7

Practical Applications of Polyvalent Iodine Compounds

Practical applications of polyvalent iodine derivatives are restricted by the low stability of many of these compounds. Among inorganic derivatives of polyvalent iodine, only iodine pentafluoride, iodine pentoxide and iodic and periodic acids and their salts are commercially available, stable products. These stable inorganic compounds have found some industrial use, mainly as powerful oxidants.

The vast majority of organic λ^3- and λ^5-iodanes lack thermal stability and some of them are explosive. Only several representatives of hypervalent iodanes with one carbon ligand are commercially available products, namely, (diacetoxyiodo)benzene (DIB or PIDA), [bis(trifluoroacetoxy)iodo]benzene (BTI or PIFA), [hydroxy(tosyloxy)iodo]benzene (HTIB), 2-iodosylbenzoic acid (IBA), 2-iodoxybenzoic acid (IBX) and Dess–Martin periodinane (DMP). These commercially available compounds are widely used in chemical laboratories as versatile and environmentally benign reagents for organic synthesis (Chapters 3–6). Organic hypervalent iodine(III) derivatives with two aryl substituents on iodine, or diaryliodonium salts, possess a higher thermal stability. Several representatives of diaryliodonium salts are commercially available products. Stable iodonium salts have found numerous practical applications, such as cationic photoinitiators in polymer chemistry, biologically active compounds and ^{18}F-fluoridating agents in positron emission tomography (PET). The biological properties of iodonium salts were summarized in 1996 in a comprehensive review on polyvalent iodine compounds [1] and a brief overview of the application of iodonium salts in PET was given in 2011 in a review on iodonium salts [2].

7.1 Applications of Inorganic Polyvalent Iodine Derivatives

Potassium iodate, KIO_3, the most thermodynamically stable and naturally occurring compound of polyvalent iodine, has found some application as a dietary supplement and a food additive. It can be used as a source of iodine in iodized salt and also as a dough conditioner [3]. In fact, because potassium iodate is more stable than iodide in the presence of air, most health authorities preferentially recommend iodate as an additive to salt for correcting iodine deficiency. Iodate is rapidly reduced to iodide in the body; iodide is essential for thyroid function. However, high levels of iodate (0.600 mg per day) have been shown to cause damage to the retina, resulting in ocular toxicity [4]. The recommended level of iodine in iodized salt is between 20 and

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80 mg per kilogram of salt, which is equal to 28 to 110 mg of potassium iodate per kilogram of salt. For a maximal daily salt intake of 15 g, this results in a human exposure of 440–1700 μg of iodate per day, which is well below the acute or chronic toxicity levels [3]. Available toxicology data indicate a negligible risk of the small oral long-term doses achieved with iodate-fortified salt.

Metal iodates are of particular interest as second-order nonlinear optical (NLO) materials [5]. NLO materials are of current interest and great importance due to their applications in photonic technologies, such as laser frequency conversion, optical parameter oscillators (OPOs) and signal communication. Lithium iodate is one of the most widely used and commercially manufactured representatives of such materials [5]. Many inorganic iodates, such as α-$LiIO_3$, NaI_3O_8 [6] and α-$Cs_2I_4O_{11}$ [7], have been reported to be promising new second-harmonic generation (SHG) materials with wide transparent wavelength regions, large SHG coefficients and high optical-damage thresholds as well as high thermal stabilities.

Iodine pentoxide, I_2O_5, is the most stable oxide of the halogens [8]. It has found some practical application as a mild oxidant, especially useful in analytical chemistry. Iodine pentoxide is one of the few chemicals that can oxidize carbon monoxide rapidly and completely at room temperature. The reaction forms the basis of a useful analytical method for determining the concentration of CO in the atmosphere or in other gaseous mixtures [8].

Periodic acid and periodates are thermodynamically potent and kinetically facile oxidants. In acid solution periodic acid is one of the few reagents that can rapidly and quantitatively convert Mn(II) into Mn(VII) [8]. In organic chemistry it specifically cleaves 1,2-diols and related compounds such as α-diketones, α-ketols, α-aminoalcohols and α-diamines; all these reactions have been widely used in carbohydrate and nucleic acid chemistry. Periodate oxidation is widely used in chemical and instrumental methods of analysis of polysaccharides, oligosaccharides, glycosides, glycoproteins and other organic products of biological origin [9–12]. Applications of periodate oxidations in instrumental methods of microanalysis were summarized in a review in 2009 [12].

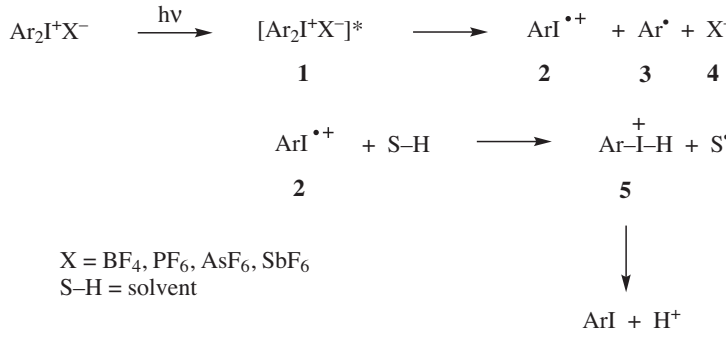
Periodate salts have seen some application in propellant formulations and their use as environmentally friendly oxidizers in pyrotechnic formulations has been reported [13]. In particular, Moretti, Sabatini and Chen have developed incendiary mixtures featuring periodate salts KIO_4 and $NaIO_4$ that perform similarly to perchlorates but are less toxic [13]. Combined with the alloy magnalium (magnesium–aluminium, 1 : 1) as the fuel, these mixtures produce a bright flash of light.

Iodine pentafluoride, IF_5, is one the most thermodynamically stable fluorides among the fluorides of Cl, Br and I. It is an important industrial fluorinating reagent, manufactured in the USA on a scale of several hundred tons per year. Iodine pentafluoride is available as a liquid in steel cylinders up to 1350 kg capacity; the price in 1992 was circa $50 kg [8]. Iodine pentafluoride is a relatively mild fluorinating agent and can be handled in glass apparatus. Nuclear power engineering, in particular, production process for volatile uranium hexafluoride, is one of the areas of practical uses of IF_5 [14]. Iodine pentafluoride is also used for the preparation of graphite fluorides, which are known for their application as lubricants or as cathode materials in primary lithium batteries [15, 16].

7.2 Applications of Hypervalent Iodine(III) Compounds as Polymerization Initiators

Diaryliodonium salts are widely used as photoinitiators for cationic photopolymerizations [17–20]. Photoinitiated cationic polymerization is of great practical interest due to its applicability for the curing of coatings and printing inks and for photoresist technology used in lithography [19,20]. General synthetic methods, properties and photochemistry of diaryliodonium salts as photoinitiators were reviewed by Crivello in 1984 [18].

Crivello and coworkers were the first to discover that iodonium salts having BF_4^-, PF_6^-, AsF_6^-, or SbF_6^- counterions are efficient photoinitiators for the polymerization of various cationically polymerizable



Scheme 7.1

monomers [21]. The study of the mechanism of photolysis of iodonium salts confirmed a pathway involving radical–cations and aryl radicals as key intermediates. The major pathway involves the facile decomposition of the excited iodonium compound **1** to aryliodo radical–cation **2**, aryl radical **3** and anion **4** (Scheme 7.1) [21]. This process should be highly efficient due to the very low bond energy of the C–I bond (26–27 kcal mol^{-1}). Interaction of the aryliodo radical–cation with the solvent (S–H) generates a protonated iodoaromatic compound **5,** which rapidly deprotonates and a radical $S^{\bullet}$ derived from the solvent. During photolysis, the BF_4^-, PF_6^-, AsF_6^-, or SbF_6^- counterions associated with the diaryliodonium salts remain unchanged and appear in the products as the corresponding Brønsted acids. These acids (HX) are credited as the true initiators of cationic polymerization when diaryliodonium salts are employed in the cationic photopolymerization of various monomers [21]. According to this mechanism of action, diaryliodonium salts belong to an important class of photoacid generators (PAGs), which find broad applications in the manufacturing of protective coatings, smart cards, 3D rapid prototyping, UV adhesives, semiconductor devices, antireflective coatings, holograms and so on.

In the same groundbreaking paper [21], Crivello and coworkers also demonstrated that the anion plays no role in determining the photosensitivity of the iodonium salt and the photolysis rates of diaryliodonium salts having the same cations but different non-nucleophilic counterions (BF_4^-, PF_6^-, AsF_6^-, or SbF_6^-) are identical. Likewise, the cation structure has little effect on the photodecomposition of diaryliodonium salts. The utility of iodonium salts as photoinitiators has been demonstrated in several cationic polymerizations using olefins, epoxides, cyclic ethers, lactones and cyclic sulfides as the monomers [21].

