Radiofluorination of a 2.63 μM solution (pH 4, NaOAc buffer) of [AlCl₃(BnMe₂-tacn)] via treatment with 2.99 mol. equiv. of [¹⁸F]KF doped with cyclotron-produced [¹⁸F]⁻ target water, with heating to 80–100 °C for 1 h, gives up to 24% ¹⁸F incorporation. SPE purification of the [Al¹⁸F⁺¹⁸F(BnMe₂-tacn)] radio-product gives >99% RCP, with excellent stability (>99% RCP after 3 h).

Positron emission tomography (PET) is a non-invasive technique for imaging internal tissues and organs in patients. Amongst the options available for this application, the positron-emitting isotope fluorine-18 offers a number of characteristics that make it particularly attractive. These include a short, but manageable half-life of ca. 110 mins., a short positron linear range in tissue (ca. 2 mm), dominant positron emission (97%), low energy positron (Eₚmax = 635 keV) and its ease of production via a cyclotron.

While current ¹⁸F-based imaging agents available in the clinic are invariably based on organofluorine moieties, the need for alternatives that offer higher selectivity for target organs, and greater convenience for clinical production, has been recognised. It has been demonstrated that an inorganic approach for the development of new radiotracers can provide options beyond C–F based ¹⁸F-PET tracers. With regards to metal chelate-based agents, a key development was the work of McBride et al. who reported a two-step, one-pot radiofluorination method where ‘Al¹⁸F’ (obtained by treating AlCl₃ with [¹⁸F]KF) is chelated to a derivative of 1,4,7-triazacyclononane-1,4,7-triacetate (NOTA) in which one of the acetic acid functions is used to conjugate to a peptide, leading to pentadentate N₃O₂ coordination, with the [¹⁸F]⁻ completing a distorted octahedral geometry at Al(III) (Scheme 1). The complexation/radiofluorination is accomplished at pH 4.1. The Al¹⁸F-chelate moiety has subsequently been conjugated to several other peptides and been used to image different tumor types in vivo. Recently, open chain polydentate mixed N/O-donor ligands, attached to temperature-sensitive peptides, have also been used to radiolabel Al¹⁸F under milder conditions (< 40 °C) and show good stability.

In our previous work, the concept of replacing chloride ligands bound to a Ga(III) complex with [¹⁸F]⁻ was demonstrated by the radiolabelling of the pre-formed [GaCl₃(BnMe₂-tacn)] (BnMe₂-tacn = 1-benzyl-4,7-dimethyl-1,4,7-triazacyclononane) and [GaCl(Bn(CH₂COO)₂-tacn)] (Bn(CH₂COO)₂-tacn = 1-benzyl-4,7-diacetate-1,4,7-triazacyclononane), exploiting the higher bond energy of Ga–F over Ga–Cl as the major thermodynamic driving force for the reaction (Scheme 2). Good [¹⁸F]⁻ incorporation (ca. 30 %) was achieved under very mild radiolabelling conditions (unbuffered aqueous MeCN solution and room temperature) for the former, while buffering to pH 4 (NaOAc) and heating to 80 °C was required for the latter.

The aim of the work in this communication was to investigate the viability of the pre-formed [AlCl₃(BnMe₂-tacn)] complex as a potential scaffold for next-generation PET imaging agents through radiofluorination by Cl/F halide exchange and to compare the results with the corresponding gallium complex. We describe...
here the radiofluorination on a 1 mg scale (μM concentration) through Cl/18F halide exchange.

Preparative scale experiments established that the Al analogues, [AlCl3(RMe2-tacn)] (R = Bn or Me), do not undergo Cl/F exchange with [Bu4NF] or [Me4NF] in anhydrous MeCN at room temperature. On heating the reaction mixture, the macrocyclic ligand was displaced and [AlF3]− was formed.12 However, fluorination (Cl/F ligand exchange) was achieved upon addition of aqueous KF to a MeCN suspension of the complex at room temperature.12 We postulated that the difference in reactivity between the two metals might be due to the smaller ionic radius of Al3+, which would disfavour an associative (A) or associative interchange (Ia) ligand substitution mechanism.14

Treatment of a 2.63 μM MeCN solution of [AlCl3(BnMe2-tacn)] (1.0 mg) with 2.99 mol. equiv. of KF doped with [18F]F− (50 MBq) in unbuffered water with heating to 80 °C for 30 mins. resulted in 18F incorporation (<10%, determined by radio-HPLC; Fig. S6, ESI). 18F incorporation was increased associative (A) or associative interchange (Ia) ligand when the labelling experiment was performed in an aqueous buffer against that of the reference compound. In the UV trace against potentially competitive anions in water have been performed using 19F and 27Al NMR spectroscopy. Solutions of [Al19F3(BnMe2-tacn)] with a 10-fold excess of NaCl, NaOAc or NaF (close to pH 7) showed no changes even after several days, while it is clear from the radiolabelling experiments that the complex is stable at pH 4 (NaOAc buffer). However, the [Al19F3(BnMe2-tacn)] is completely decomposed by the addition of a 10-fold excess of Na2CO3 (which has pH ~10), with conversion to [Al(OH)4]2− (δ27Al = +80).

