ion reacts by hydrogen atom abstraction at less than 0.3% of the collision rate. In order to probe whether a similar rate enhancement is expected for hydrogen atom abstraction from a sugar unit in DNA, a key step in the action of many antitumor drugs, tetrahydrofuran was examined as a simple model of the sugar moiety. This substrate was found to demonstrate even greater sensitivity toward fluorine substitution in the phenyl radical than the other hydrogen atom donors studied. Hence, fluorine substitution is likely to drastically increase the activity of those antitumor drugs whose action is based on DNA cleavage by polyatomic organic radicals.

## Introduction

Hydrogen atom abstraction by polyatomic radicals plays an important role in many chemical and biological processes.[1−6] For example, the antitumor activity of some powerful anticancer drugs is believed to be based on hydrogen atom abstraction from a sugar moiety in DNA which eventually leads to DNA strand cleavage.[3−6] However, the factors that control these hydrogen atom abstraction reactions are not well understood.[3−5,7] The shortage of knowledge arises, in part, from the difficulty in examining reactions of highly reactive polyatomic radicals with biological molecules under well-defined conditions.

Radicals with a remote, chemically inert charge site separated from the radical site by a phenyl ring (a class of distonic[8] radical cations) were recently suggested to react by the same pathways as neutral phenyl radicals.[9,10] Charged phenyl radicals of this type can be thought of as reactive radicals that carry a handle for mass spectrometric manipulation since the charge site allows the isolation (purification) of the reactant radical and the analysis of its products. These species provide[9,10] a useful tool for the examination of radical reactions under well-defined gas-phase conditions inside a mass spectrometer. In this work, selected charged phenyl radicals were allowed to react with different hydrogen atom donors in order to examine whether these species can be used to gain insight into the structural features that make polyatomic radicals efficient in abstracting a hydrogen atom from organic molecules. This knowledge has important implications for example in rational anticancer drug design.

## Experimental Section

All experiments were carried out using an Extrel Model 2001 Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR). This instrument contains a differentially pumped dual cell aligned within the magnetic field produced by a 3.0 T superconducting magnet operated at about 2.8 T. The nominal base pressure is $<10^{-9}$ Torr and it is maintained with two Balzers turbomolecular pumps (330 L/s), each backed with an Alcatel 2012 mechanical pump. The two cells are separated by a common wall (the conductance limit) which contains a 2-mm hole in the center. This plate and the other two trapping plates were maintained at +2 V unless otherwise stated.

Samples were introduced into the instrument by using two Extrel-manufactured single batch inlet systems equipped with variable leak valves, by using a Varian leak valve, or by using a set of pulsed valves.[11] Solid samples were introduced with a heated solids probe. The nominal reagent pressures were measured with two ionization gauges located on each side of the dual cell.

The charged phenyl radicals were generated by using a procedure reported earlier.[9,10] The halobenzenes (1,4-diiodobenzene for all other radicals, 1-bromo-3-fluoro-4-iodobenzene for **d**, 2,3,5,6-tetrafluoro-1,4-diiodobenzene for **e**, 1,3-bromoiodobenzene for the meta isomer of **b** and for **f**, and 1,3-dibromo-5-fluorobenzene for **g**) were introduced at a nominal pressure of $3 \times 10^{-7}$ Torr into one side of the dual cell by

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using the unheated solids probe. The appropriate nucleophile (trimethyl phosphite for **a**, dimethyl sulfide for **b**, and trimethylphosphine for **c**, **d**, and **e**) was added at a nominal pressure of $1 \times 10^{-7}$ Torr into the same cell through a batch inlet system. The mixture was subjected to electron ionization which resulted in an intense signal for the dihalobenzene radical cation. The ion signal was optimized for each experiment (typically 20 eV electron energy, 8 $\mu$A emission current, and 25 ms ionization time). The dihalobenzene radical cation was allowed to react with the nucleophile present in the cell. This reaction leads to ipso substitution of one of the halogen atoms.[17] Depending on the system, formation of an abundant halogen displacement product occurred in 0.750−6 s.