More recently, iodonium salts have been widely used as photoinitiators in the polymerization studies of various monomeric precursors, such as copolymerization of butyl vinyl ether and methyl methacrylate by combination of radical and radical promoted cationic mechanisms [22], thermal and photopolymerization of divinyl ethers [23], photopolymerization of vinyl ether networks using an iodonium initiator [24, 25], dual photo- and thermally-initiated cationic polymerization of epoxy monomers [26], preparation and properties of elastomers based on a cycloaliphatic diepoxide and poly(tetrahydrofuran) [27], photoinduced crosslinking of divinyl ethers [28], cationic photopolymerization of 1,2-epoxy-6-(9-carbazolyl)-4-oxahexane [29], preparation of interpenetrating polymer network hydrogels based on 2-hydroxyethyl methacrylate and *N*-vinyl-2-pyrrolidone [30], photopolymerization of unsaturated cyclic ethers [31] and many other works.

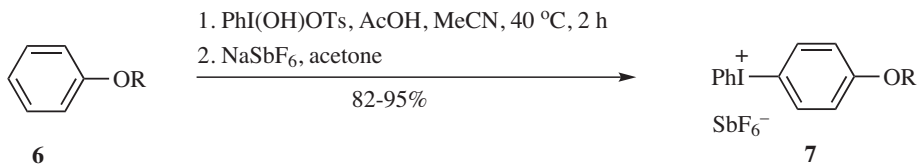
Different initiation techniques have been investigated in polymerizations induced by iodonium salts, such as visible laser irradiation [32], dual photo- and thermally initiated cationic polymerization [23, 26] and a two-photon photopolymerization initiation system [33, 34]. For example, dual photo- and thermal-initiation systems based on selective inhibition of the photoinitiated cationic ring-opening polymerization of epoxides by dialkyl sulfides have been developed [26]. Such a dual system, iodonium salt/dialkyl sulfide, in the

presence of a monomer can be activated by UV irradiation and then subsequently be polymerized by the application of heat. It is proposed that dialkyl sulfides terminate the initial or growing polyether chains at an early stage to form stable trialkylsulfonium salts. These systems are dormant at room temperature but, on heating, the sulfonium salts are capable of reinitiating ring-opening polymerization. These dual photo- and thermal-cure systems have potential applications in adhesives, potting resins and composites [26]. Another initiation system, the two-photon photopolymerization initiation system, consists of a photosensitizer dye and the photoinitiator diaryliodonium salt encapsulated by methylated-β-cyclodextrin [34]. Such a complex can be used as an effective photoinitiator for two-photon photopolymerization in an aqueous system.

Numerous publications have been devoted to the development of the more efficient photoinitiators based on iodonium salts. In contrast to the original observations of Crivello that neither the cationic part of iodonium salt nor the counterions have an effect on the photodecomposition of diaryliodonium salts [21], it has been demonstrated that both anionic and cationic portions of iodonium salts may play an important role in the overall effectiveness of the photoinitiator. Park and coworkers have published a detailed study on the participation of anion and alkyl substituents of diaryliodonium salts in photoinitiated cationic polymerization reactions of epoxides [35]. It was found that the alkyl-substituted diphenyliodonium cations, such as bis(4-*tert*-butylphenyl)iodonium and 4-cumenyl-4′-tolyliodonium salts, have higher photoacid generation efficiency than the unsubstituted diphenyliodonium salts. The lower nucleophilicity and large volume size of the anions play a decisive role in enhancing the rate of polymerization, with the general order of reactivity found to be PF_6^- < AsF_6^- < $B(C_6F_5)_4^-$ [35]. In general, the larger the anion is, the more loosely it is bound to the end of the growing cationic chain and the more active the propagating cationic species is in the polymerization. For this series, $B(C_6F_5)_4^-$ is the largest anion and the most loosely bound, while PF_6^- is the smallest and, therefore, the most tightly bound anion. For comparison, in the case of the most nucleophilic trifluoromethanesulfonate anion, cationic polymerization of epoxides was not observed [35].

Crivello and Lee have described the synthesis and characterization of a series of (4-alkoxyphenyl)phenyliodonium salts **7,** which are excellent photo- and thermal-initiators for the cationic polymerization of vinyl and heterocyclic monomers [17]. Iodonium salts **7** are conveniently prepared by the reaction of alkoxyphenols **6** with [hydroxy(tosyloxy)iodo]benzene followed by anion exchange with sodium hexafluoroantimonate (Scheme 7.2). Products **7** have very good solubility and photoresponse characteristics, which make them especially attractive for use in UV curing applications. Compounds **7** with alkoxy chains of eight carbons and longer are essentially nontoxic, compared to diphenyliodonium hexafluoroantimonate, which has an oral LD_{50} of 40 mg kg^{-1} (rats) [17].

Shirai, Kubo and Takahashi have prepared and examined a series of new substituted diaryliodonium hexafluorophosphates aiming at improved solubility and lower toxicity of the photoinitiators [36]. The alkyl substituted iodonium salts **8**–**13** (Figure 7.1) in combination with 2-ethyl-9,10-dimethoxyanthracene as the photosensitizer showed especially high photocuring ability [36].



6 **7**

R = Me, C_8H_{17}, $C_{10}H_{21}$, $C_{11}H_{23}$, $C_{14}H_{29}$, $C_{15}H_{31}$, $C_{16}H_{33}$, $C_{18}H_{37}$

Scheme 7.2

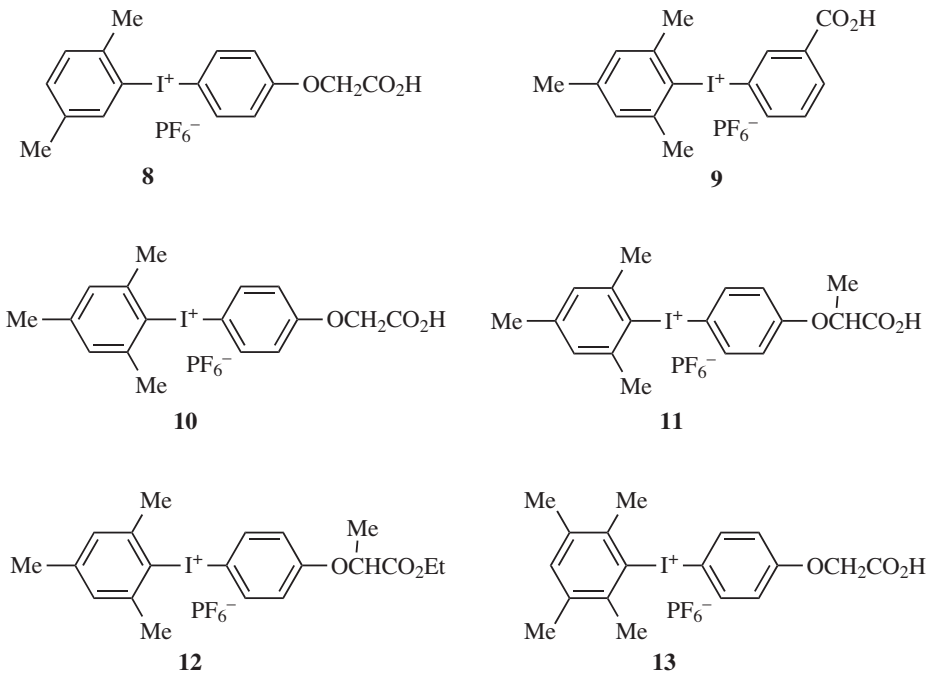
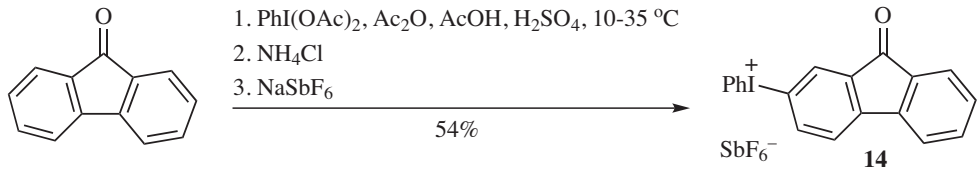


Figure 7.1 *Efficient photoinitiators with high solubility and low toxicity.*

The preparation and properties of (9-oxo-9*H*-fluoren-2-yl)phenyliodonium hexafluoroantimonate (**14**) as a new photoinitiator for the cationic polymerization of epoxides have been reported [37]. Compound **14** was prepared by the reaction of (diacetoxyiodo)benzene with fluorenone followed by treatment with sodium hexafluoroantimonate (Scheme 7.3). Photoinitiator **14** has the advantage of intramolecular photosensitization and it is a more effective initiator than the conventional iodonium salts [37].

