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Fluoridation of heteroaromatic iodonium salts—experimental evidence supporting theoretical prediction of the selectivity of the process‡

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Theoretical prediction, that the nucleophilic substitution of a range of arylheteroaryliodonium salts by fluoride ion is regioselective for the aryl ring with the exception of benzo[*b*]furan, are borne out by experimental observation.

Iodine, like the other halogens, is found typically existing in monovalent form (oxidation state: −1), however owing to its large size and polarisability it is able to form stable polycoordinate, multivalent compounds. Compounds of this type, containing hypervalent iodine, have been known for over a century and have received considerable attention. The ability of these compounds to act as both selective reagents and intermediates has formed the basis for this interest.[1–3]

Our interest in the most numerous member of this group, the diaryliodinium salts, arose as it has been demonstrated that they are suitable precursors for the formation of fluoroarenes by the action of fluoride ion.[4,5] We have extended this methodology to the introduction of the fluorine-18 label ($t_{\frac{1}{2}}$ = 109.7 min) in the form of [^{18}F]fluoride.[6,7] This reagent has distinct advantages over the standard electrophilic procedures, which employ molecular [^{18}F]F_2 and derived reagents, as it is produced in higher amounts and higher specific radioactivity by several orders of magnitude.[8] This is an important consideration as ^{18}F-labelled organics are required at very high specific radioactivity as receptor radioligands in clinical research. Positron emission tomography (PET) is an imaging technique for the absolute measurement, *in vivo*, of positron emitters,[9] enabling their pharmacokinetics and biodistribution to be elucidated by non-invasive means. It is a well established technique; for example, L-6-[^{18}F]fluoro-DOPA[10,11] is used for the study of brain dopaminergic neuron density in movement disorders such as Parkinson's disease.

The ability to control/predict the regiochemical outcome of the aromatic nucleophilic substitution process is of paramount importance. Experimental observations, by us[7,12] and others,[13,14] suggest that it is the interplay of steric demand (the so called '*ortho* effect') and/or the electron deficiency of the aromatic rings that determines the site of nucleophilic substitution. It has been proposed[13,14] that the trigonal bipyramidal iodine(III) intermediates (see Fig. 1) in this process are fluxional and that the observations can be explained by the 'reactive' ring occupying the equatorial position *syn* to the nucleophile. This simple model does account for a large number of the reported observations for the nucleophilic aromatic substitution process. However, there are a number of examples where the outcome is not as predicted using this approach.[4,15] For arylheteroaryl iodonium salts (RR′I$^+$, R = phenyl, R′ = hereroaryl), the model predicts that the product will always be fluorobenzene, resulting from substitution of the relatively electron-poor phenyl ring (*i.e.* as in the equilibrium in Fig. 1).

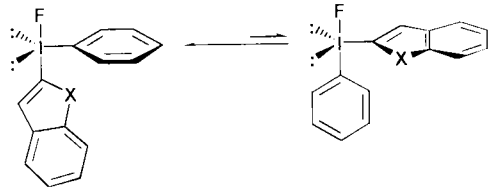

Fig. 1

We have recently applied computational modelling to the nucleophilic substitition of the structurally simpler dialkynyliodonium[16] and diphenyliodonium salts[15] in an attempt to gain a better understanding of the processes involved. This study established, *inter alia*, that the relative energies of the transition states for F–aryl extrusion, mediated by electron-withdrawing and electron-donating substituents, are the opposite of the axial/equatorial ground state equilibria, and that the latter cannot be reliably used to predict the regioselectivity of the process.

Here, we extend our model to the fluoridation of arylheteroaryliodonium salts in order to establish the method as a viable and accurate tool for predicting the outcome of such reactions. As before, quantitative models at the MNDO-d and at the Hartree-Fock *ab initio* level using the computationally efficient MIDI basis set (Table 1) were evaluated. Coordinate files for on-line viewing of the transition state models are available as ESI data.‡

The results reveal the phenyl group is more stable in the equatorial position for the ground state for all the pairs of isomers. Remarkably, the difference in energy grows along the heteroatom series N < S < O. However, the geometries and energies of the two possible transition states show significant variations from our original model. For the monocyclic systems, the transition state stability criterion is in the same sense as the ground state, which results in predicting fluorobenzene as the major product for all three heterocycles (Table 1, entries 1–3). The difference in energy between the two transition states grows in parallel with the aromaticity of the heterocycle. For the benzo-fused systems, all three ground states predict the phenyl group to be equatorial. At the transition state, however, we predict the 2-benzo[*b*]furyl group to be equatorial, resulting in 2-fluorobenzo[*b*]furan as the product. For benzo[*b*]thiophene this is reversed, and again fluorobenzene is predicted. For 1-methylindole, the energy differences are much smaller, and we predict a much less selective reaction, with fluoridation of both the phenyl and the indole rings.

As the prediction for the selectivity of the process did not appear to follow any simple trend, experimental data to assess the validity of the theoretical method was sought. Consequently, a range of arylheteroaryliodonium salts were prepared, in good yield, from the corresponding 2-trialkylstannyl derivatives by treatment with Koser's reagent [Ph(OH)OTs] (ESI‡)[17] (Scheme 1).