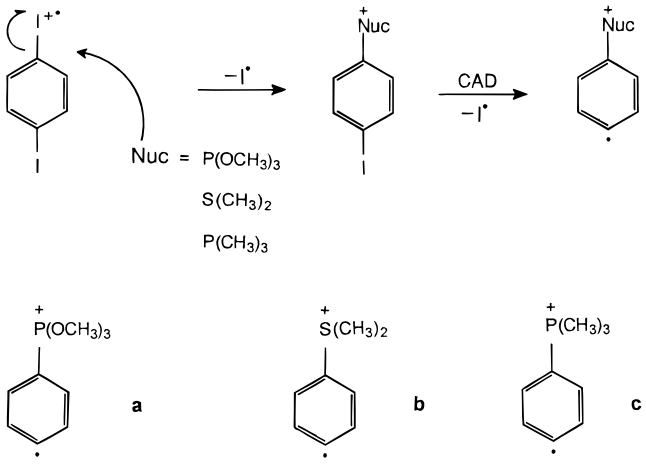
The substituted halobenzene ions, generated in one side of the dual cell as described above, were transferred into the other side by grounding the conductance limit plate for approximately 150 $\mu$s which allowed the ions to pass through a 2-mm hole in this plate. The transferred ions were cooled by allowing them to collide for 1 s with the neutral molecules present in this cell (the reagent to be used in the final stage of the experiment). The substituted halobenzene ions were then isolated by applying a stored-waveform inverse Fourier transform (SWIFT)[12] excitation pulse to the plates of the cell. After isolation, argon was introduced into the cell via a pulsed valve assembly (the nominal peak pressure in the cell was $6 \times 10^{-5}$ Torr), and the ions were collisionally activated with argon for 1 s by employing the sustained off-resonance irradiation (SORI) technique[13] at a frequency 0.5−0.8 kHz higher than the cyclotron frequency of the ions. This method led to predominant cleavage of the remaining carbon−iodine bond to yield a charged phenyl radical. The ions were then cooled for 1 s by collisions with the neutral molecules present in the cell.

The charged phenyl radicals were isolated, as described above, and allowed to react with a neutral reagent for a variable period of time (typically 1−20 s). Detection was carried out by using SWIFT excitation (0.5 cm final radius for all ions). All the spectra are the average of 50 transients and were recorded as 64k data points and subjected to one zero fill prior to Fourier transformation.

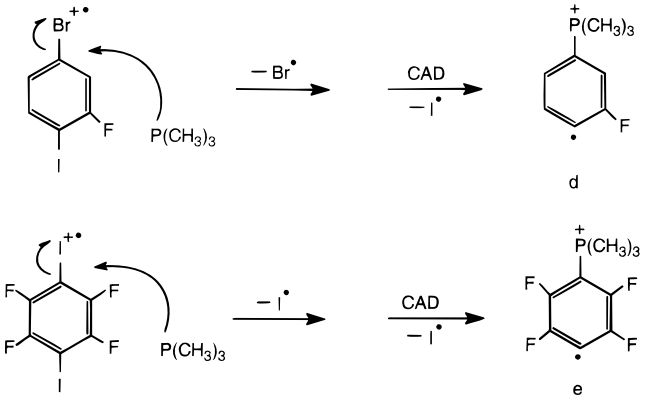
Primary products were identified based on their fixed relative abundances (branching ratios) at short reaction times. The rate constant of each reaction ($k_{exp}$) was obtained from a semilogarithmic plot of the relative abundance of the reactant ion versus time by assuming pseudo-first-order kinetics. The collision rate constant ($k_{coll}$) was calculated using the parametrized trajectory theory.[14] The reaction efficiencies are given by $k_{exp}/k_{coll}$. The accuracy of the rate constant measurements is estimated to be ±50% while the precision is better than ±10%. The greatest uncertainty arises from pressure measurement in the cell. The pressure readings of the ion gauges (located remote from the cell) were corrected for the sensitivity of the ion gauges toward each neutral reagent[15] and for the pressure gradient between the cell and the ion gauge. The latter correction factor was obtained by measuring rates of reactions with known rate constants involving the neutral reagent.

*Ab initio* MO calculations were performed using the Gaussian 92 Revision suite of programs.[16] The charged phenyl radicals were treated using the restricted Hartree−Fock (ROHF) formalism. The geometries were fully optimized using the ROHF(FC)/3-21G* basis set. Zero-point vibrational energies (ZPE) were calculated from the ROHF/3-21G* harmonic frequencies and scaled by a factor of 0.89 to account for the systematic overestimation of the vibrational frequencies by the Hartree−Fock method. Single-point energy calculations were carried out at the ROMP2/6-31G*//ROHF/3-21G*+ZPE level of theory. The force constant matrices obtained for the stationary points were checked for the correct number of negative eigenvalues (zero for equilibrium structures).

**Scheme 1**




**Scheme 2**




## Results and Discussion

Five phenyl radicals with a charged substituent in the para position, the (4-dehydrophenyl)trimethoxyphosphonium ion (**a**), the (4-dehydrophenyl)dimethylsulfonium ion (**b**), the (4-dehydrophenyl)trimethylphosphonium ion (**c**), the (3-fluoro-4-dehydrophenyl)trimethylphosphonium ion (**d**), and the (2,3,5,6-tetrafluoro-4-dehydrophenyl)trimethylphosphonium ion (**e**), were chosen for this study (Schemes 1 and 2). These species carry a coordinatively saturated and chemically inert charged group, and they have been demonstrated to possess similar chemical properties as neutral phenyl radicals.[9,10] The charged phenyl radicals were synthesized and purified by a multistep procedure described earlier in detail[9,10] (Schemes 1 and 2; Figure 1).

