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Astatine |*Hot Paper*|

Unexpected Behavior of the Heaviest Halogen Astatine in the Nucleophilic Substitution of Aryliodonium Salts

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Abstract: Aryliodonium salts have become precursors of choice for the synthesis of ^{18}F-labeled tracers for nuclear imaging. However, little is known on the reactivity of these compounds with heavy halides, that is, radioiodide and astatide, at the radiotracer scale. In the first comparative study of radiohalogenation of aryliodonium salts with $^{125}I^-$ and $^{211}At^-$, initial experiments on a model compound highlight the higher reactivity of astatide compared to iodide, which could not be anticipated from the trends previously observed within the halogen series. Kinetic studies indicate a significant difference in activation energy ($E_a = 23.5$ and 17.1 kcal mol^{-1} with $^{125}I^-$ and $^{211}At^-$, respectively). Quantum chemical calculations suggest that astatination occurs via the monomeric form of an iodonium complex whereas iodination occurs via a heterodimeric iodonium intermediate. The good to excellent regioselectivity of halogenation and high yields achieved with diversely substituted aryliodonium salts indicate that this class of compounds is a promising alternative to the stannane chemistry currently used for heavy radiohalogen labeling of tracers in nuclear medicine.

Introduction

Aryliodonium salts are attractive precursors for arylation of nucleophiles, owing to their low toxicity, the high regioselectivity they confer, and the mild reaction conditions they require compared to conventional methods.[1,2] Halogens were amongst the first nucleophiles to be closely investigated for the nucleophilic aromatic substitution (S_NAr) of aryliodonium salts more than 50 years ago,[3,4] and they are still considered for new methodologies in conventional organic synthesis.[5] However, it is only recently that applications related to halogenation with these precursors have been developed, especially in the field of radiochemistry with the radiolabeling of arenes with fluorine-18 for positron emission tomography (PET),[6–9] and improved preparation of important ^{18}F-labeled radiotracers, such as [^{18}F]flumazenil[10] or [^{18}F]mGlu5,[11] both for brain imaging.

In contrast to ^{18}F, the other halogens have received limited attention for use in the reaction with aryliodonium salts at the radiotracer level. For instance, only one study to date has been reported on the reactivity of radiochloride,[12] or of radioiodide (in a patent).[13] Moreover, to our knowledge, there have been no reports on the reactivity of radioactive bromide or astatide. However, a number of radioisotopes of the two heaviest halogens have played important roles in nuclear medicine, including ^{123}I, ^{124}I, ^{125}I, ^{131}I, and ^{211}At as the most relevant radionuclides for use in imaging and/or therapy.[14] Many of the radioiodinated and astatinated compounds of interest are aromatic. They are generally obtained by conventional methods, such as S_NAr by halogen exchange, or electrophilic approaches, such as halodemetalation or direct substitution.[15,16] However, these reactions are often associated with issues related to low radiochemical yields (RCYs), low specific activities, or concerns about the toxicity of the precursors and side products when considering human use. Consequently, the development of novel methodologies to improve the radiolabeling of arenes with heavy halogens remains an active area of research.[17,18]

Compared to iodine, the chemistry of astatine remains largely unexplored despite more than 70 years having passed since the discovery of this element.[19] Its chemical behavior is not well understood and can differ significantly from the trends for the other halogens. Good reasons exist for this deficiency and are primarily due to the fact that no stable isotope exists (for the most stable, ^{210}At, $t_{1/2} = 8.1$ h), making difficult the characterization of species by using conventional chemical and spectroscopic methods. For instance, the first ionization potential of At was only very recently accurately determined by using laser ionization spectroscopy, allowing refinement of previous estimations.[20] Nonetheless, despite noticeable divergences be-

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tween the chemical behaviors of iodine and astatine, most of the organic reactions that are applicable to iodine, such as electrophilic and nucleophilic substitutions, have also been performed with astatine. This partial understanding of astatine chemistry has allowed the preparation of various molecules of biological interest and has led to a number of pre-clinical and clinical trials, which demonstrated over the last 20 years the high potential of the ^{211}At isotope ($t_{1/2}=7.2$ h) for the treatment of cancers by targeted α-particle therapy.[16,21,22]

In light of the latest advances in astatination methodologies, electrophilic substitution of arylstannane remains the preferred method because of the RCYs generally obtained under smooth conditions.[23,24] However, since astatine can potentially adopt several oxidation states (-I, +I, +III, +V, and +VII), obtaining pure At^+ for electrophilic reactions is difficult to control, and partial over-oxidation to unwanted species can be difficult to avoid. This difficulty is mostly due to the extremely high dilution of ^{211}At (cyclotron produced and distilled from a bismuth target) available in solution (generally available at picomolar or sub-picomolar concentrations), with tiny traces of impurity being able to perturb its reactivity and lead to side reactions and inconsistent reaction yields.[25] Additionally, the +I oxidation state is not stable over time, owing to the inherent radiation arising from the decay of ^{211}At to which it is exposed in solution, leading progressively to changes in its oxidation state, as reported by Pozzi and Zalutsky.[26]