An alkynyliodonium salt, namely, phenyl(phenylethynyl)iodonium hexafluorophosphate, has been tested for application as cationic photoinitiator [38]. The high activity of phenyl(phenylethynyl)iodonium salt as a photoinitiator was verified by photo differential scanning calorimetry (photo-DSC) experiments in direct irradiation and in photosensitized initiation using 9,10-dibutylanthracene, 2-isopropylthioxanthone and benzophenone as sensitizers [38].

Neckers and coworkers have prepared diaryliodonium butyltriphenylborate salts **15**–**18** (Figure 7.2) by anion exchange of the respective diaryliodonium halides with tetramethylammonium butyltriphenylborate



Scheme 7.3

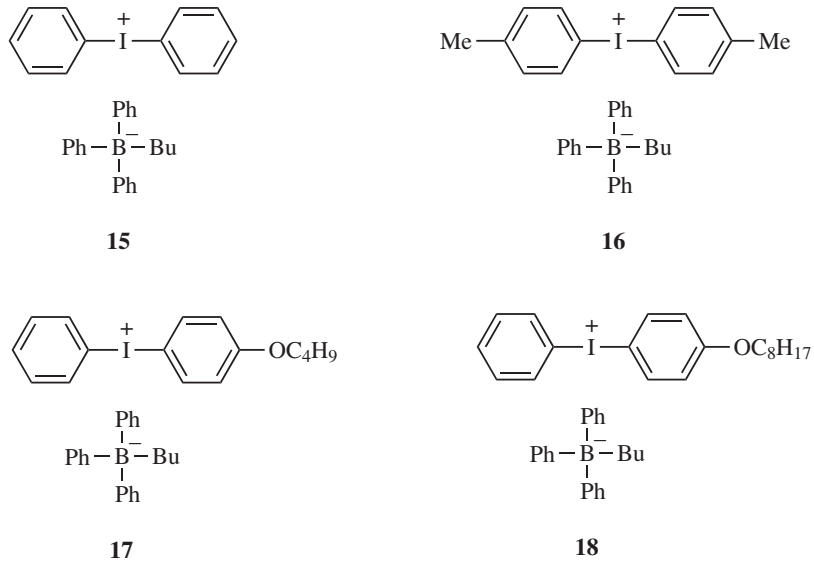
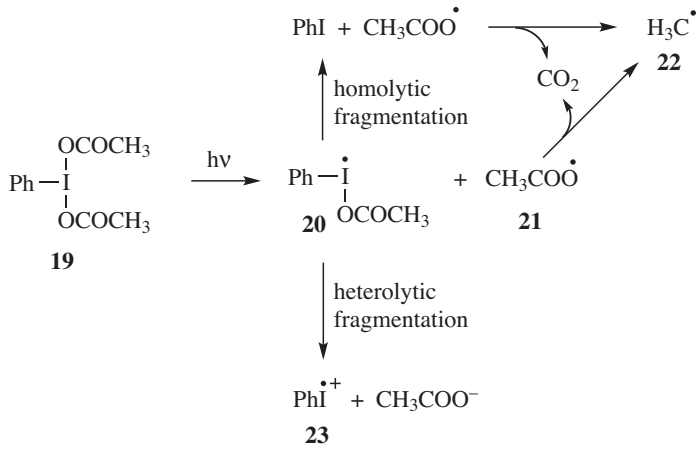


Figure 7.2 *Photoinitiators based on diaryliodonium butyltriphenylborate salts.*

and have investigated their reactivity as photoinitiators for the polymerization of acrylates [39]. Butyltriphenylborate salts **15**–**18** were found to be more efficient photoinitiators than iodonium tetraphenylborate salts, Ar_2IBPh_4. It was found from a study of the photoreaction of iodonium borate salts with a model monomer, methyl methacrylate, that iodonium butyltriphenylborate salts **15**–**18** simultaneously produce a butyl radical from the borate anion and an aryl radical from the iodonium cation upon irradiation. Both radicals initiate polymerization. Iodonium tetraphenylborate salts, Ar_2IBPh_4, were found to release an aryl radical, but only from the iodonium cation. Iodonium borate salts exhibit strong absorption below 300 nm, with a tail absorption above 400 nm. Thus, iodonium butyltriphenyl borate salts **15**–**18** are efficient photoinitiators even when used with visible light [39].

In 1985, Georgiev, Spyroudis and Varvoglis first reported that [bis(acyloxy)iodo]arenes, such as $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$, are effective photoinitiators of cationic and radical polymerization [40]. In particular, under photochemical conditions $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$ are efficient initiators for the homopolymerizations of 2-(dimethylaminoethyl) methacrylate (DMAEM) and methyl methacrylate (MMA) and also for the copolymerizations of DMAEM with MMA or styrene [40,41]. The proposed mechanism for the photoinitiation involves initial homolytic decomposition of the λ^3-iodane, for example, $PhI(OAc)_2$ (**19**), producing acyl **21** and iodanyl **20** radicals (Scheme 7.4) [41–45]. The actual initiators of radical polymerization are methyl radicals **22** generated by the decarboxylation of acyl radical **21,** as has been proved by the radical scavenger method [46]. It was proposed that the iodanyl radical **20** can further undergo both homolytic and heterolytic decomposition; homolytic fragmentation produces additional acyl and methyl radicals, while heterolytic fragmentation gives the phenyl iodide cation–radical **23,** which is a precursor of the true cationic initiator [44].

Georgiev has reported a photoiniferter ability for [bis(acyloxy)iodo]arenes during the bulk polymerization of methyl methacrylate, styrene and *N*-vinylpyrrolidone [44]. The term "photoiniferter" refers to a chemical compound that has a combined function of being a free radical initiator, transfer agent and terminator in photolytically induced polymerization [47]. Under visible light [bis(acyloxy)iodo]arenes initiate



Scheme 7.4

the "pseudo-living" radical polymerization, while a conventional radical or cationic polymerization are the consequences of the iodane decomposition under UV irradiation. It is suggested that the spectral selectivity of the iodanyl radical **20** (Scheme 7.4) decomposition and the relative instability of the ends of the iodane macromolecule are the reasons of this unusual iodane ability [44].

The acetoxy groups in (diacetoxyiodo)benzene can exchange with methacrylic acid in various solvents, yielding [acetoxy(methacryloyloxy)iodo]benzene or (dimethacryloyloxyiodo)benzene. These two λ^3-iodanes can serve as inimers due to the presence of polymerizable moiety and the easy generation of radicals upon thermal or light-induced homolysis of the I–O bonds [48]. When $PhI(OAc)_2$ is added to mixtures of methacrylic acid and methyl methacrylate and upon heating to 80 °C, branched or transiently crosslinked polymers are formed. In contrast, when homopolymerization of methyl methacrylate is initiated by $PhI(OAc)_2$ in the absence of the monomer with carboxylic acid group, no branching or gelation is observed [48].

Tsarevsky has found that hypervalent iodine compounds can be used for the direct azidation of polystyrene and consecutive click-type functionalization [49]. In particular, polystyrene can be directly azidated in 1,2-dichloroethane or chlorobenzene using a combination of trimethylsilyl azide and (diacetoxyiodo)benzene. 2D NMR HMBC spectra indicate that the azido groups are attached to the polymer backbone and also possibly to the aryl pendant groups. Approximately one in every 11 styrene units can be modified by using a ratio of $PhI(OAc)_2$ to trimethylsilyl azide to styrene units of 1 : 2.1 : 1 at 0 °C for 4 h followed by heating to 50 °C for 2 h in chlorobenzene. The azidated polymers have been further used as backbone precursors in the synthesis of polymeric brushes with hydrophilic side chains via a copper-catalyzed click reaction with poly(ethylene oxide) monomethyl ether 4-pentynoate [49].

7.3 Application of Iodonium Salts for Fluoridation in Positron Emission Tomography (PET)

Nuclear medicine – in particular, positron emission tomography (PET) – is one of the emerging, important fields of practical application of iodonium salts. PET is a powerful and rapidly developing area of molecular imaging that is used to study and visualize human physiology by the detection of positron-emitting radiopharmaceuticals [50–55]. PET experiments provide direct information about metabolism, receptor/enzyme

function and biochemical mechanisms in living tissue. Unlike magnetic resonance imaging (MRI) or computerized tomography (CT), which mainly provide detailed anatomical images, PET can measure chemical changes that occur before macroscopic anatomical signs of a disease are observed [55]. PET is emerging as a revolutionary method for measuring body function and tailoring disease treatment in living subjects and it is widely applied in both clinical research [56] and drug development [51, 57–60].

