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 $[\text{MCl}_3(L)]$ ($L = \text{Me}_3\text{-tacn}, \text{BzMe}_2\text{-tacn}, \text{M} = \text{Al}, \text{Ga}, \text{In}$) 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 RaNF ($R = \text{Me}$ or $^8\text{Bu}$) in MeCN solution, whereas no reaction occurs with the Al species under these conditions. The distorted octahedral $\text{fac}$-trifluoride coordination at M is confirmed in solution by multinuclear ($^{19}\text{F}, \, ^{27}\text{Al}, \, ^{71}\text{Ga}$ and $^{115}\text{In}$) NMR spectroscopic studies, leading to sharp resonances with $^{19}\text{F}$–$^{71}\text{Ga}$ and $^{19}\text{F}$–$^{115}\text{In}$ couplings evident. The $[\text{MF}_3(L)]$ are extremely stable in aqueous solution and at low pH; they crystallise as tetrahydrates, $[\text{MF}_3(\text{Me}_3\text{-tacn})] \cdot 4\text{H}_2\text{O}$, with extended H-bonding networks formed through both $\text{F}$–$\text{H}$–$\text{O}$ and $\text{O}$–$\text{H}$–$\text{O}$ contacts. $[\text{InF}_3(\text{BzMe}_2\text{-tacn})] \cdot 1.2\text{H}_2\text{O}$ also shows intermolecular $\text{F}$–$\text{H}$–$\text{O}$ 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 $^{18}$F radiolabelling to form $[^{18}\text{F}]\,[\text{GaF}_3(\text{BzMe}_2\text{-tacn})]$ is effected readily at room temperature in aqueous MeCN over 30–60 min on addition of 2.99 mol equiv. of $[^{19}\text{F}]\cdot\text{KF}_{\text{aq}}$ and 0.4 mL $[^{18}\text{F}]\cdot\text{KF}_{\text{aq}}$ (100–500 MBq) to $[\text{GaCl}_3(\text{BzMe}_2\text{-tacn})]$ with ca. 30% incorporation.

Introduction

The increased availability of radioisotopes of the main group metals for radiopharmaceutical applications in imaging and therapy (e.g. $^{67}\text{Ga}$, $^{68}\text{Ga}$, $^{111}\text{In}$, $^{113}\text{In}$, $^{117}\text{Sn}$) has driven the development of new coordination chemistry with specific ligand types. $^{18}$ Fluorine-18 is the radioisotope of choice for medical applications using (non-invasive) PET imaging, owing to its ease of production via cyclotrons that are now widely available, 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. 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,$^a$ Gabbaï$^a$ and Tsien.$^8$

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.$^a$ McBride et al. have also used the formation of Al–F bonds to label a wide range of biomolecules rapidly in a single step.$^a$ However, the need for elevated temperatures ($100$ °C) for fluorination in this ‘one-pot'
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 halogens. 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 ZrX4 (X = F, Cl, Br, I) readily form complexes with so many phosphines and thioethers, no analogous complexes with ZrF4 are known. Further, while GeF4 and WF6 form phosphine adducts, GeX4 and WCl6 (and WBr6) are reduced to lower oxidation states, GeX4 and WCl6 (and WBr6) are reduced to lower oxidation states. Few studies have been reported on the coordination chemistry of the Group 13 fluorides. 

We describe here the chemistry of the Group 13 trihalide complexes [MX3(L)] [L = Me3-tacn, BzMe2-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 [RN] F (R = 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 [GaCl3(BzMe2-tacn)] with 2.99 mol equiv. of aqueous [19F]−KF and 0.4 mL of [18F]−KFaq (100–500 MBq) leads to ca. 30% incorporation of the F-18, forming labelled [GaF3(BzMe2-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 °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 [GaCl3(BzMe2-tacn)] in aqueous MeCN was 5.6, while the pH of reaction formulation comprising [GaCl3(BzMe2-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. 1H NMR spectra were recorded in CDCl3 or CD2Cl2 unless otherwise stated, using a Bruker AV300 spectrometer. 19F{1H} NMR spectra used either a Bruker AV300 or Bruker DPX400 (376.5 MHz) spectrometer and are referenced (externally) to CFCl3. 27Al, 71Ga, and 115In NMR spectra were recorded using a Bruker DPX400 spectrometer and are referenced to aqueous [Al(H2O)6]3+ (104.3 MHz), aqueous [Ga(H2O)6]3+ (122.0 MHz) and aqueous [In(H2O)6]3+ at pH = 1 (87.7 MHz) respectively. Microanalyses were undertaken by Medac Ltd. Solvents were dried by distillation prior to use, CH2Cl2 from CaH2, hexane from sodium benzophenone ketyl and MeCN from CaH2. MF3-xH2O, MCl3, MBF3 and [Bu4N]F (1.0 mol dm−3 in thf) (Aldrich) were used as received. Ligands Me5-tacn18 and BzMe2-tacn19 were prepared via the literature methods. [Me5NF] (Aldrich) was dried by azotropic distillation from toluene. All preparations of chloro and bromo complexes (ESI†) were performed under an atmosphere of dry N2 using Schlenk techniques, and spectroscopic samples were prepared in a dry N2-purged glove box.