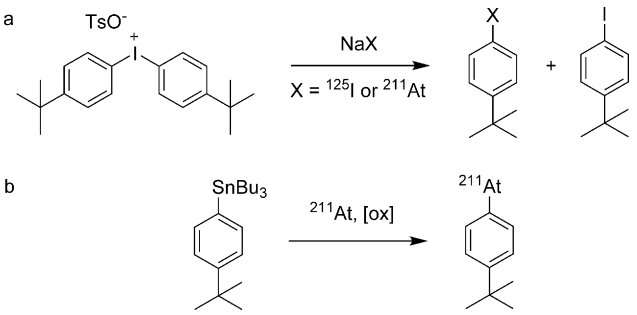
In contrast, formation of astatine as pure At^- in reducing media is considerably easier, since only one reduced species of the halogen is accessible.[27] Therefore, it appears preferable to have access to alternative methods of astatination that involve the use of At^-. Complementary to this status, the S_NAr of aryliodonium salts appears to be an interesting alternative to explore.

In this study, we aimed to probe the reactivity of iodide and astatide towards aryliodonium salts. $^{125}I^-$ and $^{211}At^-$ were investigated in parallel and their reactivity compared, with the additional purpose of expanding the understanding of the enigmatic chemistry of the heaviest of the halogens. We unveiled an unexpectedly higher reactivity of astatide over iodide that nucleophilicity difference alone cannot explain, but which involves two possible intermediates, as supported by quantum chemical calculations.

Results and Discussion

Reaction parameters

Starting from the model compound bis(4-*tert*-butylphenyl)iodonium tosylate (Scheme 1a), the influences of essential parameters were investigated by adaptation from radiofluorination of aryliodonium. DMF is generally the preferred solvent for radiofluorination, although the use of acetonitrile (MeCN) is also widely reported. This choice is dictated by the necessity of an aprotic polar solvent to perform the S_NAr reaction. The reactivity of the fluoride ion being dramatically reduced in the presence of water,[28] it is usually necessary to perform the reaction in anhydrous media to obtain satisfactory radiochemical



Scheme 1. a) Radioiodination and astatination of bis(4-*tert*-butylphenyl)iodonium tosylate; b) formation of [^{211}At]4-*tert*-butylastatobenzene by the conventional astatodestannylation approach.

yields, a parameter that requires additional drying steps of the radionuclide.

In contrast, the nucleophilicity of the larger halides, iodide and astatide, was expected to be considerably less affected by the presence of polar protic solvents such as water due to the lower strength of hydrate shell of larger anions. Consequently, available aqueous [^{125}I]NaI and [^{211}At]NaAt were used without drying to avoid loss of activity during the process. Radiolabeling was performed by heating a 95 vol.% mixture of a 5 mM iodonium salt in the desired solvent (MeCN, DMF, MeOH, or a 4:1 H_2O/MeCN mixture) with 5 vol.% of the aqueous radioiodide solution from 20 to 140 °C for 30 min. All reactions were analyzed chromatographically (HPLC), using the UV trace of 4-*tert*-butyliodobenzene as a reference for comparison with the radioactive trace of the reaction solutions (see the Supporting Information, Figure S1). The retention time of the astatination product was nearly identical to 4-*tert*-butyliodobenzene, suggesting formation of the expected [^{211}At]4-*tert*-butylastatobenzene. To further confirm the identity of the astatinated product, [^{211}At]4-*tert*-butylastatobenzene was also prepared orthogonally by electrophilic astatodestannylation of (4-*tert*-butylphenyl)tributylstannane with ^{211}At oxidized in the +I oxidation state by *N*-chlorosuccinimide (Scheme 1b), giving a congruent HPLC retention time (Figure S1).

The results of temperature and solvent impact studies show a distinct difference in reactivity between iodide and astatide (Figure 1a,b). In the case of radioiodination, use of MeCN was by far the optimal choice as this solvent provided RCYs up to 93% at 120 °C, whereas the other solvents resulted in RCYs below 25%, even up to 140 °C. In contrast, all solvent conditions gave RCYs greater than 80% for the astatination reaction; MeOH proved an even better solvent than MeCN, even though this solvent gave poor RCYs for radioiodination.