The charged radicals were allowed to react with 1,4-cyclohexadiene, phenol, thiophenol, benzeneselenol, and tetrahydrofuran, and the temporal variation of reactant and product ion abundances was recorded (for an example, see Figure 2). With the exception of phenol, hydrogen atom abstraction was observed for all the substrates (in some cases accompanied by adduct formation). Phenol reacts with the two radicals studied (**c** and **e**) by very slow addition (efficiency 1%; radical **c**) and by fast phenyl radical abstraction (87% of product distribution) accompanied by a slower adduct formation (total reaction efficiency 46%; radical **e**). The primary products and their branching ratios, together with the reaction efficiencies, are given in Table 1 for 1,4-cyclohexadiene, thiophenol, benzeneselenol, and tetrahydrofuran. In order to investigate the factors that control the reaction rates, *ab initio* molecular orbital calculations were employed to examine the exothermicities of some of the reactions.

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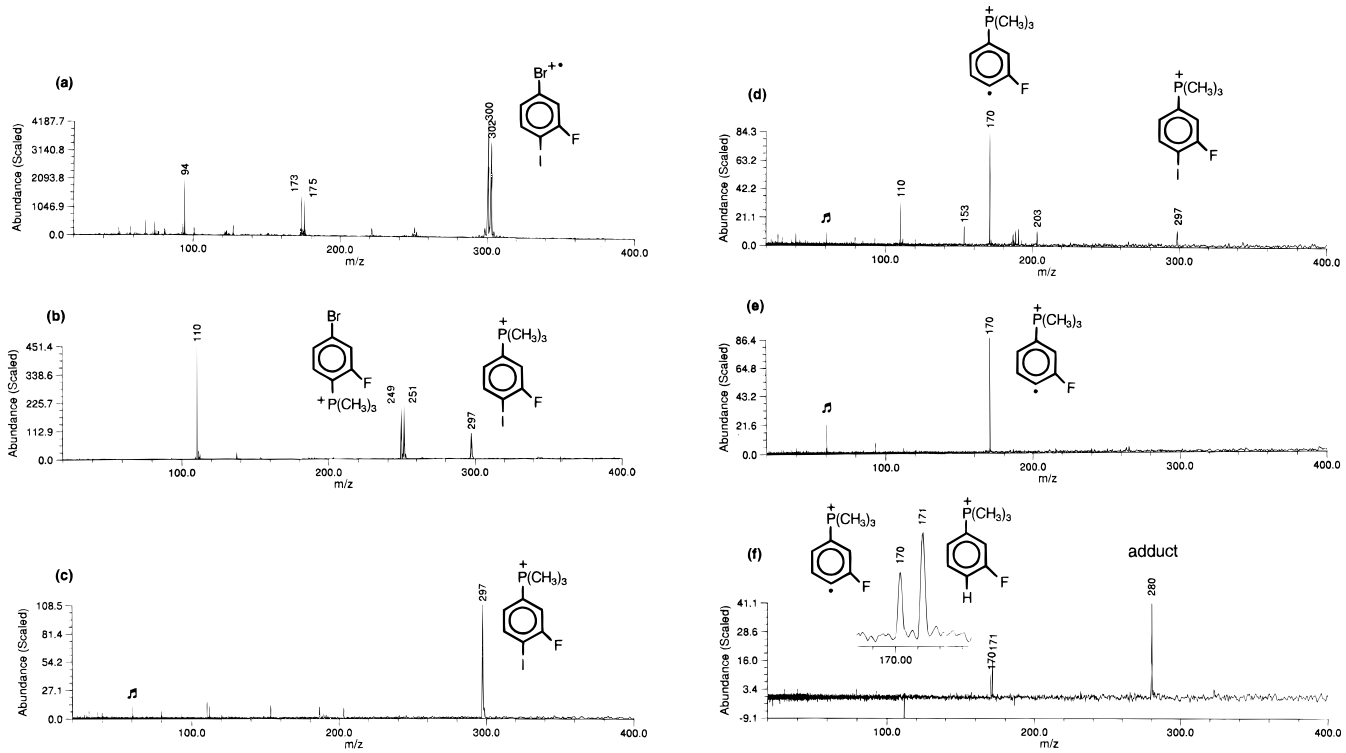


**Figure 1.** A typical experiment sequence employed in this work. (a) Electron ionization mass spectrum of 1-bromo-3-fluoro-4-iodobenzene. The peaks at *m*/*z* 300 and 302 correspond to the molecular ion. The peaks at *m*/*z* 173 and 175 arise from the loss of the iodine atom and the peak at *m*/*z* 94 from the loss of the iodine and bromine atoms from the molecular ion. (b) A spectrum collected after reaction of the radical cation of 1-bromo-3-fluoro-4-iodobenzene (*m*/*z* 300, 302) with trimethylphosphine and transfer of all ions into the other side of the dual cell reaction chamber. The peak at *m*/*z* 297 corresponds to the desired bromine atom replacement product, and those at *m*/*z* 249 and 251 correspond to the iodine atom replacement product. The peak at *m*/*z* 110 corresponds to the molecular ion of thiophenol (neutral reactant used in the last step of the experiment). (c) Partial isolation of the bromine atom replacement product (*m*/*z* 297) and (d) collision-activated dissociation to generate the charged phenyl radical, (3-fluoro-4-dehydrophenyl)trimethylphosphonium ion (**d**, *m*/*z* 170). (e) Isolation of the charged phenyl radical and (f) reaction for 7 s with thiophenol (nominal pressure $1.8 \times 10^{-7}$ Torr). Hydrogen atom abstraction (*m*/*z* 171) and adduct formation (*m*/*z* 280) are observed.