Preparations

[AlCl3(Me5-tacn)]. AlCl3 (0.067 g, 0.50 mmol) was added to a solution of Me5-tacn (0.086 g, 0.50 mmol) in CH2CN (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 CH2Cl2 solvent and dried in vacuo. Yield: 0.11 g, 72%.Colourless crystals were obtained by cooling the CH2CN solution in the fridge for several days. Crystals were washed with CH2Cl2. Required for C9H21AlCl3N3, 0.2CH2Cl2: C, 34.4; H, 6.7; N, 13.1. Found: C, 34.2; H, 7.2; N, 13.9. 1H NMR (CD2Cl2, 298 K): δ 3.23 (m, [6H], tacn-CH2), 2.86 (s, [9H], CH3), 2.67 (m, [6H], tacn-CH2). IR (Nujol, ν/cm−1): 389, 375 (Al−Cl).

[AlF3(Me5-tacn)]·xH2O

Method 1. AlF3·3H2O (0.100 g, 0.73 mmol) was suspended in freshly distilled water (7 mL). Me5-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 °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 solid which was washed.
with hexane and filtered. The resulting white solid was dried in vacuo. Yield: 0.12 g, 53%. Required for $\text{C}_9\text{H}_{21}\text{AlF}_3\text{N}_3$: C, 42.5; H, 6.0; N, 9.9. Found C, 42.2; H, 6.0; N, 9.6%.

$^1\text{H}$ NMR (CD$_2$Cl$_2$, 298 K): δ 7.62 (m, [5H], ArH), 4.71 (s, [2H], Ar-CH$_2$), 3.67 (br, [2H], tact-CH$_2$), 3.20 (br, [2H], tact-CH$_2$), 2.92 (br s, [6H], CH$_3$), 2.63 (m, [4H], tact-CH$_2$), 2.28 (m, [2H], tact-CH$_2$). IR (Nujol, ν/cm$^{-1}$): 3390, 1654 (H$_2$O), 526, 515 (Ga–F).

$\text{GaCl}_3(\text{BzMe}_2\text{tacn})$. Method as for $\text{GaCl}_3(\text{Me}_3\text{tacn})$ but using $\text{AlCl}_3 (0.067 g, 0.50 mmol) and BzMe$_2$-tacn (0.13 g, 0.50 mmol). White solid. Yield: 0.13 g, 66%. Required for $\text{C}_15\text{H}_{25}\text{Cl}_3\text{GaN}_3$: C, 42.5; H, 6.0; N, 9.9. Found C, 42.2; H, 6.0; N, 9.6%.

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$\text{GaF}_3(\text{BzMe}_2\text{tacn})$. Method as for $\text{GaF}_3(\text{Me}_3\text{tacn})$ but using $\text{AlF}_3(\text{BzMe}_2\text{tacn})$. A solution of $\text{KHF}_2$ (0.058 g, 1.00 mmol) in water (2 mL) was added drop-wise, leading to rapid dissolution and the formation of a colourless solution. The mixture was stirred for a further 1 h at room temperature. Quantitative by NMR spectroscopic analysis; data as for Method 1.

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**Chemical Science**

*Edge Article*

**F-18 radiolabelling of [GaCl₃(BzMe₂-tacn)]**

Experiments were analysed on a Gilson 322 HPLC system with a Gilson 156 UV detector. Dionex Chromeloon 6.8 Chromatography data recording software was used to integrate the UV and radiochemical peak areas. Preparative HPLC: Luna 5μ C18(2) 100 × 10 mm (mobile phase A = 100% water; B = 100% MeCN), Flow rate 3 ml min⁻¹. Gradient 0 to 5 min (10% B), 5–20 min (10–90% B), 20–25 min (90% B), 25–26 min (10% B).

Analytical HPLC: Luna 5μ C18(2) 250 × 4.6 mm (mobile phase A = 10 mM ammonium acetate, B = 100% 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).

ESI⁺ mass spectra were recorded from direct injection of the products onto a Thermo Finnigan mass spectrometer fitted with an LCQ advantage MS pump.