An important parameter that can dramatically influence the reactivity of iodonium salts is the nature of the counterion. In radiofluorination reactions, sulfonates have generally been preferred, since they are good leaving groups and are also inert in comparison to halides, which are able to react with the iodonium by thermal decomposition. We chose to study the influence of the counterion for radioiodination and astatination by using the same symmetric iodonium as above associated to sulfonates (tosylate and triflate) or halides (chloride and bro-

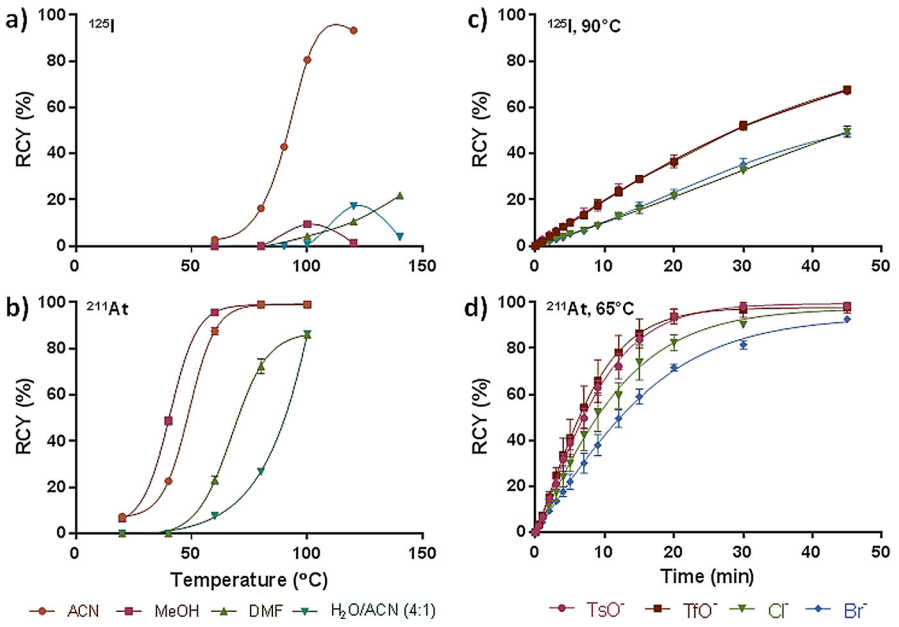


Figure 1. Influence of solvent and temperature on the radiochemical yield of [^{125}I]iodination (a) and [^{211}At]astatination (b) of bis(4-*tert*-butylphenyl)iodonium tosylate after 30 min reaction, and influence of counterion in MeCN (c, d). Reactions were performed with a 5 mM iodonium salt concentration and 1.5 MBq of $^{125}I^-$ or 5 MBq $^{211}At^-$ ($n=3$).

mide). Radioiodination performed at 90 °C indicated a significantly higher rate of reaction with sulfonate salts with RCYs ≈70% after 45 min, compared to the halide salts which gave RCYs ≈45% (Figure 1c). In the case of astatination, the same reactivity sequence was observed, albeit with a smaller difference between the counterion types and with excellent reactivity. For instance, the reaction rate was too fast at 90 °C to distinguish differences between the anions, with all iodonium salts giving RCYs of >95% within less than 10 min. When performing the reaction at a lower temperature (65 °C) the sequence OTs ≈ OTf > Cl > Br was observed with all compounds giving RCYs of >50% after 15 min and nearly quantitative RCYs with all counterions within 45 min (Figure 1d).

Overall, this preliminary study guided us to the selection of MeCN as the preferred solvent to continue the comparative study between astatide and iodide, with tosylate as counterion.

Influence of the substitution pattern of unsymmetrical iodonium salts

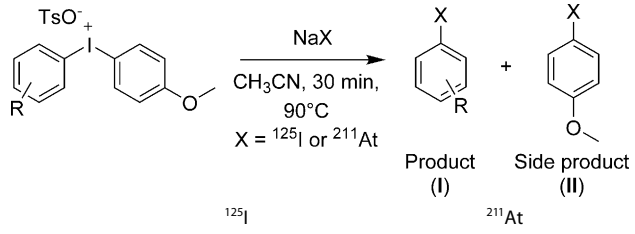
To demonstrate the potential of this reaction, we investigated the reactivity of unsymmetrically substituted iodonium salts. Unsymmetrical aryliodonium salts are generally preferred for radiohalogenation and other synthetic purposes since they are generally easier and more economical to synthesize, especially if complex aromatic structures are desired. In the context of radioiodination for biomedical use, it also appears essential to avoid the use of symmetrical iodonium salts since each aryliodonium molecule involved in the S_NAr would release an inseparable cold equivalent of the radioiodinated compound of interest by reductive elimination and which would contribute to decreasing the specific activity.