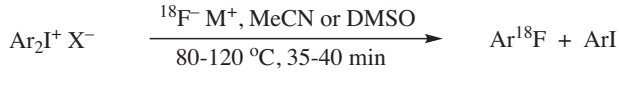
The short-lived positron-emitting isotope fluorine-18 ($t_{\frac{1}{2}} = 109.7$ min) has gained great importance as a radiolabel for probes used with PET [55]. Although [^{18}F]-2-deoxy-2-fluoro-D-glucose is currently the most widely used ^{18}F-fluorinated radiotracer [61], the main focus of recent efforts in radiotracer synthesis has been the preparation of [^{18}F]-fluorinated aromatic compounds [62–66]. Since the initial report from Pike and Aigbirhio in 1995 [67], the radiofluorination of diaryliodonium salts has attracted significant interest as a valuable methodology for late-stage introduction of fluorine into diverse aromatic substrates.

Fluorine-18 is generally produced with a cyclotron, either as molecular fluorine gas or as [^{18}F]-fluoride. Any application of fluorine-18 in PET demands rapid and efficient chemical transformation to introduce the fluorine-18 into the tracer of interest. [^{18}F]-Fluoride is the preferred precursor because it can be produced in higher radioactivity than molecular [^{18}F]-fluorine gas. There are two common pathways for the ^{18}F-labeling of the aromatic ring. The electrophilic ^{18}F-fluorination leads only to carrier-added products because of the unavoidable addition of elemental fluorine to the target gas. The other pathway, via nucleophilic displacement of adequate leaving groups (e.g., NO_2 or $^+NMe_3$), which are activated by electron-withdrawing substituents (e.g., CHO, COMe, COOMe, NO_2, CN, etc.), by no-carrier-added (NCA) [^{18}F]-fluoride, is generally used for the fluorination of electron-deficient arenes. The methodology introduced by Pike and Aigbirhio complements typical approaches based on nucleophilic aromatic substitution by providing a means to fluorinate electron-rich, as well as problematic electron-poor aromatic rings not easily accessed by direct substitution [67].

Diaryliodonium salts are becoming highly popular reagents for the efficient introduction of [^{18}F]-fluoride (fluoridation) via aromatic nucleophilic substitution. ^{18}F-Labeled imaging agents for PET have a short lifetime (due to the short radioactive half-life of ^{18}F) and require fast and convenient methods for introduction of ^{18}F into organic substrate molecules. Reactions of diaryliodonium salts provide a fast and convenient method of [^{18}F]-fluoridation as outlined in Scheme 7.5 [67–69].

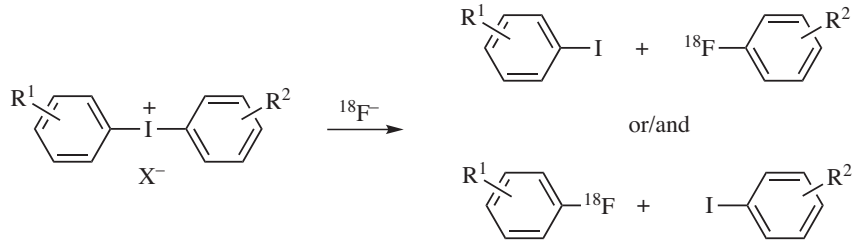
Several problems, mainly due to the low selectivity of reactions, are associated with the use of diaryliodonium salts for [^{18}F]-fluoridation. In the case of the reactions of symmetrical diaryliodonium salts, $Ar_2I^+X^-$, there is no problem with the regioselectivity of fluoridation; however, only half of a molecule of substrate is converted into the target product and the second half gives aryl iodide as a by-product (Scheme 7.5), which results in a low atom economy. In addition, in this case the separation of aryl iodide and aryl fluoride may be complicated due to their similar structure and a chromatographic purification procedure (usually HPLC) is required for separation and purification of the target fluorinated product.

The regioselectivity of fluoridation plays an especially important role in the reactions of nonsymmetrical iodonium salts (Scheme 7.6). The distribution of the fluorine-18 containing products depends on the nature of substituents in the benzene ring; in general, the presence of electron-withdrawing substituents in aromatic



M = K^+/crown ether or Bu_4N^+

Scheme 7.5



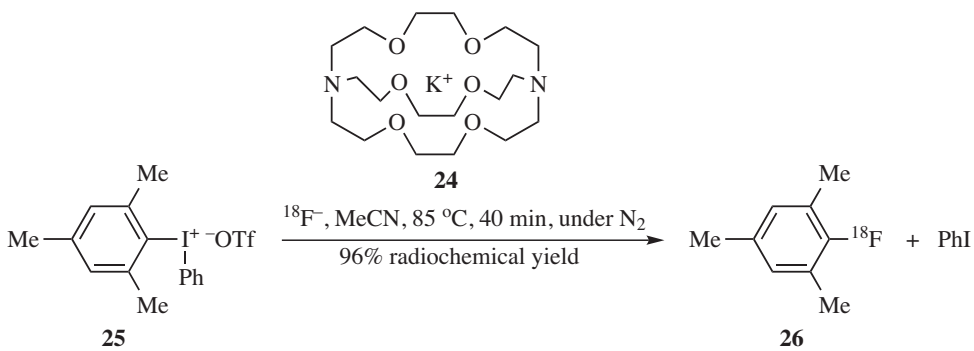
Scheme 7.6

ring is favorable for introduction of the fluoride nucleophile (see Section 3.1.22.1 for mechanistic discussion). The problem of low selectivity of the [^{18}F]-fluoridations can in principle be solved by modification of the electronic and steric properties of substituents R^1 and R^2 and by optimizing the reaction conditions.

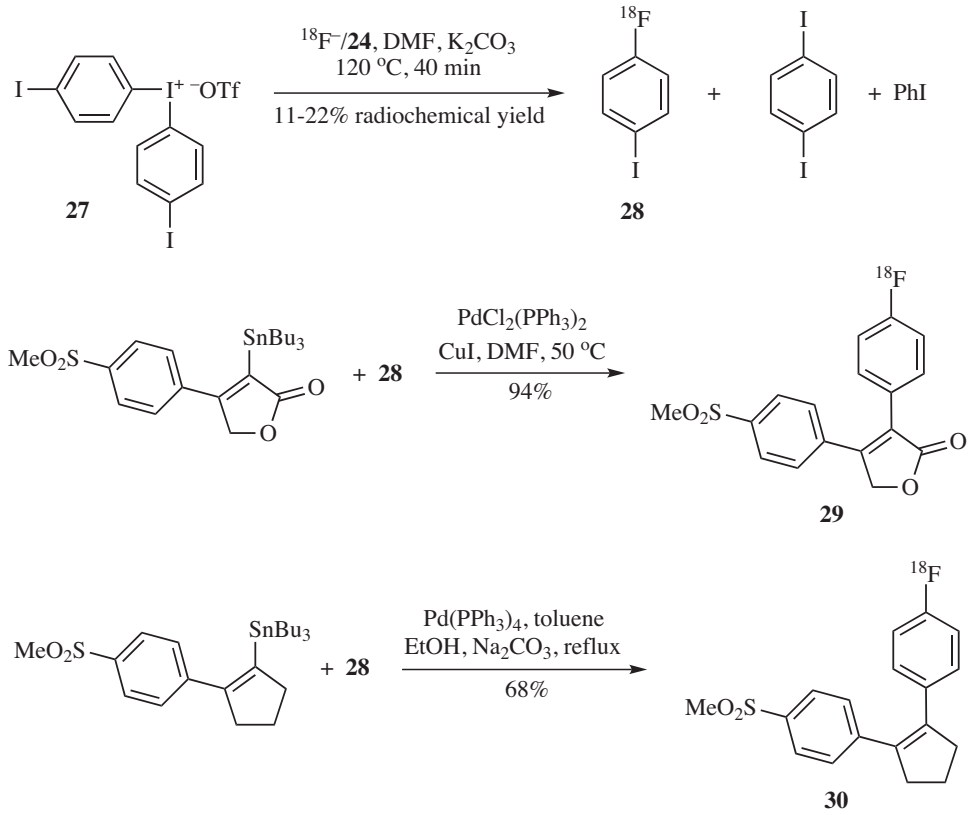
The possibility of the synthesis of aryl fluorides by thermal decomposition of diaryliodonium tetrafluoroborates was first demonstrated by Van der Puy in 1982 [70]. It was found that the reactions of diphenyliodonium salts with different anions (BF_4^-, CF_3COO^-, TsO^-, Cl^-) in DMF in the presence of KF upon heating afford fluorobenzene in 11–85% yield. The lowest yield (11%) was observed in the reaction of diphenyliodonium chloride with KF in DMF at 115 °C, while the thermolysis of $Ph_2I^+BF_4^-$ in the presence of KF at 160–170 °C without solvent gave PhF in 85% yield. The formation of benzene (2–9%) due to a parallel radical decomposition process was also observed in all these reactions [70].

