Triaza-macrocyclic complexes of aluminium, gallium and indium halides: fast $^{18}$F and $^{19}$F incorporation via halide exchange under mild conditions in aqueous solution†

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Rapid and complete fluorination of the complexes $[\text{MCl}_3(L)]$ ($L = \text{Me}_2$-tacn, BzMe$_2$-tacn, $M = \text{Al, Ga, In}$) occurs at room temperature via reaction of a MeCN solution of the complex with 3 mol equiv. of KF in water. The Ga and In complexes are also readily fluorinated using R$_4$NF ($R = \text{Me or Bu}$) in MeCN solution, whereas no reaction occurs with the Al species under these conditions. The distorted octahedral fac-trifluoride coordination at M is confirmed in solution by multinuclear ($^{19}$F, $^{27}$Al, $^{71}$Ga and $^{115}$In) NMR spectroscopic studies, leading to sharp resonances with $^{19}$F--$^{71}$Ga and $^{19}$F--$^{115}$In couplings evident. The $[\text{MF}_3(L)]$ are extremely stable in aqueous solution and at low pH; they crystallise as tetrahydrates, $[\text{MF}_3(\text{Me}_3$-tacn)]$4\text{H}_2\text{O}$, with extended H-bonding networks formed through both F--H--O and O--H--O contacts. $[\text{InF}_3(\text{BzMe}_2$-tacn)]$1.2\text{H}_2\text{O}$ also shows intermolecular F--H--O hydrogen bonding contacts. The prospects for developing this coordination chemistry further to take advantage of the high metal--fluoride bond energies to enable rapid, late-stage fluorination of large macromolecules under mild conditions for PET imaging applications in nuclear medicine are discussed. This work also demonstrates that F-18 radiolabelling to form $[^{18}$F]$[\text{GaF}_3(\text{BzMe}_2$-tacn)]$ is executed readily at room temperature in aqueous MeCN over 30–60 min on addition of 2.99 mol equiv. of $[^{19}$F]$–\text{KF}_{aq}$ and 0.4 mL $[^{18}$F]$–\text{KF}_{aq}$ (100–500 MBq) to $[\text{GaCl}_3(\text{BzMe}_2$-tacn)] with ca. 30% incorporation. Rapid and complete fluorination of complex molecules is consequently important for the development of new candidates for PET imaging in nuclear medicine. There has been a significant research effort in this area to provide routes for C--F bond formation reactions, as alternatives to the traditional nucleophilic reactions. Notable successes include the use of electrophilic ‘F’ and metal-catalysed processes, as reported by Ritter, Groves, Buchwald and others.2–5 There is also a need to develop F-18 labelling methods which permit radiofluorination under mild conditions (neutral pH, room temperature) since this will improve the compatibility of the labelling conditions with a diverse range of biomolecules. Recent efforts towards boron-based agents for F-18 capture include the work of Perrin,* Gabbaï* and Tsien.*

Recently McBride and others have reported the use of Al--F complexes based upon functionalised bis-carboxylate derivatives of 1,4,7-triazacyclononane for F-18 imaging (Scheme 1). Incorporation of F-18 via formation of M--F bonds with biologically relevant ligand scaffolds provides an exciting alternative to C--F based PET agents. McBride et al. have also used the formation of Al--F bonds to label a wide range of biomolecules rapidly in a single step.6 However, the need for elevated temperatures ($100 \, ^\circ\text{C}$) for fluorination in this ‘one-pot’

† Electronic supplementary information (ESI) available: Preparative and spectroscopic details for the corresponding bromo complexes, HPLC traces and crystal structures of $[\text{GaCl}_3(\text{Me}_3$-tacn)], $[\text{InBr}_3(\text{Me}_3$-tacn)], $[\text{InCl}_3(\text{BzMe}_2$-tacn)]$, $[[(\text{Me}_3$-tacn)$\text{Ga}](\text{α-OH})], \text{Br}_3$, 3CH$_2$Cl$_2$ and $[\text{NMe}_4]^+\text{[AlF}_4]$ and cif files for all of the crystal structures. CCDC 926503–926512. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc52104d

Introduction

The increased availability of radioisotopes of the main group metals for radiopharmaceutical applications in imaging and therapy (e.g. $^{67}$Ga, $^{68}$Ga, $^{111}$In, $^{113m}$In, $^{117m}$Sn) has driven the development of new coordination chemistry with specific ligand types.1 Fluorine-18 is the radioisotope of choice for medical applications using (non-invasive) PET imaging, owing to its ease of production and its short half-life ($t_{1/2} = 109.8$ minutes). For radioisotopes with a relative short half-life, there is a drive to introduce the radiolabel in the late stage of the synthesis (and preferably in the final step). Rapid, late-stage fluorination of complex molecules is consequently important for the development of new candidates for PET imaging in nuclear medicine.

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approach places some limitations on its utility due to the thermal instability of some important high MW biomolecules. In order to further extend the scope of this approach, an increased understanding of the chemistry and properties of fluoride complexes of the Group 13 elements is required.