The regioselectivity for S_NAr towards non-equivalent aryl groups on diaryliodonium salts can be controlled by different factors, including the difference in electron density and steric hindrance between the two rings[29,30] or the presence of a catalyst such as copper salts.[31]

As a model, the electron rich 4-methoxyphenyl was chosen as directing group, since it was shown to provide high regioselectivity toward the opposite aromatic ring with a wide range of electron-rich and electron deficient aryl counterparts in previous studies with ^{18}F.[32,33] A similar preference of radioiodide and astatide for the most electron-deficient ring was thus also expected. The 4-methoxyphenyl moiety was also chosen for its simplicity in this exploratory study although new directing groups have emerged, such as the electron-rich 2-thienyl[7] or highly sterically hindered cyclophane derivative.[34] A selection of variously substituted aryl-4-methoxyphenyl iodonium tosylates were thus prepared (for synthetic details, see the Supporting Information) and investigated in radioiodination and astatination reactions. As expected, higher RCYs (RPhX and MeOPhX combined) were obtained when electron-withdrawing groups were present, with RCYs varying from 46 to 99% in a 30 min reaction (Table 1).

In the case of astatination, the reactivity was so high that RCYs were quantitative with all substituents under these reaction conditions. The regioselectivity also clearly correlated with the electronic effects, with high selectivity towards the formation of the product of interest (RPhX) when R substituents were the most electron-withdrawing. Additionally, the effect of steric hindrance was evaluated when R was a methyl group in the *ortho* position. Similarly to what is usually observed in fluorination reactions, halogenation was favored on the *ortho*-substituted moiety in both radioiodination and astatination, which can be explained by the transition states formed as demon-

Table 1. Influence of the substituent R on the RCY and the selectivity for the target product of radioiodination and astatination ($n=3$).



	^{125}I		^{211}At	
R	RCY$_{(I+II)}$[a] [%]	(I)/(II) ratio	RCY$_{(I+II)}$[a] [%]	(I)/(II) ratio
H	57±2	4.8:1	97±1	4.2:1
4-Me	46±6	1.5:1	97±1	2:1
3-Me	61±1	4.4:1	99±1	3.7:1
2-Me	98±1	24:1	98±1	8.1:1
4-Cl	68±2	10:1	98±1	5.3:1
4-CO_2Et	92±1	38:1	98±1	8.2:1
4-CN	97±1	>50:1	99±1	16:1
3-NO_2	67±4[b]	28:1	99±1	24:1
4-NO_2	90±2	>50:1	99±1	29:1

[a] Decay corrected; [b] detected decomposition products.

strated in previous studies.[8] Notably, regioselectivity was higher for iodination than for astatination, especially with stronger electron-withdrawing substituents. To rationalize the observed impact of the substituents, a kinetic study was performed. The reaction was pseudo-first order, considering the concentration variation of the iodonium salt in large excess was negligible during the reaction (see the Supporting Information, Table S1). The results were then plotted in a Hammett diagram, using the σ value for each substituent and their reaction rate constants k_i' (Figure 2). An excellent linear correlation

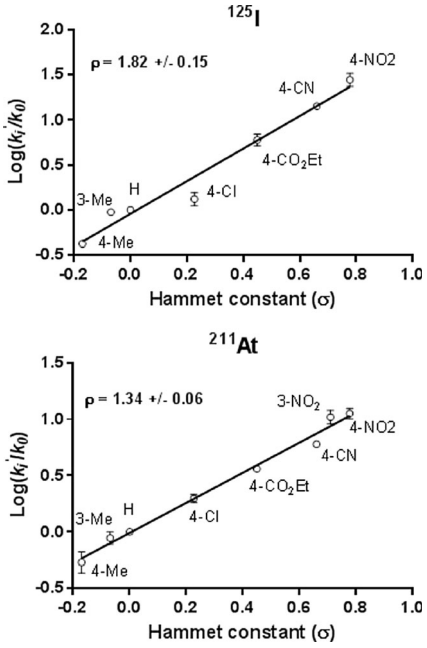


Figure 2. Hammett plot for the [^{125}I]iodination (at 90 °C) and [^{211}At]astatination (at 65 °C) of unsymmetrical iodonium tosylates in MeCN ($n=3$).

was obtained between the Hammett constants and rate constants with both radiohalides. The reaction constants (ρ) values were in line with the significant difference in the influence of the substituents observed between iodination and astatination ($\rho=1.82$ and 1.34, respectively) considering that the higher the ρ, the more the reaction is sensitive to the electronic effect of the substituent. A comparison of the regioselectivities for the S_NAr of the lighter radiohalides ($^{18}F^-$ and $^{38/39}Cl^-$) previously described for identical iodonium salts shows a global decrease in regioselectivity with increasing halide size (see the Supporting Information, Table S2).[12,28] Consequently, it can be foreseen from our observations that the design of unsymmetrical iodonium salts for radiohalogenation will require more optimization with heavier radiohalogens to obtain optimal regioselectivity and consequently high RCYs and specific activities, particularly when electron rich products are desired.