**Procedure** In a typical experiment [GaCl₃(BzMe₂-tacn)] (0.001 g, 2.36 μmol) was dissolved in a mixture of MeCN (0.5 mL) and H₂O (0.1 mL). This solution was added to 0.4 mL of an aqueous solution containing [¹⁸F]-KF (100 to 500 MBq) and [¹⁸F]-KF (7.05 μmol) and the vial was allowed to stand at room temperature for 30 to 60 min. The crude reaction solution was diluted with water so that approximately 10% of the solvent composition was organic. Preparative HPLC on the diluted crude reaction solution confirmed ca. 30% incorporation of F-18 into the metal complex (based upon integration of the radio peaks) after one hour. Peak 1: Rt = 2.2 min (¹⁸F⁻). Peak 2: Rt = 9.0 min (complex). The MeCN was then removed in vacuo and the product was made up with PBS and ethanol to give a ca. 10% ethanol final product (pH 7.2).

Peak 2 was run through an analytical HPLC system giving a single radio and UV peak at Rt 6.2 min (RCP 99%).

**Peak 2** ESI⁺ MS (MeCN/NH₄OAc): found m/z = 354 [GaF₂(BzMe₂-tacn)]⁻; 391 [GaF₃(BzMe₂-tacn) + NH₄]⁺. The product is stable to chemical and radiochemical degradation for at least two hours in phosphate buffered saline and ethanol — see ESI†.

**X-ray crystallography**

Details of the crystallographic data collection and refinement parameters are given in the ESI†. Crystals were obtained as described. Data collection used a Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with VHF Varimax optics (100 μm focus) with the crystal held at 120 K (N₂ cryostream) or a Bruker-Nikon FR591 rotating anode diffractometer fitted with confocal mirrors and with the crystal held at 120 K (N₂ cryostream). Mo-Kα X-radiation (λ = 0.71073 Å). Structure solution and refinement were generally routine, except as described below, with hydrogen atoms on C added to the model in calculated positions and using the default C–H distance. For [AlCl₃(Me₃-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 mer-[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 forms the distorted octahedral species [InF₆(1-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)]₃ and [InF₃(NH₃)(NH₄)] 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 a₁ and e stretching modes of the facial MF₃ unit of a distorted octahedron (C₆v). 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 (CD₃CN) is characteristic of facially coordinated Me₃-tacn. NMR spectroscopic measurements in 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, R_e = 1170] and ¹⁹F¹H [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···F₁ = 2.806(3) Å, H₂O···F₂ = 2.701(3) Å, H₂O···F₃ = 2.688(3) 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, CH₂Cl₂, 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(1,4,7-tacn)] [M = Al, Ga, In; X = Cl, Br] and [MX₃(1,4,8-tacn)] [M = Al, X = Cl; 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 CH₂Cl₂ 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 ²⁷Al and ⁷¹Ga 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(R₃-tacn)] (X = Cl or Br) [¹¹⁵In: I = 9/2, 95.7% abundance, Q = 1.16 × 10⁻²⁸ m², R_e = 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

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<th>Complex</th>
<th>δ²⁷Al/²⁴Ga/¹¹⁵In/ppm (w₁/₂/Hz)</th>
<th>δ¹⁹F¹H [¹H] (ppm)</th>
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<tr>
<td>[AlF₃(Me₃-tacn)]</td>
<td>19.0 (60); 18.5 (52)</td>
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<td>34.5 (30)</td>
<td>−180.9 (two br q); −173 (br)</td>
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<tr>
<td>[AlBr₃(Me₃-tacn)]</td>
<td>18.9 (80)</td>
<td>−215 (br); −192.5 (br)</td>
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<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 CH$_2$Cl$_2$ or MeCN, stronger donor solvents such as dmf or dmso lead to decomposition. The powdered solids may be stored under N$_2$ for many months without degradation.

Trace hydrolysis of [GaX$_3$(Me$_3$-tacn)] (X = Cl or Br) produces the face-sharing biocahedral dimers [(Me$_3$-tacn)Ga$_2$(μ-OH)$_3$]X$_3$ in CH$_2$Cl$_2$, and the crystal structure of the Br derivative was also determined (ESI†). Wieghardt and co-workers have described the hydrolysis of [InCl$_3$(Me$_3$-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$^-$/$^{19}$F$^-$ exchange reactions**