Metal fluoride coordination complexes are often significantly different from those containing heavier halogen atoms. The small, hard and highly electronegative F\(^-\) significantly influences the electronic environment at the metal centre and hence the binding of other ligands. For example, while ZrX\(_4\) (X = F, Cl, Br, I) readily form complexes with soft ligands such as phosphines and thioethers,\(^{11,12}\) no analogous complexes with ZrF\(_4\) are known.\(^{13}\) Further, while GeF\(_4\) and WF\(_6\) form phosphine adducts, GeX\(_4\) and WCl\(_6\) (and WBr\(_6\)) are reduced to lower oxidation states. Few studies have been reported on the coordination chemistry of the Group 13 fluorides.\(^{10,16,17}\)

We describe here the chemistry of the Group 13 trihalide complexes [MX\(_3\)(L)] (L = Me\(_3\)-tacn, BzMe\(_2\)-tacn; M = Al, Ga, In; X = F, Cl, Br) (Scheme 2), and demonstrate that using simple neutral triaza macrocyclic frameworks, exchange of Cl\(^-\) for F\(^-\) via treatment of the chloro complexes with stoichiometric [R\(_n\)N]\(_x\)F (R = \(^{19}\)Bu or Me) in MeCN solution or with aqueous KF in MeCN is rapid and complete under mild conditions (weakly acidic pH) and at room temperature. Further, we demonstrate that treatment of an aqueous MeCN solution of [GaCl\(_3\)(BzMe\(_2\)-tacn)] with 2.99 mol equiv. of aqueous [\(^{19}\)F]-KF and 0.4 mL of [\(^{19}\)F]-KF\(_{aq}\) (100–500 MBq) leads to ca. 30% incorporation of the F-18, forming labelled [GaF\(_3\)(BzMe\(_2\)-tacn)] at room temperature within 30–60 min.

The ease of fluoride (both F-18 and F-19) incorporation into these preformed complexes at room temperature and in mildly acidic aqueous solution offers potentially significant advantages over McBride’s ‘Al–F’ system\(^*\) which requires elevated temperature (100 \(^{\circ}\)C) to achieve fluoride uptake, since some biomolecules are unstable at elevated temperatures or under acidic conditions. Hence, the work reported herein provides the very appealing prospect that rapid, late stage F-18 radiolabelling of well-defined, pre-formed metal complexes is possible, and that altering the metal ion to Ga in place of Al may provide further advantages since it facilitates labelling under mild conditions. The pH measured for a freshly prepared solution of [GaCl\(_3\)(BzMe\(_2\)-tacn)] in aqueous MeCN was 5.6, while the pH of reaction formulation comprising [GaCl\(_3\)(BzMe\(_2\)-tacn)] and KF in aqueous MeCN (unbuffered) was 5.9.

### Experimental

Infrared spectra were recorded as Nujol mulls between CsI plates using a Perkin-Elmer Spectrum100 spectrometer over the range 4000–200 cm\(^{-1}\). \(^{1}\)H NMR spectra were recorded in CDCl\(_3\) or CD\(_2\)Cl\(_2\) unless otherwise stated, using a Bruker AV300 spectrometer. \(^{19}\)F\(\{^{1}\)H\}\) NMR spectra used either a Bruker AV300 or Bruker DPX400 (376.5 MHz) spectrometer and are referenced (externally) to CFCl\(_3\). \(^{27}\)Al, \(^{71}\)Ga, and \(^{115}\)In NMR spectra were recorded using a Bruker DPX400 spectrometer and are referenced to aqueous \([\text{Al(H}_2\text{O)}_{6}]^{3+}\) (104.3 MHz), aqueous \([\text{Ga(H}_2\text{O)}_{6}]^{3+}\) (122.0 MHz) and aqueous \([\text{In(H}_2\text{O)}_{6}]^{3+}\) at pH = 1 (87.7 MHz) respectively. Microanalyses were undertaken by Medac Ltd. Solvents were dried by distillation prior to use, CH\(_2\)Cl\(_2\) from CaH\(_2\), hexane from sodium benzophenone keytet and MeCN from CaH\(_2\), MF\(_3\)-xH\(_2\)O, MCl\(_3\), MB\(_3\) and \([\text{Bu}_4\text{N}]\text{F}\) (1.0 mol dm\(^{-3}\) in thf) (Aldrich) were used as received. Ligands Me\(_3\)-tacn\(^{18}\) and BzMe\(_2\)-tacn\(^{19}\) were prepared via the literature methods. \([\text{Me}_6\text{N}]\text{F}\) (Aldrich) was dried by azotropic distillation from toluene. All preparations of chloro and bromo complexes (ESI\(^+\)) were performed under an atmosphere of dry N\(_2\) using Schlenk techniques, and spectroscopic samples were prepared in a dry N\(_2\)-purgued glove box.

### Preparations

\([\text{AlCl}_{3}(\text{Me}_3\text{-tacn})]. \text{AlCl}_3 (0.067 g, 0.50 \text{mmol}) was added to a solution of Me\(_3\)-tacn (0.086 g, 0.50 mmol) in CH\(_3\)CN (5 mL) at room temperature with stirring which leads to the rapid formation of a precipitate. After 30 min the solvent was removed by filtration. The white precipitate was washed with a small amount of CH\(_2\)Cl\(_2\) solvent and dried in \textit{vacuo}. Yield: 0.11 g, 72%. Colourless crystals were obtained by cooling the CH\(_3\)CN solution in the fridge for several days. Crystals were washed with CH\(_2\)Cl\(_2\). Required for C\(_9\)H\(_{21}\)AlCl\(_3\)N\(_3\), 0.2CH\(_2\)Cl\(_2\): C, 34.4; H, 6.7; N, 13.1. Found: C, 34.2; H, 7.2; N, 13.9. \(^{1}\)H NMR (CD\(_2\)Cl\(_2\), 87.7 MHz): \(\delta\) 2.86 (s, [6\text{H}], tacn-CH\(_2\)), 2.67 (m, [6\text{H}], tacn-CH\(_2\)) IC. (Nujol, cm\(^{-1}\)): 389, 375 (Al–Cl).