Thermochemical and quantum chemical studies

To better understand the gap in reactivity between the two halogens, we investigated the reaction further in terms of kinetics and thermodynamics. Using the experimental conditions determined above on the symmetric iodonium model, the rate constants of the radiohalogenation reactions were determined at various temperatures (see the Supporting Information, Figure S2). Rate constants k_i' differed significantly between the two halogens. For instance, astatination occurred nearly 50 times faster than iodination at 80 °C (Table 2), reflecting the higher reactivity of astatide. These rate constants were then used in the Arrhenius plot for determination of E_a (Figure 3). An E_a of 23.5 kcal mol^{-1} was obtained for the radioiodination whereas astatination occurred with a significantly lower E_a of 17.1 kcal mol^{-1}. The higher nucleophilicity of the astatide anion is not sufficient to explain the sharp increase in reactivity observed as compared to the iodide. Whereas nucleophilicity increases in S_NAr reactions with increasing size of halide, this was previously shown to have little influence on the E_a of halogenation of bis(4-*tert*-butylphenyl)iodonium (Cl^-: 32.1; Br^-: 32.2; I^-: 32.2 kcal mol^{-1} in DMF).[4]

Table 2. Pseudo-first order reaction rates of the ^{125}I and ^{211}At substitution on bis(4-*tert*-butylphenyl)iodonium tosylate in MeCN ($n=3$).

T [°C]	k_i' [min^{-1}]	
	^{125}I	^{211}At
45	–	0.0231±0.0030
50	–	0.0368±0.0015
55	–	0.0494±0.0038
60	–	0.0742±0.0072
65	–	0.0992±0.0097
70	–	0.1498±0.0109
75	–	0.2226±0.0349
80	0.0082±0.0011	0.3770±0.0281
82.5	0.0122±0.0009	–
85	0.0160±0.0047	–
90	0.0225±0.0015	–
95	0.0355±0.0021	–
100	0.0535±0.0040	–

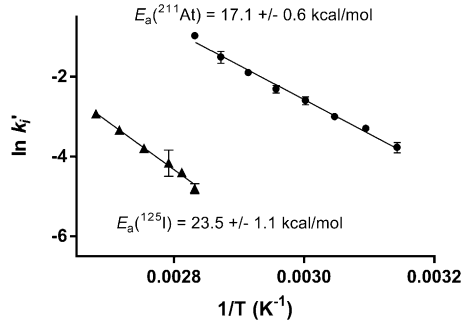


Figure 3. Arrhenius plot for the determination of E_a of the ^{125}I (▲) and ^{211}At-substitution (●) on bis(4-*tert*-butylphenyl)iodonium tosylate in MeCN ($n=3$)

Despite the lack of spectroscopic methods to probe possible mechanisms with astatine species at the radiotracer level, we tested several hypotheses to provide a rationale for the difference in reactivity. Several previously reported potential reaction courses were considered and tested. These included the presence of metallic impurities in the astatine solution, which could catalyze the reaction, as seen in the enhanced reactivity of fluoride on aryliodonium salts in the presence of copper salts.[9] However this possibility was ruled out based on our observation that the outcome of the radioiodination reaction (kinetics and RCY) was unaffected when performed in the presence of astatine stock solution after the decay of the ^{211}At activity. This test also rules out the sulfite ion as a potential cause of the reactivity change, Na_2SO_3 being otherwise absent in radioiodination solution, whereas astatine stock solution contains this reducing agent to produce the reactive $^{211}At^-$ species. The formation of a benzyne intermediate is a well-known pathway of aryliodonium salt reactivity in the presence of a strong base. Whereas the formation of benzyne in the presence of the basic fluoride anion has been reported,[35] iodide and astatide are such weak bases that they cannot be invoked as able to form such benzyne intermediates.

A more plausible explanation for the reactivity difference is the possibility of a radical mechanism, as previously proposed for a similar reaction with the astatination of diazonium salts.[36] Moreover, radical pathways have also been implicated in reactions involving iodonium with nucleophiles such as 2-nitropropanate anion via a single electron transfer mechanism.[37] It has also been suggested that, under specific conditions, aryliodonium iodide decomposed in part via a radical pathway.[13,38] However, the hypothesis of a free radical reaction was ruled out by comparing the reaction rate in the presence of atmospheric oxygen (standard conditions of this study), in the absence of oxygen (solvent degassed under argon), and in the presence of a radical scavenger (TEMPO). In all three cases, the reaction rates and products formed were essentially identical (see the Supporting Information, Table S3), which indicates that, if it ever occurs, such a radical mechanism is only a minor pathway in our reaction conditions to influence significantly the reaction at the radiotracer scale. Consequently, given the Hammett correlation obtained above, the reaction for both halides essentially follows a S_NAr-type mechanism.