Later, in 1995, Pike and Aigbirhio applied for the first time diaryliodonium salts for the preparation of ^{18}F-labeled aryl fluorides using potassium [^{18}F]-fluoride in the presence of the diaza-crown ether Kryptofix (K2.2.2; structure **24** in Scheme 7.7) in acetonitrile at 85 °C or 110 °C [67]. Under these conditions, the reaction of diphenyliodonium chloride provided [^{18}F]-fluorobenzene in 31–78% radiochemical yield. The use of Kryptofix is required for phase transfer of the [^{18}F]-fluoride ion obtained by the nuclear reaction in the cyclotron as a solution in water enriched with oxygen-18.

Further studies have demonstrated that the regioselectivity of [^{18}F]-fluoridation is controlled by electronic factors and by the bulk of the *ortho*-substituents on the rings, with the latter being the dominant factor. Pike and coworkers have performed a detailed investigation of the reactions of a wide range of iodonium salts, which contain *ortho*-substituents in aromatic rings, with [^{18}F]-fluoride in acetonitrile at 85 °C [69]. It was found that the electronic effects of substituents on aromatic rings in radiochemical fluoridation processing



Scheme 7.7

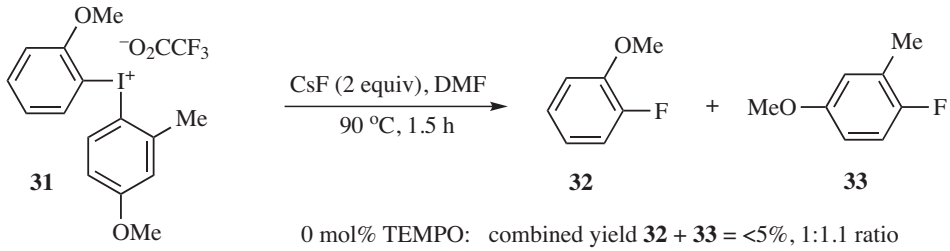


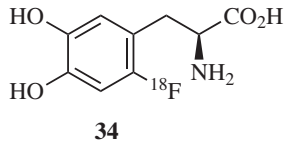
Scheme 7.8

are similar to those in the reactions of iodonium salts with other nucleophiles and fluorine-18 is introduced into the aromatic ring containing electron-withdrawing substituents. However, the presence of a bulky *ortho*-substituent changes the regioselectivity, allowing fluoridation of the electron-rich *ortho*-substituted ring. For example, the reaction of 2,4,6-trimethylphenyl(phenyl)iodonium triflate (**25**) with potassium [^{18}F]-fluoride in the presence of Kryptofix **24** exclusively affords 1-fluoro-2,4,6-trimethylbenzene **26** along with iodobenzene as a by-product (Scheme 7.7) [69].

Numerous works on the optimization of [^{18}F]-fluoridations and the preparation of specific [^{18}F]-labeled radiotracers using diaryliodonium salts have been published. Wüst and coworkers have developed a convenient access to 4-[^{18}F]fluoroiodobenzene (**28**) employing 4,4′-diiododiaryliodonium salt **27** as a precursor (Scheme 7.8) [71–73]. 4-[^{18}F]Fluoroiodobenzene (**28**) has been further utilized in Sonogashira or Stille cross-coupling reactions for the preparation of numerous radiotracers. For example, the Stille reaction with 4-[^{18}F]fluoroiodobenzene has been used for the synthesis of radiotracers for monitoring COX-2 expression by means of PET. By using optimized reaction conditions ^{18}F-labeled COX-2 inhibitors **29** and **30** could be obtained in radiochemical yields of up to 94% and 68%, respectively, based upon 4-[^{18}F]fluoroiodobenzene (**28**) [72].

Carroll and coworkers have published a series of papers on the use of aryliodonium salts in the synthesis of fluorine-containing aromatic and heterocyclic products [63, 74, 75]. It has been found that the addition of radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) during the fluoridation of diaryliodonium salts leads to a significant improvement of both the reproducibility of the process and the



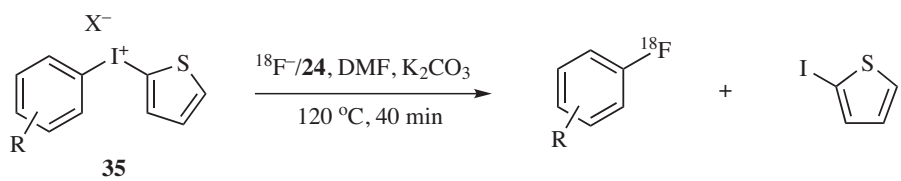


Scheme 7.9

material yield of the desired fluoroarene products without affecting the regioselectivity of the process [74]. In a specific example, the reaction of diaryliodonium trifluoroacetate **31** with cesium fluoride in different solvents (DMF, DMSO, acetonitrile, dimethylacetamide) in the absence of a radical trap affords mixture of fluoroarenes **32** and **33** in the ratio 1 : 1 with a combined yield below 5%. Carrying out this reaction in the presence of 20 mol% TEMPO leads to increased yields of **32** and **33** of up to 35% with almost unchanged regioselectivity (Scheme 7.9) [74]. This methodology is potentially applicable in the production of fluorine-18 labeled radiopharmaceuticals including L-6-[^{18}F]fluoroDOPA **34,** which is an important radioligand for the study of brain dopaminergic neuron density in movement disorders, such as Parkinson's disease.

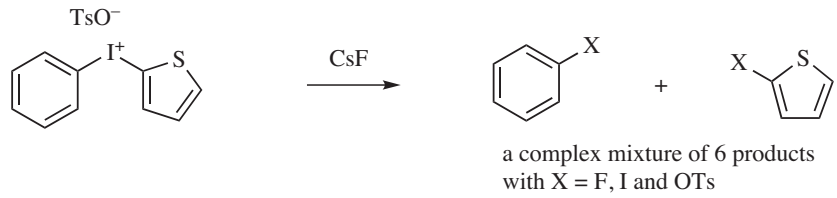
The fluoridation reactions of several classes of heteroaromatic iodonium salts have been studied extensively by different research groups [63, 75–78]. In general, a theoretical prediction that the nucleophilic substitution of aryl(heteroaryl)iodonium salts by fluoride ion is regioselective for the aryl ring has been confirmed by experimental observation [76]. Coenen and coworkers have reported a highly efficient fluoridation method using aryl-(2-thienyl)iodonium salts **35** (Scheme 7.10) [77]. The 2-thienyl group is a very electron-rich group that allows ^{18}F to be introduced directly into even electron-rich arenes like anisoles. It has been also found that the selectivity of the fluoridation of iodonium salts **35** depends on the nature of the counteranion X^- with the highest yields of $Ar^{18}F$ (up to 60% radiochemical yield) achieved in the reactions of iodonium bromides [77].