\([\text{AlF}_3(\text{Me}_3\text{-tacn})]: x\text{H}_2\text{O}\). \(x\text{H}_2\text{O}\) (0.100 g, 0.73 mmol) was suspended in freshly distilled water (7 mL). Me\(_3\)-tacn (0.125 g, 0.73 mmol) was then added and the pale yellow suspension was transferred into a Teflon container and loaded into a stainless steel high pressure vessel (Parr) and heated to 180 \(^{\circ}\)C for 15 h. The vessel was then allowed to cool. A dark yellow-brown solution had formed. A small aliquot of the reaction solution was retained to grow crystals. For the remaining reaction mixture the volatiles were removed in \textit{vacuo}, giving a light brown solid which was washed.
with hexane and filtered. The resulting white solid was dried in vacuo. Yield: 0.12 g, 53%. Required for C₁₅H₃₄AlF₃N₃·3H₂O: C, 34.9; H, 8.8; N, 13.6. Found: C, 34.3; H, 8.9; N, 14.7%. ¹H NMR (CD₃CN, 298 K): δ 2.84–2.76 (m, [6H], tacn-CH₂), 2.72–2.65 (m, [6H], tacn-CH₂), 2.55 (s, [9H], CH₃), 2.19 (s, H₂O). IR (Nujol, ν/cm⁻¹): 3438 br (H₂O), 1668 (H₂O), 633, 614 (Al-F). Slow evaporation of the reaction solvent gave crystals suitable for X-ray diffraction.

Method 2. A solution of KF (0.058 g, 0.99 mmol) in water (2 mL) was added to a suspension of [AlCl₃(Me₃-tacn)] (0.100 g, 0.18 mmol) in MeCN (5 mL) at room temperature. A white precipitate formed initially which redissolved after a few minutes. NMR spectroscopic data on the solution were as for Method 1.

[AlCl₃(BzMe₂-tacn)]. Method as for [AlCl₃(Me₃-tacn)] but using AlCl₃ (0.067 g, 0.50 mmol) and BzMe₂-tacn (0.13 g, 0.50 mmol). White solid. Yield: 0.13 g, 66%. Required for C₁₅H₃₄AlCl₃N₃·2H₂O: C, 33.4; H, 6.1; N, 12.1. ¹H NMR (CD₂Cl₂, 298 K): δ 7.62 (m, [5H], ArH), 4.26 (s, [2H], Ar-CH₃), 3.01 (m, [4H], tacn-CH₂), 2.89 (m, [4H], tacn-CH₂), 2.85 (s, [6H], CH₃), 2.74 (m, [4H], tacn-CH₂), 1.53 (br s, H₂O). IR (Nujol, ν/cm⁻¹): 3392 br (OH), 1665 (H₂O), 1639 (Bz aromatic CC), 635, 601 (Al-F).

[GaCl₃(Me₃-tacn)]. Me₃-tacn (0.09 g, 0.52 mmol) was added to a solution of GaCl₃ (0.088 g, 0.50 mmol) in anhydrous CH₂Cl₂ (8 mL) at room temperature with stirring. After ca. 30 min, a white precipitate started to appear. After 2 h stirring was stopped and the mixture was concentrated to afford more precipitate, the white powdered product was filtered from the solution and dried in vacuo. Yield: 0.110 g, 60%. Required for C₁₅H₃₄GaCl₃N₃·2H₂O: C, 42.5; H, 6.0; N, 9.9. Found: C, 42.2; H, 6.0; N, 9.6%. ¹H NMR (CD₂Cl₂, 298 K): δ 7.30 (br s, [5H], ArH), 4.71 (s, [2H], Ar-CH₂), 3.67 (br s, [2H], tacn-CH₂), 3.20 (br s, [2H], tacn-CH₂), 2.92 (br s, [6H], CH₃), 2.75 (br s, [2H], tacn-CH₂), 2.62 (br s, [2H], tacn-CH₂), 2.40 (br m, [2H], tacn-CH₂). IR (Nujol, ν/cm⁻¹): 529, 492 (Ga-F).

[GaCl₃(BzMe₂-tacn)]. Method as for [GaCl₃(Me₃-tacn)] but using BzMe₂-tacn (0.125 g, 0.50 mmol) and GaCl₃ (0.088 g, 0.50 mmol). White solid. Yield: 0.089 g, 42%. Required for C₁₅H₃₄GaCl₃N₃·3H₂O: C, 42.5; H, 6.0; N, 9.9. Found C, 42.2; H, 6.0; N, 9.6%. ¹H NMR (CD₂Cl₂, 298 K): δ 7.30 (br s, [5H], ArH), 4.71 (s, [2H], Ar-CH₂), 3.67 (br s, [2H], tacn-CH₂), 3.20 (br s, [2H], tacn-CH₂), 2.92 (br s, [6H], CH₃), 2.75 (br s, [2H], tacn-CH₂), 2.62 (br m, [2H], tacn-CH₂), 2.40 (br m, [2H], tacn-CH₂). IR (Nujol, ν/cm⁻¹): 301, 280 (Ga-Cl).

[GaF₃(BzMe₂-tacn)]·H₂O

Method 1. [GaCl₃(BzMe₂-tacn)] (0.05 g, 0.10 mmol) was suspended in 5 mL anhydrous CH₂Cl₂. The suspension was treated with [NeMe₄]F (0.03 g, 0.30 mmol) and stirred at room temperature for 1 h. The [NeMe₄]Cl by-product was removed by filtration. The resulting colourless filtrate was treated with 5 mL hexane, resulting in a white precipitate which was isolated by filtration and dried in vacuo. Yield: 0.035 g, 80%. Required for C₁₅H₃₄GaF₃N₃·3H₂O: C, 40.4; H, 8.8; N, 8.6, Found C, 40.9; H, 8.8; N, 8.6%. ¹H NMR (D₂O, 298 K): δ 7.30 (m, [5H], ArH), 4.73 (s, [2H], Ar-CH₂), 3.17 (m, [4H], tacn-CH₂), 2.88 (m, [4H], tacn-CH₂), 2.73 (s, [6H], CH₃), 2.36 (m, [4H], tacn-CH₂), 2.25 (s, H₂O). IR (Nujol, ν/cm⁻¹): 3390, 1654 (H₂O), 526, 515 (Ga-F).