Fluoridation of the resultant iodonium tosylates was carried out by treatment with caesium fluoride in acetonitrile at 80 °C

† Undergraduate research participant.

‡ Electronic supplementary information (ESI) available: typical experimental and coordinate files for on line viewing of the transition state models. See http://www.rsc.org/suppdata/cc/b0/b000868k/

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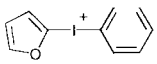
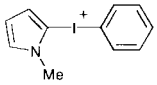
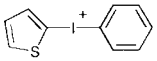
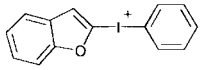
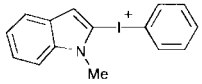
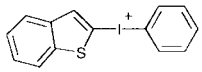
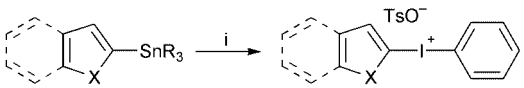
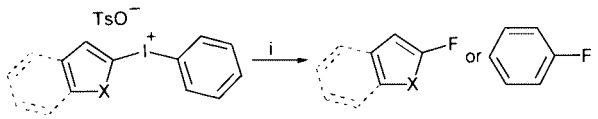
Table 1 Fluoridation of iodonium tosylates

Entry	Diaryliodonium tosylate[a]	Product PhF[b]	Product HetF[b]	$E_{TS1} - E_{TS2}$[c] ($E_{GS1} - E_{GS2}$)[d]	Agrees with prediction	Prediction for 3-substituted systems $E_{TS1} - E_{TS2}$[c] ($E_{GS1} - E_{GS2}$)[d]
1		Yes	No	−0.1, *−2.6* (−4.1, *−9.7*)	Yes	−4.9 (0.0)
2		Yes	No	−3.4, *−3.6* (−1.3, *−3.1*)	Yes	−7.0 (+1.7)
3		Yes	No	−6.1, *−6.2* (−2.4, *−4.6*)	Yes	−2.8 (0.0)
4		No	Yes	+2.0, *+0.8* (−4.8, *−10.2*)	Yes	−0.7 (−0.7)
5		Yes[e]	Yes[e]	−0.3, *+1.7* (−2.4, *−3.8*)	Yes	−6.5 (+0.8)
6		Yes	No	−4.5, *−3.5* (−3.1, *−4.6*)	Yes	−2.3 (−0.7)

[a] All diaryliodonium salts were characterised by ^1H, ^{13}C NMR, FTIR, mp, MS, HRMS and elemental analysis (except entry 2 which proved too labile for elemental analysis). [b] Typical radiochemical yields have already been reported for the process.[6,7] [c] E_{TS1} and E_{TS2} are the transition state energies for the generation of PhF and HetF, respectively (MNDO-d, *RHF/MIDI!*). [d] E_{GS1} and E_{GS2} are the ground state energies for the iodonium salts with the equatorial position occupied by Ph and Het, respectively (MNDO-d, *RHF/MIDI!*). [e] Ratio 7.7:1 fluorobenzene:2-fluoro-1-methylindole.



Scheme 1 *Reagents and conditions*: i, Ph(OH)OTs, DCM, room temp., 16 h. *Monocyclic series*: R = Bu^n, X = O, 77%; R = Me, X = NMe, 96%; R = Bu^n, X = S, 74%. *Bicyclic series*: R = Me, X = O, 98%; R = Me, X = NMe, 67%; R = Me, X = S, 96%.



Scheme 2 *Reagents and conditions*: i, CsF, MeCN, 80 °C, 16 h.

overnight (Scheme 2) and the reaction mixture analysed by GC–MS (ESI‡).

The results from these reactions are summarised in Table 1. As expected the 2-substituted five-membered rings (Table 1, entries 1–3) gave fluorobenzene as the sole fluoroaromatic product. The small value for $E_{TS1} - E_{TS2}$ (−0.1, −2.6 kcal mol^{-1}) for the 2-furylphenyliodonium salt (Table 1, entry 1) suggests that 2-fluorofuran may also be a product. However, owing to the volatile nature of this material we are not able to discount its presence.

The fluoridation products from the reaction of the benzoheteroaromatics (Table 1, entries 4–6), with the exclusive formation of 2-fluorobenz[*b*]furan and the generation of 2-fluoro-1-methylindole, strikingly confirm our transition state model of stability, and not that adopted by the simple model[13,14] where the products should all be fluorobenzene.

We have also included predictions for the 3-substituted series of heteroaromatics (Table 1). In general, fluorobenzene is predicted as the product for all the systems. Specific differences from the 2-series include a much greater specificity predicted for the phenyl 3-(1-methylindolyl) system, and that the aromatic rings show little or no preference in the ground state for either the equatorial or axial position ($E_{GS1} - E_{GS2}$ values are small).

In summary, we have demonstrated, by the fluoridation of arylheteroaryliodonium salts, efficiency prepared from the corresponding aryltrialkylstannanes, that the computational techniques employed are a reliable way of predicting the outcome of the fluoridation process and that the process is therefore transition state and not ground state controlled.

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