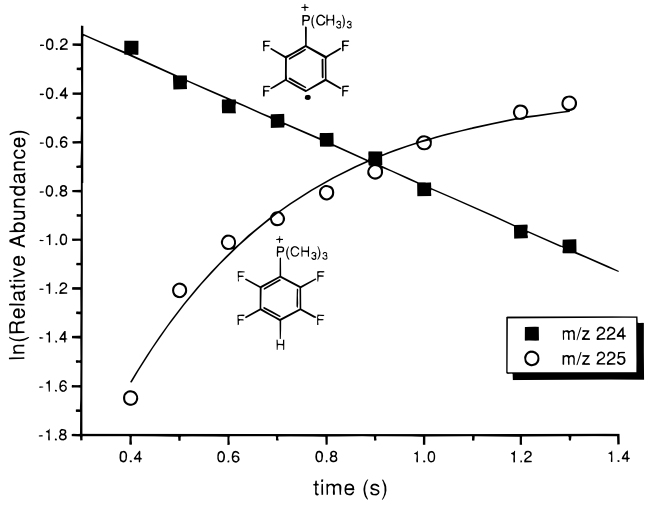


**Figure 2.** Temporal variation of the abundances of the reactant ion and the ionic products generated upon reaction of the (2,3,5,6-tetrafluoro-4-dehydrophenyl)trimethylphosphonium ion (**e**) with tetrahydrofuran. The nominal pressure of tetrahydrofuran was $2.4 \times 10^{-7}$ Torr.

**Efficiencies of the Hydrogen Atom Abstraction Reactions.** The rate of hydrogen atom abstraction by alkyl radicals often correlates with the reaction exothermicity which for a given radical is determined by the strength of the cleaving bond (*i.e.*, *t*-BuSH > PhSH > PhSeH[18]). Hence, hydrogen atom abstraction by organic radicals in solution occurs faster for example from benzeneselenol than from thiophenol.[18,22] However, the correlation between the bond strength and the reaction rate is not universal. For example, primary alkyl radicals abstract a hydrogen atom from 1,4-cyclohexadiene about 10 000 times less readily than from benzeneselenol even though the former reaction is more exothermic (Table 2).[22]

Similar findings were made for the gaseous charged phenyl radicals studied here. While the reaction efficiency toward different hydrogen atom donors cannot be readily determined for the radicals **a** (Nuc = $P(OCH_3)_3$, Scheme 1) and **c** (Nuc = $P(CH_3)_3$; Table 1) due to competing adduct formation, hydrogen atom abstraction is the only reaction observed for **b** (Nuc = $S(CH_3)_2$), the fluorinated radical **e** (Nuc = $P(CH_3)_3$), and in most instances **d** (Nuc = $P(CH_3)_3$). These three species abstract a hydrogen atom faster from benzeneselenol than from thiophenol (the efficiencies are 7% *vs* 1% for **b**, 24% *vs* 7% for **d**, and 51% *vs* 21% for **e**). Also 1,4-cyclohexadiene was found to be a less efficient hydrogen atom donor than benzeneselenol (see Table 1).

The fluorinated phenyl radicals show enhanced reactivity toward all the hydrogen atom donors examined. For example, the (3-fluoro-4-dehydrophenyl)trimethylphosphonium ion (**d**, Scheme 2) abstracts a hydrogen atom from thiophenol >20 times as efficiently as the corresponding unfluorinated radical

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**Table 1.** Reactions of Charged Phenyl Radicals with Hydrogen Atom Donors

| | benzeneselenol | | thiophenol | | 1,4-cyclohexadiene | | tetrahydrofuran | |
|---|---|---|---|---|---|---|---|---|
| ion | reaction (%) | eff[a] | reaction (%) | eff | reaction (%) | eff | reaction (%) | eff |
| **c** | H• abstraction (20%); adduct (80%) | 0.14 | H• abstraction (74%); adduct (26%) | ~0.003[b,c] | H• abstraction (58%); adduct (42%) | ~0.03[b] | H• abstraction (100%) | ~0.002[b] |
| **d** | H• abstraction (100%) | 0.24 | H• abstraction (30%); adduct (70%) | 0.07 | H• abstraction (100%) | 0.13 | H• abstraction (100%) | 0.04 |
| **e** | H• abstraction (100%) | 0.51 | H• abstraction (100%) | 0.21 | H• abstraction (100%) | 0.18 | H• abstraction (100%) | 0.32 |

[a] eff = $k_{exp}/k_{coll}$. [b] The efficiency was corrected for an interfering reaction involving neutral trimethylphosphine which was leaking over from the other side of the dual cell. [c] The efficiency was corrected for an interfering reaction with oxygen.