Method 2. As described for [GaF₃(BzMe₂-tacn)] Method 3, using [GaCl₃(BzMe₂-tacn)] (0.05 g, 0.10 mmol) and KF (0.017 g, 0.30 mmol) in water. White solid. 0.035 g, 73%. Spectroscopic data as for Method 1.

[InCl₃(Me₃-tacn)]. Method as for [GaCl₃(Me₃-tacn)], but using Me₃-tacn (0.086 g, 0.50 mmol) and InCl₃ (0.110 g, 0.50 mmol). White solid. Yield: 0.113 g, 57%. Required for C₁₅H₃₄InCl₃N₃·2H₂O: C, 27.5; H, 5.4; N, 10.7. Found C, 27.8; H, 5.4; N, 10.9%. ¹H NMR (CDCl₃, 298 K): δ 3.1 (br m, [6H], tacn-CH₂), 2.8 (br m, [15H], Me and tacn-CH₂). IR (Nujol, ν/cm⁻¹): 287, 269 (In-Cl).
[InF₃(Me₅-tacn)]⁺ xH₂O

Method 1. [InCl₃(Me₅-tacn)] (0.214 g, 0.54 mmol) was added to CH₂Cl₂ (8 mL) and stirred for ca. 15 min, this gave a cloudy suspension. [N⁵Bu₄]F in thf (1 mol dm⁻³, 1.63 mL, 1.63 mmol) was added to the mixture via a syringe and stirred for ca. 2 h. The solution was filtered and the white precipitate collected, washed with hexane and dried in vacuo. Yield: 0.150 g, 70%. Required for C₃H₁₅F₂InN₃·H₂O: C, 29.9; H, 6.4; N, 11.6. Found: C, 30.1; H, 6.1; N, 11.3.

1H NMR (CD₂Cl₂, 298 K): δ 3.09–3.15 (br m, [6H], tacn-CH₂), 2.93 (m, [6H], Me), 2.72–2.82 (br m, [6H], tacn-CH₂), 2.19 (s, H₂O). IR (Nujol, cm⁻¹): 3392 br (H₂O), 1669 (H₂O), 479, 462, 443 (In–F).

Method 2. [InCl₃(Me₅-tacn)] (0.060 g, 0.17 mmol) was suspended in 5 mL anhydrous CH₂Cl₂. The suspension was treated with [NMe₄]F (0.047 g, 0.51 mmol) and stirred at room temperature for 1 h. The [NMe₄]Cl by-product was removed by filtration. The resulting colourless filtrate was treated with 5 mL anhydrous hexane, forming a white precipitate which was isolated by filtration and dried in vacuo. Yield: 0.044 g, 76%. Spectroscopic data as for Method 1.

Method 3. A Teflon reactor vessel was charged with freshly distilled water (7 mL), InF₃·3H₂O (0.200 g, 0.90 mmol) and Me₅-tacn (0.154 g, 0.90 mmol). The Teflon container was loaded into a stainless steel high pressure vessel (Parr) and heated to 180 °C for 15 h. The vessel was then allowed to cool. A dark yellow-brown solution had formed. A small aliquot of the reaction solution was retained to grow crystals. For the remaining reaction mixture the volatiles were removed in vacuo, giving a light brown gum which was washed with hexane. The hexane was decanted and the remaining volatiles removed in vacuo to give a light brown solid. Yield 0.246 g, 0.62 mmol, 69%. Spectroscopic data as for Method 1.

[InCl₃(BzMe₂-tacn)]⁻. Method as for [GaCl₃(BzMe₂-tacn)]⁻, but using BzMe₂-tacn (0.125 g, 0.50 mmol) and InCl₃ (0.110 g, 0.50 mmol). White solid. Yield: 0.093 g, 40%. Required for C₂₅H₂₃F₀In₃·H₂O: C, 38.5; H, 5.4; N, 9.0. Found C, 38.8; H, 5.8; N, 8.7.

1H NMR (CD₂Cl₂, 298 K): 7.2–7.4 (m, [3H], ArH), 4.37 (s, [2H], Ar-CH₂), 3.45 (br, [2H], tacn-CH₂), 3.10 (br, [2H], tacn-CH₂), 2.80 (s, [6H], CH₃), 2.75 (br m, [2H], tacn-CH₂), 2.60 (br m, [2H], tacn-CH₂), 2.40 (br m, [2H], CH₂). IR (Nujol, cm⁻¹): 289, 271 (In–Cl). Crystals formed from the CH₂Cl₂ solution of the product stored in the freezer at −18 °C.

[InF₃(BzMe₂-tacn)]⁻ xH₂O. [InCl₃(BzMe₂-tacn)]⁻ (0.06 g, 0.10 mmol) was suspended in 5 mL anhydrous CH₂Cl₂. The suspension was treated with [NMe₄]F (0.047 g, 0.51 mmol) and stirred at room temperature for 1 h. The [NMe₄]Cl by-product was removed by filtration. The resulting colourless filtrate was treated with 5 mL anhydrous hexane, forming a white precipitate which was isolated by filtration and dried in vacuo. Yield: 0.02 g, 48%. C₁₅H₂₅F₃InN₃ (384) was obtained. Crystals were mounted at the window of an FR-E+ SuperBright molybdenum X-ray diffractometer equipped with an enhanced sensitivity (HG) Saturn724+ detector and using the default C–H distance. For [AlCl₃(Me₅-tacn)]⁻ the data were collected as orthorhombic, but during the structure solution it became clear that in fact the crystal was monoclinic. The data were therefore reprocessed as monoclinic, giving 96% completeness. The refinement used TWIN/BASF commands to model disorder. For [InCl₃(BzMe₂-tacn)]⁻ the crystal quality was.
rather poor, hence the final residuals are higher than normal, although the coordination environment is not in doubt.