In contrast to Coenen's results [77], a detailed study of the reaction of aryl(thienyl)iodonium salts with CsF by Carroll and coworkers has demonstrated a very low selectivity of this reaction, producing a mixture of six products as illustrated by Scheme 7.11 [75]. The authors suggested that the previous reports of the absence of

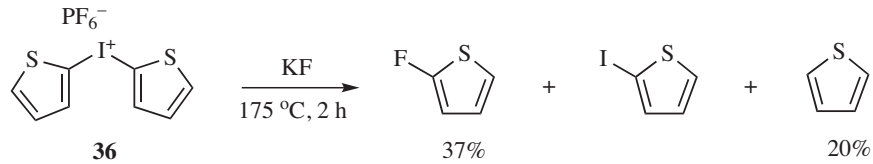


X = Br, I, OTs, OTf
R = 2-OMe, 3-OMe, 4-OMe, 4-OBn, H, 4-I, 4-Br, 4-Cl

Scheme 7.10



Scheme 7.11

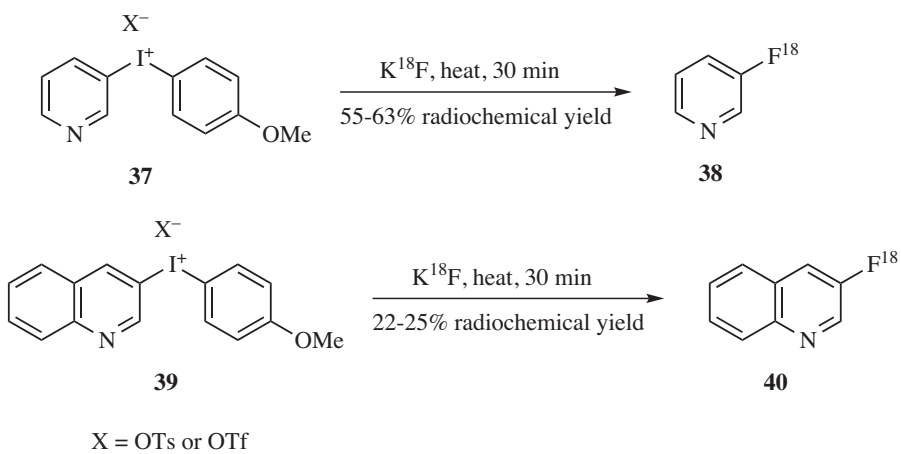


Scheme 7.12

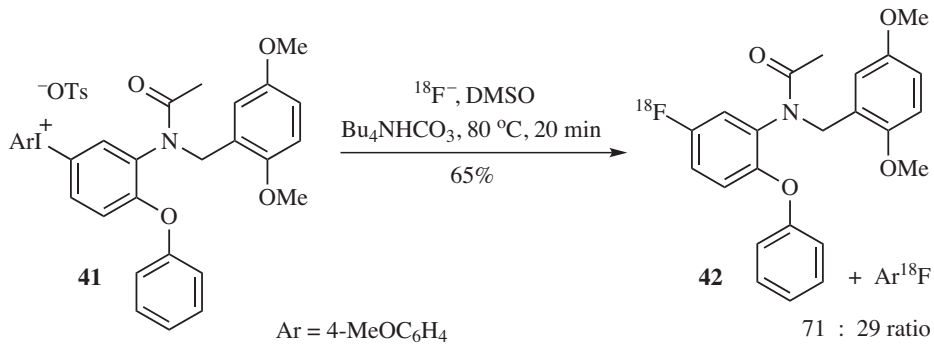
2-fluorothiophene among the reaction products of aryl-(2-thienyl)iodonium salts were misleading. This lack of detection may be due the highly volatile nature of 2-fluorothiophene (boiling point 82 °C), which may be lost under the reaction conditions or on workup/analysis [75].

Onys'ko, Gakh and coworkers have shown that 2-fluorothiophene can be synthesized selectively by heating bis(2-thienyl)iodonium salts with potassium fluoride [78]. Specifically, treatment of bis(2-thienyl)iodonium hexafluorophosphate (**36**) with potassium fluoride (as a mechanical mixture) at 172–175 °C for 2 h yields 2-fluorothiophene, 2-iodothiophene and thiophene (Scheme 7.12). Bis(2-thienyl)iodonium salts with more nucleophilic anions, such as trifluoroacetate, yielded only trace amounts of the desired 2-fluorothiophene [78].

Carroll and coworkers have developed a practical and selective route to fluorine-18 labeled 3-fluoropyridine (**38**) and 3-fluoroquinoline (**40**) by [^{18}F]-fluoridation of iodonium salts **37** and **39** (Scheme 7.13) [63]. The use of 4-methoxyphenyl as the other aromatic ring in iodonium salts **37** and **39** provides the necessary degree of



Scheme 7.13

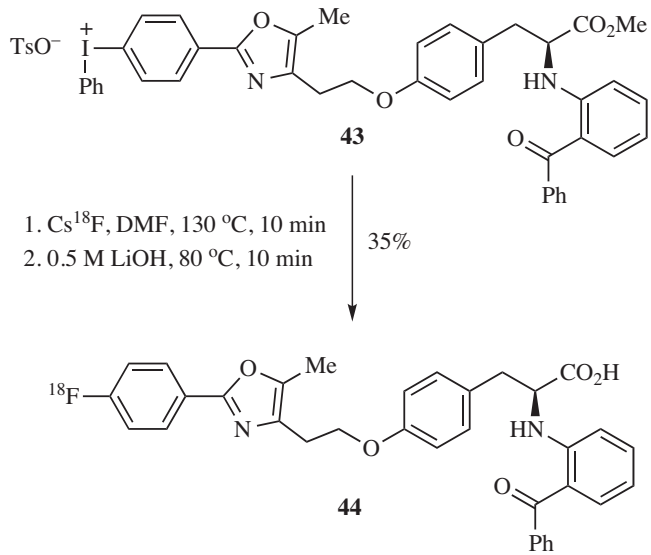


Scheme 7.14

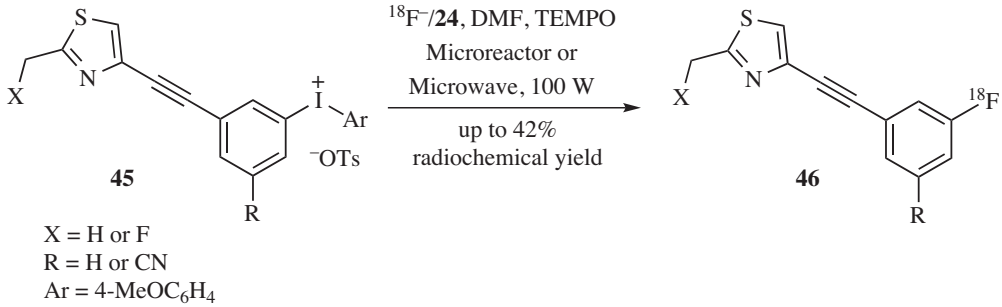
selectivity in the fluoridation process. Fluorine-18 labeled fluoropyridines have found increasing applications in medical imaging technique by positron emission tomography (PET) [63].

Zhang and coworkers reported a successful synthesis of the PET ligand [^{18}F]DAA1106 (**42**) from diaryliodonium salt **41** with the radioactive ^{18}F anion (Scheme 7.14) [79]. The electron-rich 4-methoxyphenyl is essential as the second aromatic substituent in iodonium salt **41;** the analogous phenyliodonium salt gave the desired product **42** in only 3% yield. Compound **42** is used as a PET ligand for imaging a peripheral-type benzodiazepine receptor [79].

Katzenellenbogen and coworkers have reported the radiochemical synthesis and evaluation of two ^{18}F-labeled analogues of the potent and selective PPARγ agonist farglitazar [80]. In particular, the radioligand **44** has been prepared by the fluoridation of phenyliodonium salt **43** in good radiochemical yield (Scheme 7.15) [80]. Interestingly, the reactions of iodonium salts **43** bearing of 3-methoxyphenyl or 2-thienyl substituents instead of the phenyl did not afford any fluorinated product **44.**



Scheme 7.15

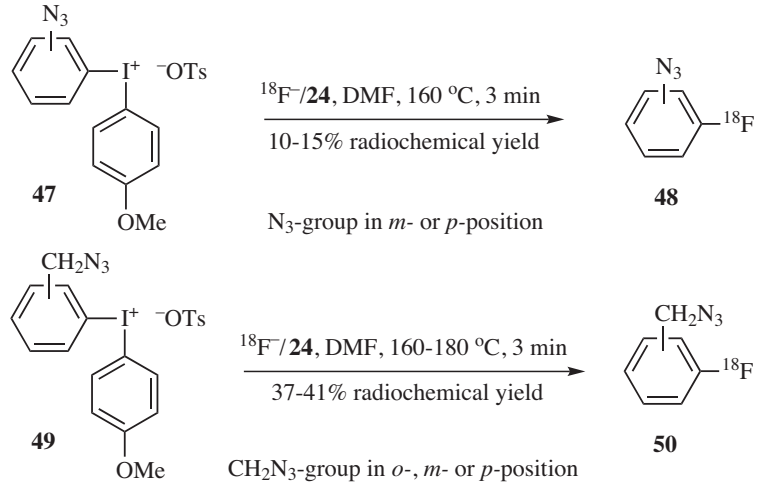


Scheme 7.16

Pike and coworkers have explored the scope of the radiofluoridation of diaryliodonium salts with [^{18}F]fluoride ion for the preparation of otherwise difficult to access *meta*-substituted [^{18}F]fluoroarenes [81, 82]. These studies have led to the development of a synthetic approach to 3-fluoro-1-[(thiazol-4-yl)ethynyl]benzenes **46** through the radiofluorination of diaryliodonium tosylates **45** (Scheme 7.16) [82]. 3-Fluoro-1-[(thiazol-4-yl)ethynyl]benzenes constitute an important class of high-affinity metabotropic glutamate subtype 5 receptor (mGluR5) ligands; fluorine-18 labeled compounds **46** are used as radioligands for molecular imaging by PET of brain mGluR5 in living animal and human subjects [82].