**Table 2.** Homolytic X−H (X = S, Se, O, C) Bond Dissociation Energies (kcal mol$^{-1}$), Ionization Energies (eV), and Dipole Moments (D)

| reagent | X−H homolytic bond dissociation energy (kcal mol$^{-1}$) | ionization energy (eV) | dipole moment (D) |
|---|---|---|---|
| 1,4-cyclohexadiene | 73[a] | 8.8[d] | 0.0[e] |
| benzeneselenol | 79[b] | 8.3[b] | 1.0[f] |
| thiophenol | 83[c] | 8.3[d] | 1.07[e] |
| phenol | 87[c] | 8.5[d] | 1.2[e] |
| tetrahydrofuran | 92[c] | 9.8[d] | 1.7[e] |

[a] Value assumed to be the same as that of 1,3-cyclohexadiene; ref 18a. [b] Value obtained from ref 19. [c] Value obtained from ref 23. [d] Value obtained from ref 20. [e] Values obtained from ref 21. [f] Value obtained from PM3 semiempirical calculations; see ref 19.

**c**. Even greater efficiencies were measured for the tetrafluorinated phenyl radical, the (2,3,5,6-tetrafluoro-4-dehydrophenyl)-trimethylphosphonium ion **e**. For example, the efficiency measured for the reaction of **e** toward thiophenol is 3 times that measured for the monofluorinated radical **d**. The tetrafluorinated radical **e** is less sensitive than the other radicals toward the type of hydrogen atom donor. In fact, all the hydrogen atom abstraction reactions of this radical were found to be highly efficient (reaction efficiencies 18−51%).

The results obtained for the fluorinated radicals **d** and **e** are in agreement with the solution findings that electron-withdrawing substituents often enhance the reactivity of neutral phenyl and alkyl radicals toward electron-rich reagents.[24−26] In order to explore the generality of the gas-phase results, two additional charged phenyl radicals of a different type were examined. The radicals **f** and **g** (Figure 3) carry the 3-fluoropyridinium charge site in the meta position. In addition, **g** contains a fluorine atom in the meta position with respect to both the radical site and the charge site. Again, fluorination of the phenyl ring results in significantly faster hydrogen atom abstraction reactions (the reaction efficiencies for benzeneselenol are 18% for **f** and 27% for **g**; Figure 3). Hence, fluorine substituents in the meta as well as the ortho position in the phenyl radical enhance the reactivity toward hydrogen atom donors.

**Thermochemistry.** The exothermicity of hydrogen atom abstraction by charged phenyl radicals was explored by calculating the homolytic phenyl C−H bond dissociation energies of the dimethylphenylsulfonium ion (Scheme 3) and the phenylsulfonium ion (Scheme 4) at the 4-position. Both these species, as well as the radicals derived from them by hydrogen atom abstraction, were found to have $C_s$ symmetry. Energies calculated at the ROMP2/6-31G*//ROHF/3-21G*+ZPE level of theory for the reactants and products of the two isodesmic reactions[27] shown in Scheme 3 yield a difference of 10.9 and

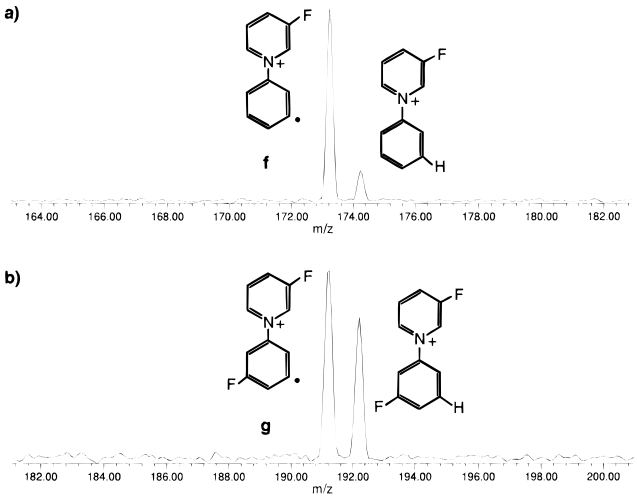
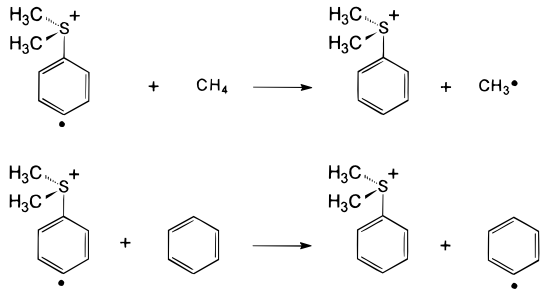
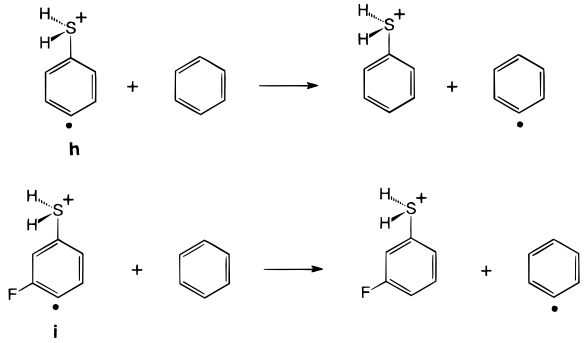