Iodonium salts are known to exist as dimers in the solid and gaseous phase, as well as in solution.[39,40] Similarly, we found that bis(4-*tert*-butylphenyl)iodonium iodide [$(Ar_2I)I$] adopts a dimeric structure in the solid state (see the Supporting Information, Figure S3).[41] Thus, we aimed to probe the influence of the monomeric and dimeric intermediates on the reaction by quantum chemical calculations. The X-Ray structure of iodonium iodide was used to construct monomeric $(Ar_2I)I$, $(Ar_2I)At$, and $(Ar_2I)OTs$, as well as homodimeric $[(Ar_2I)OTs]_2$. Given the extremely low concentrations of radioiodide (nanomolar to picomolar) or astatide (picomolar to femtomolar) involved in the reaction at radiotracer level, the probability for the iodonium radiohalide (^{125}I or ^{211}At) to form a homodimer is extremely low. Rather, given the much higher concentration of $(Ar_2I)OTs$ in solution (5 mM), it would be as the heterodimer $[(Ar_2I)X][(Ar_2I)OTs]$ [Equation (1)].

$$(Ar_2I)OTs + (Ar_2I)OTs \rightleftharpoons [(Ar_2I)OTs]_2 \rightleftharpoons [(Ar_2I)OTs][(Ar_2I)X] \quad (1)$$

Energy calculations (see the Supporting Information) indeed indicate that $(Ar_2I)OTs$ is more stable in its dimeric form by $\Delta G = -0.7$ kcal mol^{-1}. Our calculations also indicate that the exchange of a tosylate in $[(Ar_2I)OTs]_2$ with iodide from NaI or with astatide from NaAt to form the heterodimeric structures is thermochemically favorable by $\Delta G = -14.0$ kcal mol^{-1} and -15.1 kcal mol^{-1}, respectively (see the Supporting Information, Figure S4).

Ground states (GS) and transition states (TS) were then calculated, taking into account two possible pathways: either from the heterodimer or from the monomer in equilibrium (exemplified for iodination in Figure 4).

The calculated E_a, corresponding to the difference of the sum of the electronic energy and zero-point vibrational energy between the GS and the TS, is 17.9 kcal mol^{-1} for iodination and 17.2 kcal mol^{-1} for astatination from the monomeric complex, whereas it is 23.2 kcal mol^{-1} and 22.6 kcal mol^{-1} from the dimeric complex for iodination and astatination, respectively. The extra charge interaction provided by $(Ar_2I)OTs$ is likely responsible for the increase of E_a in the dimer pathway. For example, the nucleophilic iodide in the GS_1 has to overcome the charge attraction provided by the central iodine atom of $(Ar_2I)OTs$ to form a bond with the C^{ipso}. The good agreement between the calculated E_a for iodination via the heterodimer (23.2 kcal mol^{-1}) and the experimental E_a (23.5 $+/-$1.1 kcal mol^{-1}) suggests that the radioiodination occurs in a dimeric environment. In contrast, the calculated E_a for astatination via the monomer (17.2 kcal mol^{-1}) agrees with the experimental E_a (17.1 $+/-$0.6 kcal mol^{-1}) which indicates that the astatination likely occurs in a monomeric environment. It is noted that the calculated difference of E_a for iodination and astatination is only 0.6–0.7 kcal mol^{-1} in either the monomeric or heterodimeric form, which suggests that the difference in nucleophilicity between astatide and iodide plays a minor role in the reaction. The proposed mechanism (Figure 4), another representation of the Curtin–Hammett principle,[42] further indicates that the relative stability of monomers over dimers modulates the