Reagents such as Me$_3$SiF and Me$_3$SnF are often convenient fluoride sources in synthetic chemistry, e.g. [AlCl$_3$(py)$_n$] (n = 1 to 3) and Me$_3$SiF in pyridine affords [AlF$_3$(py)$_2$]Cl.$^{29}$ 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 NaF (or KF or R$_4$NF). 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 [N$^4$Bu$_4$]F to a suspension of [MCl$_3$(R$_3$-tacn)] in MeCN. For the Ga systems this led to rapid and complete dissolution at room temperature over ca. 5 min, and in situ $^{71}$Ga and $^{19}$F($^1$H) NMR studies (Table 2) show complete conversion to [GaF$_3$(R$_3$-tacn)]. For the more symmetrical Me$_3$-tacn system, a quartet is observed in the $^{71}$Ga NMR spectrum (MeCN) due to coupling to three F$^-$ ligands ($\delta^{71}$Ga = 42.0, $J_{GaF} \sim 490$ Hz - Fig. 2), and although not fully resolved, the $^{19}$F($^1$H) NMR spectrum shows a single resonance (~180.0 ppm) with coupling to $^{69/71}$Ga, providing unequivocal evidence for formation of [GaF$_3$(Me$_3$-tacn)].
Table 2 Key structural data for $[\text{MX}_3(\text{L})]$

<table>
<thead>
<tr>
<th>Complex</th>
<th>$d(\text{M-X})$/Å</th>
<th>$d(\text{M-N})$/Å</th>
<th>$\angle (\text{X-M-X})^\circ$</th>
<th>$\angle (\text{N-M-N})^\circ$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{AlF}_3(\text{Me}_3\text{-tacn})] \cdot 4\text{H}_2\text{O}$</td>
<td>1.740(2), 1.744(2), 1.757(2)</td>
<td>2.098(3), 2.106(3), 2.115(3)</td>
<td>96.95(12), 96.00(11), 95.81(12)</td>
<td>82.20(13), 82.13(13), 82.37(13)</td>
</tr>
<tr>
<td>$[\text{AlCl}_3(\text{Me}_3\text{-tacn})]$</td>
<td>2.267(2), 2.274(2), 2.276(2)</td>
<td>2.111(3), 2.126(4), 2.141(4)</td>
<td>94.03(7), 93.74(6), 94.21(7)</td>
<td>83.03(14), 81.64(14), 81.97(14)</td>
</tr>
<tr>
<td>$[\text{GaF}_3(\text{Me}_3\text{-tacn})] \cdot 4\text{H}_2\text{O}$</td>
<td>1.581(3), 1.585(3), 1.881(3)</td>
<td>2.126(4), 2.126(4), 2.140(4)</td>
<td>95.81(12), 94.87(13), 94.23(12)</td>
<td>82.21(1), 82.4(2), 81.6(2)</td>
</tr>
<tr>
<td>$[\text{GaCl}_3(\text{Me}_3\text{-tacn})]$</td>
<td>2.3087(5), 2.3177(9), 2.1644(13), 2.1755(13), 2.1960(14)</td>
<td>94.38(2), 94.98(2), 94.49(2)</td>
<td>81.90(5), 80.80(5), 80.83(5)</td>
<td>78.68(6), 78.91(6), 78.44(6)</td>
</tr>
<tr>
<td>$[\text{InF}_3(\text{Me}_3\text{-tacn})] \cdot 4\text{H}_2\text{O}$</td>
<td>2.0318(11), 2.0391(12), 2.0570(11)</td>
<td>2.287(2), 2.289(2), 2.292(1)</td>
<td>96.33(5), 95.04(5), 94.79(5)</td>
<td>76.42(6), 76.8(2), 76.2(2)</td>
</tr>
<tr>
<td>$[\text{InCl}_3(\text{BzMe}_2\text{-tacn})]$</td>
<td>2.5987(8), 2.6006(8), 2.6046(8)</td>
<td>2.344(4), 2.345(4), 2.347(4)</td>
<td>96.66(3), 95.06(2), 96.15(3)</td>
<td>77.96(6), 77.14(6), 77.80(6)</td>
</tr>
<tr>
<td>$[\text{InF}_3(\text{BzMe}_2\text{-tacn})] \cdot 1.2\text{H}_2\text{O}$</td>
<td>2.4443(13), 2.4518(14), 2.4581(14)</td>
<td>2.312(4), 2.342(4), 2.371(4)</td>
<td>96.72(3), 96.72(3), 98.24(5)</td>
<td>79.76(6), 77.14(6), 77.80(6)</td>
</tr>
<tr>
<td>$[\text{InCl}_3(\text{BzMe}_2\text{-tacn})]$</td>
<td>2.4443(13), 2.4518(14), 2.4581(14)</td>
<td>2.312(4), 2.342(4), 2.371(4)</td>
<td>95.32(3), 96.26(5), 98.31(3)</td>
<td>77.1(2), 77.4(2), 76.3(2)</td>
</tr>
</tbody>
</table>

Fig. 2 $^{71}\text{Ga}$ NMR spectrum of $[\text{GaF}_3(\text{Me}_3\text{-tacn})]$ (CH$_2$Cl$_2$) showing the quartet coupling ($J_{\text{GF}} \sim 490$ Hz).