**Figure 3.** Reaction of benzeneselenol (nominal pressure 1.8 × 10$^{-7}$ Torr) for 1 s with (a) the (3-dehydrophenyl)-3-fluoropyridinium ion (**f**) and (b) the (3-fluoro-5-dehydrophenyl)-3-fluoropyridinium ion (**g**).

**Scheme 3**



**Scheme 4**



2.0 kcal mol$^{-1}$ (at 0 K) for the homolytic C−H bond dissociation energy of the dimethylphenylsulfonium ion and those of $CH_4$ and benzene, respectively (Table 3). These values, in conjunction with the experimentally determined[28,29] homolytic C−H bond dissociation energies of $CH_4$ (103.3 kcal mol$^{-1}$ at 0 K) and benzene (112.0 kcal mol$^{-1}$ at 0 K), yield a homolytic C−H

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**Table 3.** Calculated Absolute Energies (hartrees) and Homolytic Bond Dissociation Energies (kcal mol$^{-1}$) for the C−H Bond in the 4-Position

| molecule | absolute energy (hartrees)[a] | $D$(C−H) (kcal mol$^{-1}$) (determined based on $D$(C−H) of benzene[b] and methane[b]) |
|---|---|---|
| (4-dehydrophenyl)dimethylsulfonium ion (**b**) | −706.935 73 | |
| dimethylphenylsulfonium ion | −707.601 77 | 114.0, 114.2 |
| (4-dehydrophenyl)sulfonium ion (**h**) | −628.616 24 | |
| phenylsulfonium ion | −629.283 51 | 114.8, 115.0 |
| (3-fluoro-4-dehydrophenyl)sulfonium ion (**i**) | −627.630 92 | |
| (3-fluorophenyl)sulfonium ion | −728.302 74 | 117.7, 117.9 |
| 2-fluorophenyl radical | −329.717 99 | |
| fluorobenzene | −330.385 47 | 114.9, 115.1 |
| phenyl radical | −230.696 24 | |
| benzene | −231.359 05 | 112.0,[b] 112.2 |
| methyl radical | −39.641 085 | |
| methane | −40.289 699 | 103.1, 103.3[b] |

[a] For odd-electron species: ROMP2/6-31G*//ROHF/3-21G*+ZPE. For even-electron species: MP2/6-31G*//HF/3-21G*+ZPE. [b] $D$(C−H) = 112.0 kcal mol$^{-1}$ for benzene (0 K; ref 29) and $D$(C−H) = 103.3 kcal mol$^{-1}$ for methane (0 K; ref 28).

bond dissociation energy of 114.0−114.2 kcal mol$^{-1}$ (at 0 K) for the dimethylphenylsulfonium ion at the 4-position. Similar calculations carried out for the phenylsulfonium ion (Table 3; Scheme 4) suggest that the slightly more electron withdrawing sulfonium substituent makes the C−H bond about 0.8 kcal mol$^{-1}$ stronger (114.8−115.0 kcal mol$^{-1}$; Table 3) than the dimethylsulfonium substituent. An estimate for the error associated with the calculated bond dissociation energies was obtained by calculating the difference between the homolytic C−H bond dissociation energies of $CH_4$ and benzene. The calculated difference (8.9 kcal mol$^{-1}$ at the ROMP2/6-31G*//ROHF/3-21G*+ZPE level of theory; Table 3) is in error by only 0.2 kcal mol$^{-1}$ when compared to the difference obtained by using the known experimental values[28,29] (8.7 kcal mol$^{-1}$).

The homolytic C−H bond dissociation energies calculated for the dimethylphenylsulfonium and phenylsulfonium ions at the 4-position (114.0−114.2 and 114.8−115.0 kcal mol$^{-1}$, respectively) are somewhat greater than the C−H bond energy of neutral benzene (112.0 kcal mol$^{-1}$ at 0 K).[29] This result is as expected since the homolytic C−H bond dissociation energies of molecules with charged substituents are generally somewhat greater than those of the corresponding neutral molecules.[30] For example, the homolytic methyl C−H bond dissociation energy[30] in $CH_3CH_2OH_2^+$ is 106 kcal mol$^{-1}$ while that in $CH_3CH_2OH$ is 95 kcal mol$^{-1}$.[30]