## Results and discussion

The Group 13 fluorides, MF₃·3H₂O, are poorly soluble in organic solvents, and hence there are rather few examples where these have been used directly to form metal fluoro-complexes with neutral ligands under conventional conditions. Notable exceptions include met-[GaF₃(pyridine)] [prepared by prolonged refluxing of the constituents in THF], [GaF₃(1,4,7-tris(2-amino-3,5-di-butylbenzyl)-1,4,7-triazacyclononane)] and direct reaction of InF₃·3H₂O with 2,2'-bipy or 1,10-phen (L) forms the distorted octahedral species [InF₃(L)H₂O].

Diimine and amine complexes of MF₃ (M = Al, Ga, In) have been obtained using hydrothermal syntheses at elevated temperature (~180 °C), while reaction of AlN or InN and NH₄F in supercritical ammonia (400 °C) forms [AlF₃(NH₃)] and [InF₃(NH₃)] respectively.

Direct reaction of AlF₃·3H₂O and Me₃-tacn under hydrothermal conditions (180 °C, 15 h) led to formation of [AlF₃(Me₃-tacn)]·4H₂O as a white solid in good yield. The IR spectrum shows two bands in the far-IR region attributed to the a and e stretching modes from the facial MF₃ unit of a distorted octahedron (C₃v). There is also clear evidence for H-bonded H₂O, which turn out to be an important feature of these complexes and is described in more detail below. The ¹H NMR spectrum of D₂O also confirm the stability of the trifluoro species in aqueous solution. The ²⁷Al [I = 5/2, 100% abundance, Q = 0.149 × 10⁻²⁸ m², Rₑ = 1170] and ¹⁹F{¹H} NMR spectra (Table 1) each show a singlet.

The crystal structure is consistent with the spectroscopic data, confirming the distorted octahedral coordination at Al via a tridentate Me₃-tacn ligand and three fac F⁻ ligands (Fig. 1(a)).

The asymmetric unit contains four H₂O molecules as well as one [AlF₃(Me₃-tacn)] molecule. The water molecules are involved in an array of H-bonding interactions both with the F⁻ atoms in the [AlF₃(Me₃-tacn)], as well as between the H₂O molecules themselves, giving H₂O···F = 2.806(3), H₂O···F = 2.701(3), H₂O···F = 2.688(3), H₂O···F = 2.802(4) Å. This gives rise to the extensively H-bonded array illustrated in Fig. 1(b).

The GaF₃ analogue, [GaF₃(Me₃-tacn)]·4H₂O, obtained and characterised similarly, also crystallises as a tetrahydrate (below). These [MF₃(Me₃-tacn)]·4H₂O species are remarkably stable in the solid and also in solution in H₂O, CH₃Cl, MeCN etc. This led us to consider the possibility of that introduction of F⁻ via exchange reactions with the heavier halide analogues (Cl⁻ or Br⁻) may be synthetically viable and serve as an alternative route to the [MF₃(Me₃-tacn)] (M = Al, Ga or In), by virtue of the M–F bonds formed being stronger than those involving the heavier halides.

In order to test this idea, the complexes, fac-[MX₃(Me₃-tacn)] (M = Al, Ga, In; X = Cl, Br) and [MX₃(BzMe₂-tacn)] (M = Al, X = Cl, Br; M = Ga, X = Cl; M = In; X = Cl or Br) were obtained in high yield from direct reaction of MX₃ with the triaza macrocycle in anhydrous CH₃Cl or MeCN. Confirmation of their identities follows from microanalyses, IR and ¹H NMR spectroscopic data and from crystal structures of representative examples.

### Multinuclear solution ²⁷Al, ⁷¹Ga and ¹¹⁵In NMR studies

support the formulations – Table 1. For the Al and Ga complexes, the spectra show a single resonance despite the moderate quadrupole moments associated with the metal nuclei (Q = 0.112 × 10⁻²⁸ m², Rₑ = 322) nuclei. This is consistent with the proposed distorted six-coordinate geometry with local C₃ᵥ symmetry, leading to the electric field gradient (EFG) being close to zero, and hence relatively sharp lines.

The ¹¹⁵In NMR spectra were less informative due to the much larger quadrupole moment, which sometimes led to the resonance not being observed for [InX₃(Me₃-tacn)] (X = Cl or Br) [¹¹⁵In: I = 9/2, 95.7% abundance, Q = 1.16 × 10⁻²⁸ m², Rₑ = 1920]. The multinuclear NMR studies show that the chloro complexes are more resistant to hydrolysis/solvolysis in solution than the bromo species, and that while the