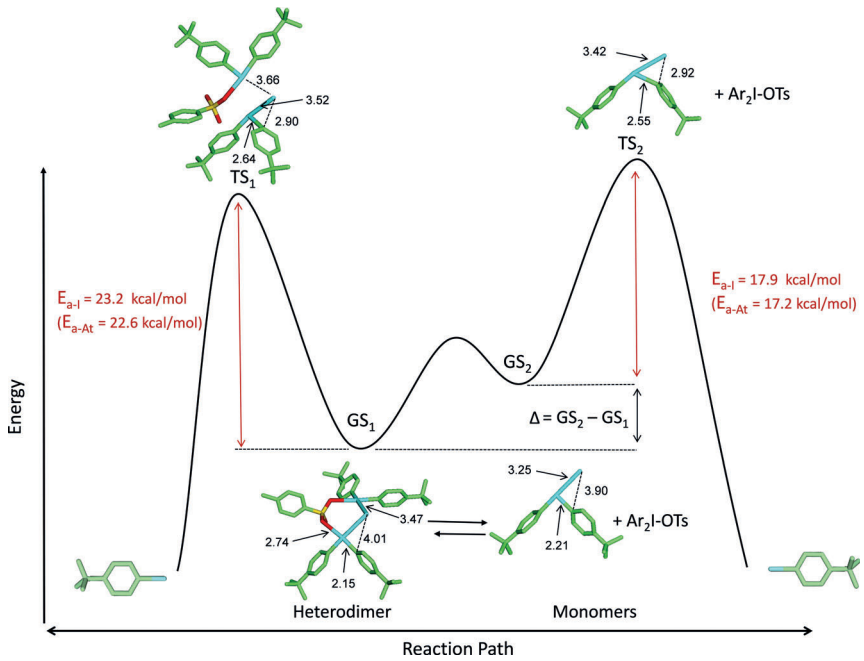


Figure 4. Reaction diagram of radioiodination depicting both possible transition states (TS), either via a monomeric iodonium iodide or by a heterodimeric intermediate. The heterodimer exists in equilibrium with its monomers, and interconversion between the two is likely much faster than the iodination. Accordingly, depending on the energy of both TS_1 and TS_2, the reaction follows either a dimeric or a monomeric pathway. The TS of the monomeric $(Ar_2I)I$ is characterized by the sp^3 hybridization of the C^{ipso} due to the incoming iodide. The distance between the two atoms at the TS is considerably shorter (2.92 Å) than that in the ground state (GS; 3.90 Å). The $I–C^{ipso}$ distances of the heterodimer are 2.90 Å in the TS and 4.01 Å in the GS. Note that the TS_2 energy is the sum of the E_a of the monomer and the dimer-dissociation energy (Δ), which is the difference between the energy of both monomers (GS_2) and that of the dimer (GS_1). Product does not show Ar_2I-OTs. Atoms are colored as follows: green, carbon; red, oxygen; yellow, sulfur; dark green, iodine. Hydrogen atoms are not shown. All distances are in Å. A similar diagram can be constructed for astatination. $E_{a\text{-}At}$ values are provided for comparison and optimized structures with bond lengths are given in Figure S5 (see the Supporting Information).

energy barrier of halogenation in a monomer, which in turn dictates whether iodination or astatination occurs within a monomeric or a dimeric complex.

The ΔG value for dimerization (-2.0 kcal mol^{-1} at 298.15 K) in both cases, calculated by subtracting the sum of the free energy of each monomer from that of the dimer, favors the formation of the heterodimers. However, the contribution of translational and rotational entropy of each monomer to dimerization in the liquid phase is known to be much lower than in the gas phase, due to solvent-restricted movement of monomers.[43] Accordingly, the above ΔG value, including both translational and rotational entropy based on the ideal gas approximation, can be more negative than -2.0 kcal mol^{-1}. Therefore, this ΔG alone may not be a reliable marker for determining whether the reaction follows either a dimeric or a monomeric pathway.

In the case of astatination, it is likely that, due to its higher polarizability, astatide forms a stronger complex than iodide with the iodonium, similarly to the reported case of diazonium, which also exhibits greatly enhanced reactivity with astatide as compared to iodide.[36] The higher polarizability of astatide induces a higher delocalization of the charge from the halide to the iodonium compared to lighter halogens, leading to a tighter ion pair by virtue of electrostatic interactions. In this context, it can be expected that the extra charge interaction of $(Ar_2I)OTs$ with astatide is considerably lower than with iodide, resulting in a thermodynamically less favorable heterodimeric structure. Further investigation will be necessary to corroborate this point.

Conclusion

In summary we have explored the reactivity of heavy halides towards aryliodonium salts at the radiotracer scale. We unveiled an unexpected and significantly higher reactivity of astatide as compared to the trend observed for other halides. Quantum chemical calculations led us to propose that astatination occurs via the monomeric form of an iodonium complex whereas iodination occurs via a more stable heterodimeric iodonium intermediate. Overall, it appears that iodonium salts are a promising alternative class of precursor to organotin-based chemistry for radioiodination and astatination. Iodonium salts achieved more consistent and nearly quantitative astatination RCYs under mild conditions by using the $-$I oxidation state, which is simpler to control in organic media at the radiotracer level than the $+$I oxidation state needed for electrophilic substitutions. As expected, the regioselectivity of S_NAr of non-symmetrical diaryliodonium salts was governed by electronic and steric effects. However, the lower regioselectivity that is observed in iodination and, to a greater extent, in astatination, as compared to previously reported radiofluorinations, suggests that carefully designed diaryliodonium salts will be required for efficient synthesis and optimal specific activity of aryl radioiodide and aryl astatide compounds, especially in the

case of aryl substituted by electron donating groups. Ultimately, we anticipate that this radiolabeling approach will become a highly useful tool for the radiolabeling of biomolecules with heavy radiohalogens with applications in nuclear imaging and targeted radiotherapy. Through the development of specifically designed iodonium salts, such efforts are underway in our laboratory.