Based on the C−H bond dissociation energy calculated for the dimethylphenylsulfonium ion, the enthalpy changes for hydrogen abstraction by the (4-dehydrophenyl)dimethylsulfonium ion (**b**) are estimated to be −35, −31, and −41 kcal mol$^{-1}$ for benzeneselenol, thiophenol, and 1,4-cyclohexadiene, respectively. Despite of the high exothermicity, hydrogen atom abstraction from these substrates occurs at a rate significantly less than the theoretical gas-phase collision rate. This finding suggests that a high barrier exists on the reaction coordinate. Indeed, relatively large barriers are known to exist in hydrogen atom abstraction reactions involving simple alkyl radicals.[31,32] For example, activation energies of approximately 22 and 12 kcal mol$^{-1}$ have been determined for the reaction of methyl radical with methane and trifluoromethane, respectively.[31,32]

The origins of the enhanced reaction efficiencies observed for the fluorinated radicals **d** and **e** were explored by estimating the homolytic C−H bond dissociation energy for the (3-fluorophenyl)sulfonium ion (Scheme 4) as described above for other sulfonium ions. The lowest energy conformers of the (3-fluorophenyl)sulfonium ion and the corresponding radical **i** were found to have $C_s$ symmetry (see Scheme 4); these are the conformers used in the calculations. Examination of two isodesmic reactions, hydrogen atom abstraction by the (3-fluorophenyl)sulfonium ion from benzene and from methane, suggests that the introduction of a fluorine atom increases the dissociation energy of the adjacent C−H bond in the phenylsulfonium ion by about 3 kcal mol$^{-1}$ (ROMP2/6-31G*//ROHF/3-21G*+ZPE level of theory; Table 3). In agreement with this result, the introduction of a fluorine atom was calculated to increase the adjacent C−H bond dissociation energy of neutral benzene by the same amount (3 kcal mol$^{-1}$). Hence, adjacent monofluorination has a significant effect on the exothermicity of hydrogen atom abstraction reactions of phenyl radicals.

An additional explanation for the rate enhancement caused by fluorine substitution in the charged phenyl radicals is possible lowering in the barrier height for hydrogen atom abstraction. According to the curve crossing model,[31] the height of the energy barrier for hydrogen atom abstraction by a radical that is a good electron acceptor is likely to be significantly influenced by a charge transfer configuration contributing to the electronic structure of the transition state. For the reaction of a charged phenyl radical X$^\bullet$ and a hydrogen atom donor R−H, this charge transfer configuration can be represented by [X$^-$][RH$^{\bullet+}$]. This configuration is stabilized (reaction barrier lowered) by increasing the electron affinity of the radical. Hence, fluorine substitution in the reactant radical is expected to facilitate the reaction.

The energy of the charge transfer configuration is also lowered by lowering the ionization energy of the hydrogen atom donor. This partially explains why benzeneselenol (ionization energy[19] 8.3 eV) was found to donate a hydrogen atom to all the charged phenyl radicals more readily than 1,4-cyclohexadiene (ionization energy[20] 8.8 eV) inspite of its higher homolytic bond dissociation energy (see Table 2). However, it should also be mentioned here that the dipole moment of 1,4-cyclohexadiene is very small (Table 2). Hence, the potential energy well corresponding to the collision complex of the charged phenyl radicals with 1,4-cyclohexadiene is shallow (estimated[33,34] to be 2 kcal mol$^{-1}$ vs 25 kcal mol$^{-1}$ estimated for benzeneselenol), making this reagent a poor solvent for the charged phenyl radicals. This collision complex will have only a small amount of energy to overcome energy barriers on the reaction coordinate.

**Hydrogen Atom Abstraction from Tetrahydrofuran and Thymine.** Hydrogen atom abstraction reactions involving

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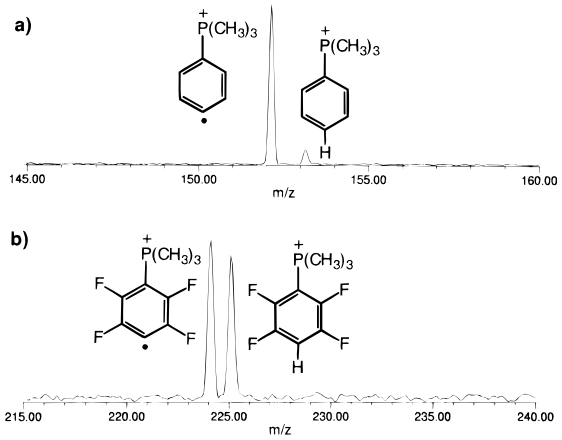


**Figure 4.** Reaction of tetrahydrofuran (nominal pressure $1.4 \times 10^{-7}$ Torr) with (a) the (4-dehydrophenyl)trimethylphosphonium ion (**c**) for 10 s and (b) (2,3,5,6-tetrafluoro-4-dehydrophenyl)trimethylphosphonium ion (**e**) for 1 s.