<table>
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<th>Complex</th>
<th>²⁷Al/¹⁴Ga/¹¹⁵In/ppm (w₁/₂/Hz)</th>
<th>¹⁹F{¹H} (ppm)</th>
<th>Solvent</th>
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<td>[AlF₃(Me₃-tacn)]</td>
<td>19.0 (60); 18.5 (52)</td>
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<td>—</td>
<td>CH₃Cl</td>
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<tr>
<td>[GaF₃(Me₃-tacn)]</td>
<td>42.0 [Jₕₕₕ ~ 490 Hz]; 44.6 (br q)</td>
<td>−180.9 (two br q); −173 (br)</td>
<td>CH₃Cl; D₂O</td>
</tr>
<tr>
<td>[GaCl₃(Me₃-tacn)]</td>
<td>93.9 (60)</td>
<td>—</td>
<td>CH₃Cl</td>
</tr>
<tr>
<td>[GaBr₃(Me₃-tacn)]</td>
<td>29.3 (180)</td>
<td>—</td>
<td>MeCN</td>
</tr>
<tr>
<td>[InF₃(Me₃-tacn)]</td>
<td>64 [Jₕₕₕ ~ 600 Hz]; n.o.</td>
<td>−215 (br); −192.5 (br)</td>
<td>MeCN; D₂O</td>
</tr>
<tr>
<td>[InCl₃(Me₃-tacn)]</td>
<td>268 (750)</td>
<td>—</td>
<td>CH₃Cl</td>
</tr>
<tr>
<td>[InBr₃(Me₃-tacn)]</td>
<td>n.o.</td>
<td>—</td>
<td>MeCN</td>
</tr>
<tr>
<td>[AlF₃(BzMe₂-tacn)]</td>
<td>19.8 (100)</td>
<td>−161.5 (F); −161.7 (2F)</td>
<td>MeCN</td>
</tr>
<tr>
<td>[AlCl₃(BzMe₂-tacn)]</td>
<td>36.5 (45)</td>
<td>—</td>
<td>CH₃Cl</td>
</tr>
<tr>
<td>[AlBr₃(BzMe₂-tacn)]</td>
<td>20.1 (35)</td>
<td>—</td>
<td>CH₃Cl</td>
</tr>
<tr>
<td>[GaF₃(BzMe₂-tacn)]</td>
<td>44.9 [Jₕₕₕ ~ 445Hz]</td>
<td>−172.8 (br)</td>
<td>D₂O</td>
</tr>
<tr>
<td>[GaCl₃(BzMe₂-tacn)]</td>
<td>92.8 (360)</td>
<td>—</td>
<td>MeCN</td>
</tr>
<tr>
<td>[InF₃(BzMe₂-tacn)]</td>
<td>n.o.</td>
<td>−220 (br)</td>
<td>MeCN</td>
</tr>
<tr>
<td>[InCl₃(BzMe₂-tacn)]</td>
<td>265 (2200)</td>
<td>—</td>
<td>MeCN</td>
</tr>
</tbody>
</table>

* n.o. = not observed.
complexes are stable in anhydrous CH₂Cl₂ or MeCN, stronger donor solvents such as dmf or dmso lead to decomposition. The powdered solids may be stored under N₂ for many months without degradation.

Trace hydrolysis of [GaX₃(Me₃-tacn)] (X = Cl or Br) produces the face-sharing bioctahedral dimers [(Me₃-tacn)Ga₂(μ-OH)₃]⁻X₃CH₂Cl₂, and the crystal structure of the Br derivative was also determined (ESI†). Wieghardt and co-workers have described the hydrolysis of [InCl₃(Me₃-tacn)] to form dinuclear μ-hydroxy and tetranuclear μ-oxo derivatives.²⁸

While the bromo complexes are readily hydrolysed, the chloro species are much more stable, and therefore considered excellent candidates for the fluorination studies.

**Cl⁻/¹⁹F⁻ exchange reactions**

Reagents such as Me₃SiF and Me₃SnF are often convenient fluoride sources in synthetic chemistry, e.g. [AlCl₃(py)]ₙ (n = 1 to 3) and Me₃SiF in pyridine afford [AlF₃(py)]ₙCl.²⁹ However, for F-18 applications, the radio-fluorine is produced as F⁻ ions, and hence it is more desirable to be able to use the fluoride directly as Na₁⁸F or K₁⁸F. Therefore, in this work we have investigated both tetraalkylammonium fluorides (in organic solvents) and aqueous KF as the fluoride source.

Initial studies were performed by addition of three mol equiv. of a 1 mol dm⁻³ thf solution of [NBu₄]F to a suspension of [MCl₃(R₃-tacn)] in MeCN. For the Ga systems this led to rapid and complete dissolution at room temperature over ca. 5 min, and in situ ⁷¹Ga and ¹⁹F{¹H} NMR studies (Table 2) show complete conversion to [GaF₃(R₃-tacn)]. For the more symmetrical Me₃-tacn system, a quartet is observed in the ⁷¹Ga NMR spectrum (MeCN) due to coupling to three F⁻ ligands (δ⁷¹Ga = 42.0, J₀-GaF ≈ 490 Hz – Fig. 2), and although not fully resolved, the ¹⁹F{¹H} NMR spectrum shows a single resonance (≈ 180.0 ppm) with coupling to ⁶⁹/⁷¹Ga, providing unequivocal evidence for formation of [GaF₃(Me₃-tacn)].
Notably, like \([\text{AlF}_3(\text{Me}_3-\text{tacn})]\), \([\text{GaF}_3(\text{Me}_3-\text{tacn})]\) also crystallises as a tetrahydrate, \([\text{InF}_3(\text{Me}_3-\text{tacn})]\) allows the fate of the complex to be monitored in parallel with acid (aqueous HBF4) and (v) the presence of excess F– ion.

The \([\text{GaF}_3(\text{R}_3-\text{tacn})]\) complexes were subjected to a range of experimental conditions that showed the trifluoro-complexes are unaffected by (i) prolonged heating (2 h at 40–50 °C) in MeCN, (ii) the presence of a 10-fold excess of Cl– in MeCN, (iii) standing for several days in aqueous solution, (iv) the presence of acid (aqueous HBF4), and (v) the presence of excess F– either in MeCN or H2O.

For the gallium systems, clean fluorination is also effected using \([\text{NMe}_4]F\) in MeCN (the \([\text{NMe}_4]Cl\) by-product is more readily separated than \([\text{N}^\text{Bu}_4]Cl\)). Addition of aqueous KF to a suspension of \([\text{GaCl}_3(\text{R}_3-\text{tacn})]\) in MeCN also leads to rapid and complete fluorination at room temperature. This confirms that Cl– /F– exchange is faster than any competing hydrolysis reactions under these conditions.

The \([\text{InCl}_3(\text{R}_3-\text{tacn})]\) behave similarly with both \([\text{NR}_4]F\) in MeCN, although the Cl– /F– exchange reaction is slower (ca. 30–45 min) to reach completion at room temperature compared to the Ga systems. The 115In spectrum (MeCN) of \([\text{InF}_3(\text{Me}_3-\text{tacn})]\) shows a well-resolved 1 : 3 : 3 : 1 quartet (Fig. 4) at 64 ppm (\(J_{\text{InF}} \sim 600 \text{ Hz}\)), confirming the complete exchange of Cl– for F–.