Chun and Pike described the rapid, single-step radiosynthesis of azido- or azidomethyl-bearing [^{18}F]fluoroarenes **48** and **50** from the reactions of diaryliodonium salts **47** or **49,** respectively, with no-carrier-added [^{18}F]fluoride ion within a microfluidic apparatus to obtain these previously poorly accessible ^{18}F-labeled click synthons in good radiochemical yields (Scheme 7.17) [83]. The radiosynthesis of synthons **50** was also possible with "wet" cyclotron-produced NCA [^{18}F]fluoride ion, in the presence of about 70 vol.% water and thus obviating the need to dry the cyclotron-produced [^{18}F]fluoride ion and greatly enhancing the practicality of the method [83].

Griffiths and coworkers reported the syntheses and characterization of phenyl(3-formylphenyl)iodonium salts containing four different counter-anions (OTf, Cl, Br, OTs) and the ^{18}F-fluoridation of these



Scheme 7.17

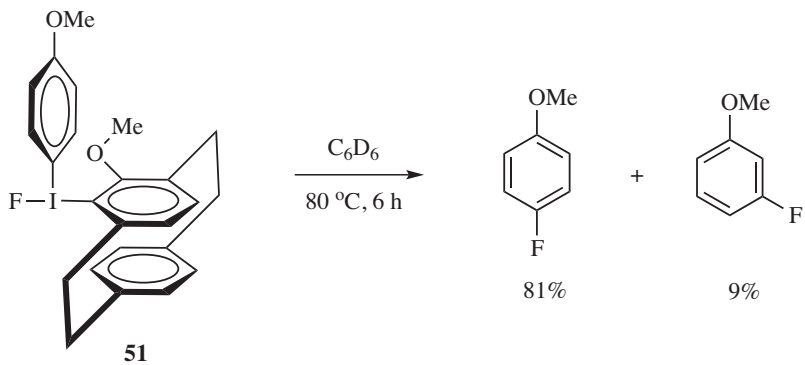
iodonium salts leading to *m*-[^{18}F]fluorobenzaldehyde and *m*-[^{18}F]fluorobenzyl bromide [84]. In particular, *m*-[^{18}F]fluorobenzaldehyde was prepared by the reaction of phenyl(3-formylphenyl)iodonium bromide with $Cs^{18}F/Cs_2CO_3$ in dimethylformamide at 100 °C for 5 min in a microwave in the presence of 1 equivalent of TEMPO [84]. The obtained 3-[^{18}F] fluorobenzaldehyde was further reduced to benzyl alcohol and converted into 3-[^{18}F] fluorobenzyl bromide. 3-[^{18}F]Fluorobenzyl bromide was subsequently used in the synthesis of ^{18}F-radiolabeled lapatinib, a potential tracer for PET imaging of ErbB1/ErbB2 tyrosine kinase activity [85].

Several mechanistic and structural studies of fluoridation reactions of iodonium salts have been published [86–88]. DiMagno and coworkers have found that diaryliodonium salts undergo rapid, fluoride-promoted aryl exchange reactions at room temperature in acetonitrile [86]. This exchange is highly sensitive to the concentration of fluoride ion in solution; the fastest exchange is observed as the fluoride concentration approaches a stoichiometric amount at 50 mM substrate concentration. It was demonstrated that free fluoride ion or a four-coordinate anionic I(III) species may be responsible for the exchange [86]. The fluoride-promoted aryl exchange reaction is general and allows direct measurement of the relative stabilities of diaryliodonium salts featuring different aryl substituents.

It has also been found that the selectivity of fluoridation and yields of products can be improved by changing the reaction conditions [87]. In particular, the use of low polarity aromatic solvents (benzene or toluene) and/or the removal of inorganic salts result in dramatically increased yields of fluorinated arenes from diaryliodonium salts [87].

Lee, Pike and coworkers have investigated the conformational structure and energetics of 2-methylphenyl(2-methoxyphenyl)iodonium chloride [88]. In particular, X-ray structural analysis revealed that 2-methylphenyl(2-methoxyphenyl)iodonium chloride has a conformational dimeric structure with hypervalent iodine as a stereogenic center in each conformer. In addition, LC-MS of this iodonium chloride showed the presence of dimeric and tetrameric anion-bridged clusters in organic solution. This evidence of the existence of dimeric and higher order clusters of iodonium salts in solution is important for a general understanding of the mechanism and outcome of reactions of diaryliodonium salts in organic media with nucleophiles, such as the [^{18}F]fluoride ion [88].

DiMagno and coworkers have shown that exceptionally electron-rich arene rings can be fluoridated with high regioselectivity by the reductive elimination reactions of 5-methoxy[2.2]paracyclophan-4-yl diaryliodonium salt **51** (Scheme 7.18) [89, 90]. Application of the sterically hindered cyclophane directing group permits a high degree of control in fluorination reactions of diaryliodonium salts. Despite excellent selectivity, this approach has obvious disadvantages, such as the use of inaccessible starting compounds and complex synthetic procedures.



51

Scheme 7.18

Pike and coauthors have developed a microreactor for [^{18}F]fluoridations using diaryliodonium salts. This apparatus allows the reaction between the [^{18}F]fluoride anion and iodonium salt to be carried out rapidly and efficiently [81, 91].

7.4 Biological Activity of Polyvalent Iodine Compounds

A summary of the biological properties of iodonium salts has been provided in a 1996 review [1]. Among the numerous known structural types of polyvalent organic iodine compounds, only aryl- and heteroaryliodonium salts and iodonium ylides have considerable, practically useful biological activity. Table 7.1 provides a brief description of the specific biological activity of several patented iodonium derivatives.

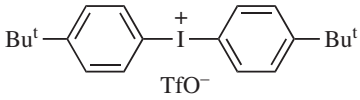
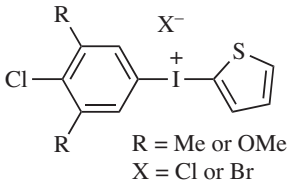
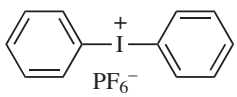
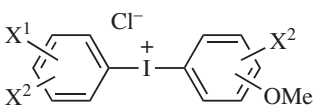
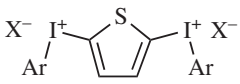
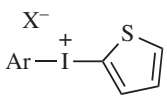
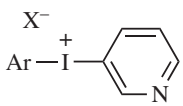
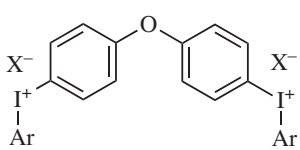
The data published in patents have established the biocidal and antimicrobial activity of numerous diaryl- and heteroaryliodonium salts [92–103]. They describe the activities of iodonium salts against a wide variety of both Gram positive and Gram negative bacterial species, such as *Staphylococcus aureus, Mycobacterium phlei*, *Trichophyton mentagrophytes, Bacillus subtilis, Cephalvaucus fragons* and *Escherichia coli* (Table 7.1). Another patent claims antimicrobial activity for a wide range of iodonium ylides [104]. While exhibiting significant activity against microorganisms most iodonium salts have relatively low toxicity towards mammals: the LD_{50} in mice for Ph_2ICl is 56 mg kg^{-1} of body weight and for (4-chlorophenyl)(thienyl)iodonium chloride it is over 4000 mg kg^{-1} [99]. Potential applications of iodonium salts due to their potent antifungal and antimicrobial activity include disinfectants as well as preservatives for diverse materials such as paints, adhesives, inks, paper, textiles, lubricants, cosmetics and so on [92–103, 105].

Menkissoglu-Spiroudi and coworkers have found that hypervalent iodine compounds are potent antibacterial agents against ice nucleation active (INA) *Pseudomonas syringae* [106]. *Pseudomonas syringae* is a potent bacterial plant pathogen, which can reduce the productivity of many plant species, including tree fruits such as citrus, pear and almonds. Several hypervalent iodine compounds belonging to aryliodonium salts, aryliodonium ylides and (diacyloxyiodo)arenes were tested for their antibacterial activities against INA *Pseudomonas syringae* and the MIC and EC_{50} values were determined [106]. All of the compounds examined caused a dose-dependent decrease in bacterial growth rates. Aryliodonium salts, especially those with electron-withdrawing groups, exhibit higher antibacterial activities with MIC = 8–16 ppm, whereas the nature of the anion does not seem to affect the activities of the diaryliodonium salts [106].