Experimental Section

Radiochemistry

[^{125}I]NaI was obtained commercially in 10^{-5} M NaOH solution with a volumic acitivity of 50 μCi μL^{-1} (1.85 MBq/μL) and was diluted 12 times in deionized water before use. ^{211}At was produced by using the ^{209}Bi(α,2*n*)^{211}At reaction by bombarding a disposable internal bismuth target with α-particles from the Cyclotron Corporation CS-30 cyclotron in the National Institutes of Health Positron Emission Tomography Department. ^{211}At was recovered from the irradiated target in acetonitrile by using a previously described dry-distillation procedure.[44] Before use, the ^{211}At solution was diluted twice in a 10 mg mL^{-1} aqueous solution of Na_2SO_3, resulting in a 1:1 MeCN/water solution of sodium astatide. Iodonium salts were obtained commercially or synthesized as described in the Supporting Information.

Reaction of iodonium salts with $^{125}I^-$ and $^{211}At^-$

To iodonium salt (950 nmol) in the selected solvent (190 μL) equilibrated at the appropriate temperature of reaction was added [^{125}I]NaI or [^{211}At]NaAt solution (10 μL, typically 1.5 MBq), prepared as described above. At desired times, aliquots were withdrawn and deposited on a silica gel TLC plate and eluted with the appropriate solvent, and/or diluted in a 1:1 water/MeCN mixture and analyzed by reverse-phase HPLC using the appropriate elution system. Retention indices and elution systems used for all compounds of this study are given in the Supporting Information. Aromatic ^{125}I and ^{211}At species were identified by comparison of the retention index of authentic samples of the non-radioactive iodinated compound.

Astatination via electrophilic destannylation

To a 2.5 mg mL^{-1} solution of tributyl(4-*tert*butylphenyl)-stannane in 99:1 MeCN/AcOH (20 μL) was added 2 mg mL^{-1} *N*-chlorosuccinimide in MeCN (5 μL), followed by the ^{211}At (5 MBq activity) in MeCN (75 μL). The solution was heated for 30 min at 60 °C and after cooling down to room temperature, the solution was diluted with water (100 μL) and an aliquot was analyzed by HPLC, using the same chromatographic system as described above.

Quantum chemistry

The X-ray structure of bis(4-*tert*-butylphenyl)iodonium iodide was used as a template to construct both the monomeric and heterodimeric structures of Ar_2I^+ complexed with iodide or astatide. Quantum chemical calculations were carried out with the density functional theory at the B3LYP level with small-core pseudopotentials[45] for the I and At atoms with the cc-pVDZ basis set for their 25 valence electrons, together with the all-electron cc-PVDZ basis set for the rest of the atoms. All calculations were carried out in the reaction field of MeCN with the polarizable continuum model, together with the UAKS parameters set as implemented in Gaussian 09 software.[46] For each TS, a single imaginary frequency was obtained. Coordinates of the calculated structures are given in Table S4 (see the Supporting Information).

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Keywords: astatine · halogenation · iodonium salts · nucleophilic substitution · radiopharmaceuticals

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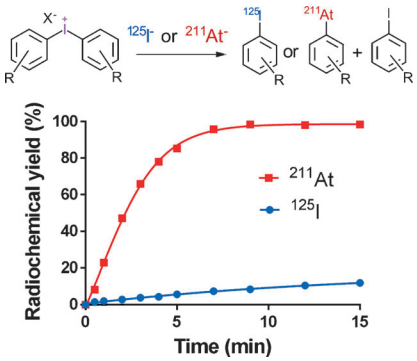
FULL PAPER

Wherever I lay my At: Radiohalogenation of diaryiodonium salts has been investigated and a significantly higher reactivity of astatide has been observed. Regioselectivity and reaction kinetics can be controlled by varying the nature of substituents. The high reactivity of these precursors makes them an attractive alternative to the conventional arylstannane chemistry for radiolabeling with iodine and astatine.



Astatine

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■■ – ■■

Unexpected Behavior of the Heaviest Halogen Astatine in the Nucleophilic Substitution of Aryliodonium Salts