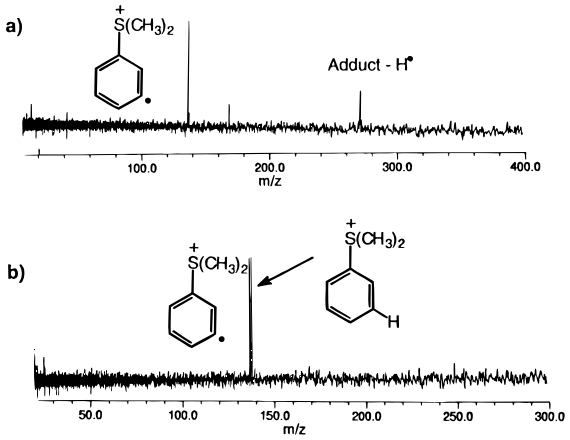


**Figure 5.** Reaction of the meta isomer of radical **b** (a) for 10 s with adenine (nominal pressure $2.1 \times 10^{-7}$ Torr) and (b) for 5 s with thymine (nominal pressure $3.3 \times 10^{-7}$ Torr).

polyatomic organic radicals are believed to play a major role in the degradation of DNA by certain powerful anticancer drugs.[4,35] One possible mechanism leading to DNA degradation involves removal of a hydrogen atom from the C-4′ position on the sugar moiety, followed by decomposition of the DNA strand.[4,35] Not much is currently known about the factors that control the rate of the abstraction of the hydrogen atom by different organic radicals,[4,7] such as substituted phenyl radicals.[36] In order to explore the effects that fluorine substitution has on the efficiency of a phenyl radical to abstract a hydrogen atom from DNA, several charged phenyl radicals were allowed to react with tetrahydrofuran (a simple model for the sugar moiety in DNA).

Slow hydrogen atom abstraction is the only reaction observed upon interaction of the unfluorinated (4-dehydrophenyl)trimethylphosphonium ion (**c**) with tetrahydrofuran (Figure 4a). Fluorine substitution at the atom adjacent to the radical site (**d**) causes an observable increase in the reaction efficiency (0.2% *vs* 4%). The reaction rate is further enhanced upon additional fluorine substituents: the (2,3,5,6-tetrafluoro-4-dehydrophenyl)-trimethylphosphonium ion (**e**) reacts with tetrahydrofuran more efficiently than any other radical studied (32% efficiency; Table 1; Figure 4).

Interestingly, the tetrafluorinated radical **e** shows greater reactivity toward tetrahydrofuran than toward most of the other substrates studied. Only the reaction with benzeneselenol occurs at an efficiency greater than that measured for tetrahydrofuran. Further, the relative rate enhancement observed upon addition of four fluorine atoms to the attacking phenyl radical is greater for tetrahydrofuran than for the other hydrogen atom donors studied. Hence, tetrahydrofuran seems to be especially sensitive to substituents in an attacking phenyl radical.

Although radical-induced DNA strand cleavage is thought to be initiated by hydrogen atom abstraction from the sugar moiety, radicals may also attack the nucleobases. Many neutral radicals are thought to react with the DNA bases by addition.[4c,37−39] In order to investigate whether similar reactivity might be expected for the charged phenyl radicals, two nucleobases were allowed to react with the charged phenyl radical (3-dehydrophenyl)dimethylsulfonium ion (the meta isomer of **b**). As expected, adenine reacts with this phenyl radical by a slow formation of an adduct which rapidly loses a hydrogen atom (Figure 5a). In sharp contrast, slow hydrogen atom abstraction is the only reaction observed for thymine (Figure 5b). These results suggest that different DNA bases may demonstrate unique reactivity toward phenyl radicals. Interestingly, these findings parallel those made for the hydroxyl radical. This radical adds to adenine but shows addition as well as hydrogen atom abstraction upon interaction with thymine.[39]

## Conclusions

Slow hydrogen atom transfer was observed upon the reaction of the hydrogen atom donors benzeneselenol, thiophenol, and 1,4-cyclohexadiene with several differently substituted charged phenyl radicals. In agreement with solution results obtained for neutral carbon-centered radicals, hydrogen abstraction occurs most readily from benzeneselenol and least readily from 1,4-cyclohexadiene. All the hydrogen atom abstraction reactions studied are estimated to be highly exothermic by using molecular orbital calculations. Despite the large driving force, most of the reactions occur slowly. These findings suggest the presence of a significant barrier on the reaction coordinate. Fluorine substitution in the phenyl radical was found to cause a remarkable rate enhancement for all the hydrogen atom donors studied. However, the greatest rate increase was observed for tetrahydrofuran studied as a simple model of the sugar moiety in DNA. This result suggests that the sugar units in DNA might also be sensitive to substituents in the attacking radical, and that the incorporation of fluorine atoms is likely to lead to greater antitumor activity for those anticancer drugs that cleave DNA through mechanisms involving polyatomic organic radicals. Substituent effects on the reactivity of phenyl radicals toward different types of substrates are currently being explored in our laboratories.

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