Goldstein and coworkers have investigated the *in vitro* activities of several iodonium salts against oral and dental anaerobes [107]. In particular, the comparative *in vitro* activities of 11 iodonium salts, chlorhexidine and four other antimicrobial agents against 322 anaerobic and fastidious potential dental and periodontal bacterial pathogens have been studied. It has been demonstrated that the activities of iodonium salts are comparable to that of chlorhexidine and that these compounds may be suitable for incorporation into an oral mouthwash [107].

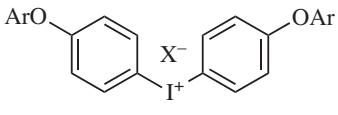
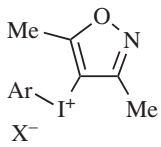
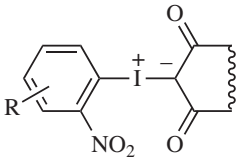
Just and coworkers have synthesized a series of cyclic and noncyclic organoiodine(V) compounds (periodinanes) and tested them as protein tyrosine phosphatase (PTP) inhibitors [108]. Protein tyrosine phosphatases play important roles in glucose metabolism and inhibition of PTP preserves the active insulin receptor and mimics the insulin activity. Previously, peroxovanadium compounds have been shown to be very active in the inhibition of the PTP and this activity is believed to be due to the oxidation of active cysteine residue by the metal complex. However, the application of peroxovanadium compounds to clinical use is limited by their toxicity, poor absorption and lack of specificity. Organoiodine(V) compounds have been found to have better PTP inhibition activity than vanadate and their synthesis is relatively simple. Among periodinanes studied, the noncyclic iodylarenes with a *para*-substituted electron-withdrawing group (e.g., 4-$NO_2C_6H_4IO_2$) have been shown to be the strongest PTP inhibitors [108].

Table 7.1 *Biological activity of some iodonium salts and ylides.*

Compound	Biological activity and application	Reference
	Antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*. Can be used as components of effective industrial antimicrobial agents with low mutagenicity	[92]
 R = Me or OMe X = Cl or Br	Active against *Escherichia coli* and *Streptococcus aureus* and nontoxic toward human epithelial cells. Can be used as highly active antimicrobial agents nontoxic toward plants and mammals	[93]
	Antimicrobial component that is added to hardenable antimicrobial dental compositions	[94]
 X^1, X^2, X^3 = F, Cl, Br	Antibacterial and anthelmintic agents	[95]
 X = Cl, Br, I, HSO_4, NO_3, BF_4, CF_3CO_2, lactate	Antimicrobials for inhibition of the growth of many bacterial and fungal organisms that attack seeds, roots and above-ground portions of plants	[96]
 X = Cl, CF_3CO_2, CCl_3CO_2	Controls several bacterial organisms as well as molds, mildews, fungi and slimes	[97–99]
 X = F, Cl, Br, I, CF_3CO_2, CCl_3CO_2, HSO_4, NO_3, BF_4	Inhibition against growth of bacteria, fungi and organisms that attack seeds, roots and above-ground portions of plants and microorganisms responsible for mold, mildew, rot, decay	[100]
 X = F, Cl, Br, I, CF_3CO_2, CCl_3CO_2, HSO_4, NO_3, BF_4, lactate	Antimicrobial agents against bacteria, fungi and organisms that attack seeds, roots and above-ground portions of plants; viricidal against small RNA viruses	[101]

(*continued*)

Table 7.1 *(Continued)*

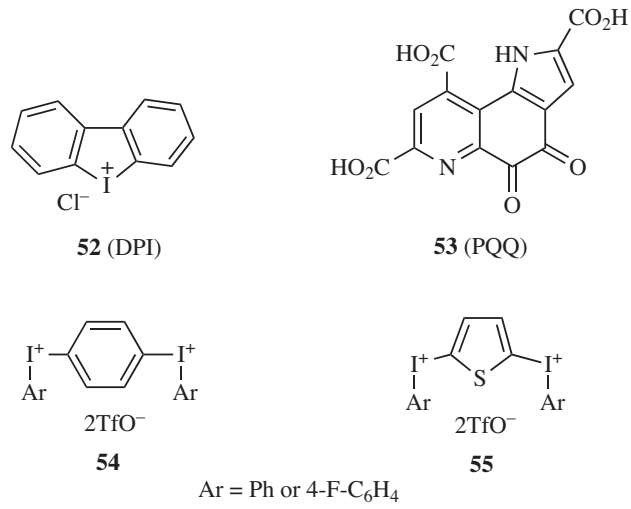
Compound	Biological activity and application	Reference
 X = F, Cl, Br, HSO_4, etc.	Antimicrobial agents against bacteria that attack seeds, roots and above-ground portions of plants. The compounds may be included in adhesives, cooling waters, inks, plasticizers, latices, polymers, resins, fuels, greases, soaps, detergents, cutting oils and oil or latex paints to prevent mold and mildew and the degradation of such products resulting from microbial attack	[102]
 X = Cl, Br, CF_3CO_2, CCl_3CO_2	Antimicrobial agents against various bacteria, fungi and yeasts	[103]
	Active against *Bacillus subtilis, Pseudomonas* species, *Escherichia coli, Staphylococcus* species, fungi, algae and yeasts	[104]

Bis(*p*-tolyl)iodonium chloride, Tol_2ICl, is a potent inhibitor of microbes that deaminate amino acids in ruminating animals, thereby preventing maximum food utilization. The use of Tol_2ICl as a food additive (about 25 mg kg^{-1}), along with a methane inhibitor, in lambs [109] and growing cattle [110, 111] increased feed utilization efficiency by about 10%. Presumably, iodonium salts act as a deaminase inhibitor. The parent bis(phenyl)iodonium chloride, Ph_2ICl, inhibits casein degradation at extremely low concentrations [112].

More recently, the physiological effects of several diaryliodonium salts and in particular bis(phenyl)iodonium chloride (BPI), Ph_2ICl and diphenyleneiodonium chloride (DPI, structure **52** in Figure 7.3), have been extensively explored. The initial work by Lardy and coworkers established DPI as a potent hypoglycaemic agent at a dose as low as 4 mg kg^{-1} body weight [113]. It is assumed that DPI binds covalently to a 23.5 kDa protein within Complex I causing irreversible inhibition of NADH oxidation [113, 114]. DPI inhibits gluconeogenesis in isolated rat hepatocytes [115], causes swelling of rat liver mitochondria [116] and induces cardiomyopathy [117]. Diaryliodonium salts have been shown to be effective in the treatment of hypertension [118]. Both BPI and DPI induce mitochondrial myopathy [119, 120], inhibit the superoxide production of neutrophils [121–124], as well as nitric oxide synthase [125, 126] and NADPH oxidase [127–129]. In particular, DPI has found broad application in modern biochemical and pharmacological research as an NADPH oxidase inhibitor [130–153].

The 1,3-dichloro substituted DPI catalyzes chloride exchange across the inner membrane of rat liver mitochondria and also inhibits succinate oxidation and stage 3 respiration [154, 155].

BPI has also been shown to inhibit cytochrome P450 reductase [156]. Cohen, Gallop and coworkers demonstrated that DPI as well as the bis(2-thienyl)iodonium triflate inhibit superoxide anion formation *in vivo* in rabbit aorta [157]. It was proposed that the physiological activity of iodonium species is due to their



52 (DPI) **53** (PQQ)

54 **55**

Figure 7.3 *PQQ (**53**) and iodonium salts active as PQQ inhibitors.*

interaction with PQQ (**53,** Figure 7.3) [158, 159]. Methoxatin or PQQ (**53**), a pyrroloquinoline quinone, is an organic cofactor, analogous to flavins, found in an increasing number of biological redox processes. It is widely distributed in microorganisms, animal cells, tissues and fluids and was first isolated from cultures of a methylotrophic soil bacterium *Pseudomonas* sp. in 1979 [160].

Various iodonium salts are potent sequestering agents for PQQ [161]. In particular, bis-iodonium salts **54** and **55** inhibit PQQ at a nanomolar level (7–13 nM) and are nearly a 1000 times better inhibitors of PQQ than Ph_2ICl and DPI (**52**). The potential implication of this activity is in the possible uses of bis-iodonium salts as biocides and in particular as a new class of antimicrobial agents [161].

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