Notably, like $[\text{AlF}_3(\text{Me}_3\text{-tacn})]$, $[\text{GaF}_3(\text{Me}_3\text{-tacn})]$ also crystallises as a tetrahydrate, $[\text{GaF}_3(\text{Me}_3\text{-tacn})] \cdot 4\text{H}_2\text{O}$ (Fig. 3), with an extensive H-bonding array involving intermolecular O···F and O···O interactions.

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 HBF$_4$) and (v) the presence of excess F$^-$ either in MeCN or H$_2$O.

For the gallium systems, clean fluorination is also effected using [NMe$_4$]F in MeCN (the [NMe$_4$]Cl by-product is more readily separated than [N$^\text{Bu}_4$]Cl). Addition of aqueous KF to a suspension of [GaCl$_3$(R$_3$-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 [InCl$_3$(R$_3$-tacn)] behave similarly with both [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 $^{115}$In 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 ($J_{\text{IF}} \sim 600$ Hz), confirming the complete exchange of Cl$^-$ for F$^-$. Both $[\text{InF}_3(\text{Me}_3\text{-tacn})] \cdot 4\text{H}_2\text{O}$ (Fig. 5) and $[\text{InF}_3(\text{BzMe}_2\text{-tacn})] \cdot 1.2\text{H}_2\text{O}$ (Fig. 6) were also characterised crystallographically. Although none of the [MF$_3$(Me$_3$-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 [InF$_3$(BzMe$_2$-tacn)] · 1.2H$_2$O shows the H$_2$O molecules form significant interactions with F1 and F2, F···H--OH ··· 2.8 Å.

Unlike the Ga and In analogues, [AlCl$_3$(Me$_3$-tacn)] does not react with either [N$^\text{Bu}_4$]F or [NMe$_4$]F in neat MeCN at room temperature, even over several hours. Heating the reaction mixture causes partial decomposition, forming [AlF$_4$]$^-$ and releasing the R$_3$-tacn, but there is no evidence in the $^{19}$F/$^1$H and $^{27}$Al NMR spectra for formation of [AlF$_4$(Me$_3$-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 Al$^{3+}$, which would disfavour an associative (A) or associative interchange (I$_a$) ligand substitution mechanism. However, we were able to demonstrate that addition of aqueous KF to a MeCN suspension of [AlCl$_3$(Me$_3$-tacn)] does lead to clean conversion to form [AlF$_4$(Me$_3$-tacn)] at room temperature, the spectroscopic signature of the product matching that formed via hydrothermal synthesis from AlF$_3$·3H$_2$O (above). This suggests that the more polar (cf. MeCN) H$_2$O solvent is involved in a solvent assisted substitution mechanism.$^{20}$

F-18 radiolabelling

Based upon the results from the Cl$^-$/$^{19}$F$^-$ exchange reactions the gallium(III) systems were identified as the most promising candidate for the F-18 radiolabelling experiments. Furthermore, inclusion of the benzyl chromophore in [GaCl$_3$(BzMe$_2$-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 [GaCl$_3$(BzMe$_2$-tacn)] in aqueous MeCN, adding 2.99 mol equiv.
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$^+$.† 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 $[\text{NH}_4]^+$ cation introduced during the labelling experiments and HPLC analysis – similar to the strong F–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).†

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) – ESI†.

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 triamine 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
macrocycle may be too large for optimal facial coordination to the smallest Al3+ ion, whereas the larger Ga3+ and In3+ fit rather better. This may also account for the differences observed in the Cl−/F− exchange reactions in MeCN solution; i.e. the Al3+ centre is sterically less accessible to the F− entering group in MeCN, whereas the halide exchange in aqueous MeCN probably undergoes a solvent (H2O) 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 Al3+ and Ga3+ complexes are essentially invariant (±8°), whereas the halide exchange in aqueous MeCN probably undergoes a solvent (H2O) assisted substitution.

Notes and references


20 G. M. Sheldrick, *SHELXS-97, Program for crystal structure solution*, University of Göttingen, Germany, 1997.
21 G. M. Sheldrick, *SHELXL-97, Program for crystal structure refinement*, University of Göttingen, Germany, 1997.