We reported previously that the corresponding [GaCl3(BnMe2-tacn)] undergoes radiofluorination (with ca. 30% [18F]F− incorporation) at room temperature in unbuffered aqueous MeCN.12 Thus, a significant difference in the behaviour of the Al(III) vs. Ga(III) analogues is evident. Likely factors contributing to the differences observed are the higher Al–F bond dissociation energy (664 kJ mol−1) compared to Ga–F (577 kJ mol−1) and the higher Lewis acidity of the Al system.15 The pH is an important factor for the radiolabelling of the Al system; in this case it may be that competition with hydroxide anions for the more Lewis acidic Al(III) is important. This work has demonstrated that [AlCl3(BnMe2-tacn)] can be radiolabelled readily in buffered pH 4 solution in the presence of 2.99 equiv. of KF doped with 18F− at 80 °C/10 mins. and that cyclotran-produced [18F]F− target water can be added directly to the buffered solution. The radiolabelled Al(III) complex shows excellent stability in PBS buffered ethanolic solution over several hours.

Comparing the results presented here with our earlier [GaF3(BnMe2-tacn)] and the ‘AlF’ system described by McBride et al. suggests that the size of the metal ion, its Lewis acidity and the specific ligand donor set are important considerations in determining the conditions necessary for effective radiofluorination at micromolar concentrations or lower.

Figure 1 Analytical HPLC chromatogram of the crude product from reaction of [AlCl3(BnMe2-tacn)] (1 mg, 2.63 μmol) at pH 4 (NaOAc buffer) with 2.99 eq of KF doped with 0.1 mL of aqueous [18F]F− at 80 °C for 90 mins. Radio (red) and UV (blue). Peak 1: Rt = 2.51 min 76% (18F−). Peak 2: Rt = 6.95 min 24% ([Al18F19F2(BnMe2-tacn)]).
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Further, McBride et al. were able to radio-fluorinate their ‘AlF’ system using a lower Al concentration. We have found that our [AlCl₃(BnMe₂-tacn)] is successfully radiofluorinated using 2.63 µM concentration (1 mg of complex in 1 mL), whereas ¹⁸⁷F incorporation was not observed using 0.1 mg of the metal precursor.

The results described here also provide strong encouragement that pre-formed Group 13 metal trihalide complexes of the type [MCl₃(BnMe₂-tacn)] bearing neutral triaza-macrocycles are promising candidates as alternatives to organofluorine compounds for incorporation into next generation imaging agents for PET applications. Future work will aim to rationalise how the choice of the metal ion influences the radiolabelling so that the optimum candidates for bioconjugation with peptides can be identified. We thank GE Healthcare and the EPSRC for support through EP/L505651/1.

Notes and references

† Synthetic procedure and method. [AlCl₃(BnMe₂-tacn)] was prepared according to literature method (ESI).12 Experiments were analysed on an Agilent 1290 HPLC system with an Agilent 1260 DAD UV detector (G4212B). Dionex Chromeleon 6.8 Chromatography data recording software was used to integrate the UV and radiochemical peak areas.

Analytical HPLC method: Column: Phenomenex Luna 5 um C18(2) 250 x 4.6 mm. Mobile phase A: 10 mM ammonium acetate. B: MeCN. Flow rate: 1 mL min⁻¹. Gradient: 0-15 min (10-90 % B), 15-20 min (90 % B), 20-21 min (90-10 % B), 21-26.5 min (10 % B).

Cl⁻/¹⁸⁷F Exchange Radiolabelling Procedure: Method 1: [AlCl₃(BnMe₂-tacn)] (0.001 g, 2.63 µmol) was dissolved in MeCN (0.6 mL). 2.99 equiv. of KF in cyclotron target [¹⁸⁷F]F− water (0.4 mL, 50 MBq) was added. The mixture was heated to 80–100 °C for 30 mins. Analytical HPLC analysis of the crude reaction solution showed ca. 9% ¹⁸⁷F incorporation.

Method 2: In a typical experiment, [AlCl₃(BnMe₂-tacn)] (0.001 g, 2.63 µmol) was dissolved in pH 4 sodium acetate buffer solution (1 mL). 2.99 eq of KF in cyclotron target [¹⁸⁷F]F− water (0.1-1 mL, 20-280 MBq) was added. The mixture was heated to 80-100 °C for 60-90 mins. Analytical HPLC analysis of the crude reaction solution showed up to 24% ¹⁸⁷F incorporation (n = 7).

Peak 1: Rt = 2.51 min [¹⁸⁷F−]. Peak 2: Rt = 6.95 min [Al¹⁸⁷⁷F₂(BnMe₂-tacn)] complex.

SPE purification procedure: The crude product was trapped on a HLB cartridge, washed with water (5 mL) to remove the [¹⁸⁷F]F− and eluted from the cartridge with 1 mL of ethanol. pH 7.4 PBS solution was used to dilute the product to give a 50% ethanolic formulation. The purified product was analysed by analytical HPLC, giving a pure product Rt = 6.92 min (RCP >99%). The product was stable for at least three hours (RCP = >99% at t = 180 min).

Figure 2 Analytical radio-HPLC chromatogram of: A: SPE purified product at t = 20 min. Peak: Rt = 6.92 min >99% ([Al18F19F2(BnMe2tacn)]); B: SPE purified product at t = 180 min. Peak: Rt = 6.92 min >99% ([Al18F19F2(BnMe2tacn)]).