Both \([\text{InF}_3(\text{Me}_3-\text{tacn})]\)–4H2O (Fig. 5) and \([\text{InF}_3(\text{BzMe}_2-\text{tacn})]\)–1.2H2O (Fig. 6) were also characterised crystallographically. Although none of the \([\text{MF}_3(\text{Me}_3-\text{tacn})]\) complexes in this study are isomorphous, they all adopt very similar structures and crystallise as tetrahydrates, showing a very strong tendency for the F ligands to engage in extensive F––H–OH hydrogen-bonding, while \([\text{InF}_3(\text{BzMe}_2-\text{tacn})]\)–1.2H2O shows the H2O molecules form significant interactions with F1 and F2, F––H–OH ~ 2.8 Å.

Unlike the Ga and In analogues, \([\text{AlCl}_3(\text{Me}_3-\text{tacn})]\) does not react with either \([\text{N}^\text{Bu}_4]F\) or \([\text{NMe}_4]F\) in neat MeCN at room temperature, even over several hours. Heating the reaction mixture causes partial decomposition, forming \([\text{AlF}_3]^-\) and releasing the R3-tacn, but there is no evidence in the 19F{1H} and 27Al NMR spectra for formation of \([\text{AlF}_3(\text{Me}_3-\text{tacn})]\) under these conditions. This was unexpected, and the reason for the failure is not entirely clear, however, it may be a result of the smaller ionic radius of Al3+, which would disfavour an associative (A) or associative interchange (Ia) ligand substitution mechanism.

However, we were able to demonstrate that addition of aqueous KF to a MeCN suspension of \([\text{AlCl}_3(\text{Me}_3-\text{tacn})]\) does lead to clean conversion to form \([\text{AlF}_3(\text{Me}_3-\text{tacn})]\) at room temperature, the spectroscopic signature of the product matching that formed via hydrothermal synthesis from \([\text{AlF}_3]3\text{H}_2\text{O}\) (above). This suggests that the more polar \((\text{cf. MeCN})\) H2O solvent is involved in a solvent assisted substitution mechanism.29

F-18 radiolabelling

Based upon the results from the Cl– /18F– exchange reactions the gallium(m) systems were identified as the most promising candidate for the F-18 radiolabelling experiments. Furthermore, inclusion of the benzyl chromophore in \([\text{GaCl}_3(\text{BzMe}_2-\text{tacn})]\) allows the fate of the complex to be monitored in parallel with the radio-trace by using UV-visible spectroscopy. Radiolabelling was carried out on a 1 mg scale by dissolving \([\text{GaCl}_3(\text{BzMe}_2-\text{tacn})]\) in aqueous MeCN, adding 2.99 mol equiv.

![Fig. 2 71Ga NMR spectrum of [GaF3(Me3-tacn)] (CH2Cl2) showing the quartet coupling (\(J_{\text{Gaf}} \sim 490 \text{ Hz}\)).](image-url)
of aqueous $[^{19}\text{F}]$-KF and 0.4 mL of $[^{18}\text{F}]$-KF$_{aq}$ (100–500 MBq) and allowing the solution to stand at room temperature for between 30 and 60 min. The crude reaction solution was purified by preparative HPLC using a water–MeCN mobile phase. This gave a single product peak at $R_t = 9.0$ min (ca. 30% incorporation after one hour). The purified species was eluted through an analytical HPLC system using a 10 mM aq. NH$_4$OAc–MeCN mobile phase, giving a single peak in the radio-chromatograph at $R_t = 6.1$ min. ESI$^+$ mass spectrometric analysis of this species post elution gave an $m/z$ and isotope pattern consistent with the species $[\text{GaF}_3(\text{BzMe}_2\text{-tacn}) + \text{NH}_4]^+$ ($m/z = 391; 100\%$) – see ESI.$^\dagger$ The presence of associated $[\text{NH}_4]^+$ in these species was also confirmed from independent mass spectrometry experiments on the preformed $[\text{GaF}_3(\text{BzMe}_2\text{-tacn})]$ complex with and without added cation. Thus, introduction of one mol equiv. of $[\text{NH}_4][\text{PF}_6]$ leads to the appearance of a strong peak at $m/z = 391$.

This behaviour is attributed to the presence of the highly electronegative facial GaF$_3$ fragment which can form electrostatic and/or H-bonding interactions with the hard [NH$_4]^+$ cation introduced during the labelling experiments and HPLC analysis – similar to the strong F$\cdots$H–OH interactions to the associated water molecules observed crystallographically ($vide$ $supra$). There is also literature precedent for this behaviour in alkaline earth or lanthanide complexes of AsF$_3$ such as $[\text{Ca(AsF}_3)(\text{AsF}_6)_2]$, in which the pyramidal AsF$_3$ molecule behaves as a Lewis base, bonding to the metal cation via bridging fluorides (with further interactions between Ca$^{2+}$ and the $[\text{AsF}_6]^{3-}$ anions).$^{31}$

The purified species was dried under vacuum and treated with phosphate buffered saline (PBS) and ethanol, giving a
formulation of 10% ethanol with pH 7.2. Subsequent analysis by analytical HPLC confirmed that the species was stable under these conditions for at least 2 hours. The radiochemical purity (RCP) of the purified product remained high over this period (98–99% RCP) — ESL†

X-ray structural comparisons

In view of the very different stabilities of the [MX₃(R₃-tacn)] complexes and the differing reactivities towards F⁻/Cl⁻ exchange observed across the series, it was of interest to compare the structural properties of the species to attempt to ascertain any significant structural trends which might provide some insights. For comparison with the trifluoro complexes already described, crystal structures of [MX₃(R₃-tacn)] were therefore determined for a range of M with X = Cl or Br, specifically for [MX₃(Me₃-tacn)] (M = Al, X = Cl; M = Ga, X = Cl; M = In, X = Br) — Fig. 7 and ESI, and for [InCl₃(BzMe₂-tacn)] (ESI†). Each structure shows the expected distorted octahedral coordination environment at M, comprising a tridentate tri-amine macrocycle and three mutually facial X ligands.

In contrast to the fluorides, the chloro- and bromo-complexes are discrete molecular entities, and show no incorporation of solvent molecules in the crystal lattice.

Table 2 summarises the key geometric parameters for the series of complexes. Comparing the M–Na and M–F distances within the series [MF₃(Me₃-tacn)] · 4H₂O (M = Al, Ga, In) reveals that upon going from Al to Ga the M–F bond distances increase by ~0.12 Å, and from Ga to In the increase is ~0.19 Å. These changes are almost exactly in line with expectation based on the increasing ionic radii for the six-coordinate trivalent metal ions down Group 13 (Al³⁺ = 0.535 Å; Ga³⁺ = 0.62 Å; In³⁺ = 0.80 Å).³²

In contrast however, the M–N bond distances for Ga complex are only ~0.02 Å longer than for the Al complex, whereas from Ga to In the M–N bonds increase by ~0.17 Å. Also, comparing the Al–N bond distances in [AlF₃(Me₃-tacn)] · 4H₂O with those in [AlCl₃(Me₃-tacn)] reveals a very small increase of only ~0.02 Å, whereas in the Ga systems [GaF₃(Me₃-tacn)] · 4H₂O the Ga–N distances are ca. 0.04–0.05 Å shorter than in [GaCl₃(Me₃-tacn)]. These observations suggest that the 9-membered triaza
macrocyle may be too large for optimal *facial* coordination to the smallest Al$^{3+}$ ion, whereas the larger Ga$^{3+}$ and In$^{3+}$ fit rather better. This may also account for the differences observed in the Cl$^-$/F$^-$ exchange reactions in MeCN solution; i.e. the Al$^{3+}$ centre is sterically less accessible to the F$^-$ entering group in MeCN, whereas the halide exchange in aqueous MeCN probably undergoes a solvent (H$_2$O) assisted substitution.

The trend in X–M–X and N–M–N angles across the series correlates with the trends in bond distances. In all cases the Cl$^-$ to produce very stable [MF$_3$(R$_3$-tacn)] complexes, all of which are ca. 30% incorporation of F-18, forming [GaF$_3$(BzMe$_2$-tacn)] rapidly at room temperature under mildly acidic conditions which is stable over at least 2 hours in PBS buffered solution. The rapidly growing interest in metal complexes as high affinity binders for F-18 in PET imaging applications in nuclear medicine, together with the remarkably high stability of the Group 13 metal trifluoro complexes described herein, lead to an enticing prospect for producing new generations of metal-fluoride based PET imaging agents. It is notable that McBride’s ‘Al–F’ system requires elevated temperature (100 °C) to achieve fluoride uptake, whereas in the chemistry described here, Cl$^-$/F$^-$ exchange is achieved rapidly using KF at room temperature in aqueous solution both on a preparative and radio-tracer scale.

This suggests that rapid, late stage F-18 radiolabelling of pre-formed metal complexes may be an attractive alternative strategy, and provides evidence that introducing metal ions such as Ga in place of Al may offer further advantages. It should be noted that in order to demonstrate the radiolabelling of the Ga compound in the present work at room temperature, we have used 1 mg (2.36 μmol) of the pre-formed [GaCl$_3$(Me$_2$Bz-tacn)] complex, whereas McBride *et al.* in their systems were able to label at lower quantity, but require heating to achieve good labelling. Further work in our laboratories is aimed at modifying the ligands to enable room temperature radiolabeling of the complexes using less material.

**Conclusions and outlook**

This work has shown that direct fluorination of the distorted octahedral Group 13 tacn-based complexes, [MCl$_3$(R$_3$-tacn)] (M = Al, Ga, In) occurs cleanly and rapidly at room temperature in aqueous MeCN using KF as well as in MeCN solution via [NR$_2$iF] to produce very stable [MF$_3$(R$_3$-tacn)] complexes, all of which are isolated as hydrates. We have also shown that radiolabelling an aqueous solution of [GaF$_3$(BzMe$_2$-tacn)] with F-18 doped [19F]KF leads to ca. 30% incorporation of F-18, forming [GaF$_3$(BzMe$_2$-tacn)] rapidly at room temperature under mildly acidic conditions which is stable over at least 2 hours in PBS buffered solution. The rapidly growing interest in metal complexes as high affinity binders for F-18 in PET imaging applications in nuclear medicine, together with the remarkably high stability of the Group 13 metal trifluoro complexes described herein, lead to an enticing prospect for producing new generations of metal-fluoride based PET imaging agents. It is notable that McBride’s ‘Al–F’ system requires elevated temperature (100 °C) to achieve fluoride uptake, whereas in the chemistry described here, Cl$^-$/F$^-$ exchange is achieved rapidly using KF at room temperature in aqueous solution both on a preparative and radio-tracer scale. This suggests that rapid, late stage F-18 radiolabelling of pre-formed metal complexes may be an attractive alternative strategy, and provides evidence that introducing metal ions such as Ga in place of Al may offer further advantages. It should be noted that in order to demonstrate the radiolabelling of the Ga compound in the present work at room temperature, we have used 1 mg (2.36 μmol) of the pre-formed [GaCl$_3$(Me$_2$Bz-tacn)] complex, whereas McBride *et al.* in their systems were able to label at lower quantity, but require heating to achieve good labelling. Further work in our laboratories is aimed at modifying the ligands to enable room temperature radiolabeling of the complexes using less material.

**Notes and references**


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