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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 $[MCl_3(L)]$ (L = Me_3-tacn, $BzMe_2$-tacn, M = 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_4NF (R = Me or ^{n}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 $[MF_3(L)]$ are extremely stable in aqueous solution and at low pH; they crystallise as tetrahydrates, $[MF_3(Me_3\text{-tacn})]\cdot 4H_2O$, with extended H-bonding networks formed through both F···H–O and O···H–O contacts. $[InF_3(BzMe_2\text{-tacn})]\cdot 1.2H_2O$ 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 [F-18] $[GaF_3(BzMe_2\text{-tacn})]$ is effected readily at room temperature in aqueous MeCN over 30–60 min on addition of 2.99 mol equiv. of [^{19}F]–KF_{aq} and 0.4 mL [^{18}F]–KF_{aq} (100–500 MBq) to $[GaCl_3(BzMe_2\text{-tacn})]$ 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}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 *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,[6] Gabbaï[7] 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.[9] McBride *et al.* have also used the formation of Al–F bonds to label a wide range of biomolecules rapidly in a single step.[9] However, the need for elevated temperatures (100 °C) for fluorination in this 'one-pot'

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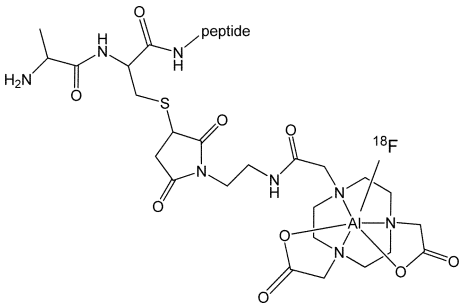
† Electronic supplementary information (ESI) available: Preparative and spectroscopic details for the corresponding bromo complexes, HPLC traces and crystal structures of $[GaCl_3(Me_3\text{-tacn})]$, $[InBr_3(Me_3\text{-tacn})]$, $[InCl_3(BzMe_2\text{-tacn})]$, $[\{(Me_3\text{-tacn})Ga\}_2(\mu\text{-}OH)_3]Br_3\cdot 3CH_2Cl_2$ and $[NMe_4]_3[Al_2F_9]$ 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



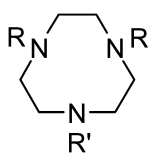
Scheme 1

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.[10] 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 = 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[14] and WF_6[15] 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 $[R_4N]F$ (R = ^{n}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 $[GaCl_3(BzMe_2\text{-tacn})]$ with 2.99 mol equiv. of aqueous $[^{19}F]$–KF and 0.4 mL of $[^{18}F]$–KF_{aq} (100–500 MBq) leads to *ca.* 30% incorporation of the F-18, forming labelled $[GaF_3(BzMe_2\text{-tacn})]$ 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[9] 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 $[GaCl_3(BzMe_2\text{-tacn})]$ in aqueous MeCN was 5.6, while the pH of reaction formulation comprising $[GaCl_3(BzMe_2\text{-tacn})]$ and KF in aqueous MeCN (unbuffered) was 5.9.



R = R' = Me: Me_3-tacn
R = Me, R' = Bz: $BzMe_2$-tacn

Scheme 2

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 $CDCl_3$ or CD_2Cl_2 unless otherwise stated, using a Bruker AV300 spectrometer. $^{19}F\{^1H\}$ 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 $[Al(H_2O)_6]^{3+}$ (104.3 MHz), aqueous $[Ga(H_2O)_6]^{3+}$ (122.0 MHz) and aqueous $[In(H_2O)_6]^{3+}$ at pH = 1 (87.7 MHz) respectively. Microanalyses were undertaken by Medac Ltd. Solvents were dried by distillation prior to use, CH_2Cl_2 from CaH_2, hexane from sodium benzophenone ketyl and MeCN from CaH_2. $MF_3 \cdot xH_2O$, MCl_3, MBr_3 and $[^nBu_4N]F$ (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. $[Me_4N]F$ (Aldrich) was dried by azeotropic 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-purged glove box.

Preparations

$[AlCl_3(Me_3\text{-tacn})]$. $AlCl_3$ (0.067 g, 0.50 mmol) was added to a solution of Me_3-tacn (0.086 g, 0.50 mmol) in CH_3CN (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_2Cl_2 solvent and dried *in vacuo*. Yield: 0.11 g, 72%. Colourless crystals were obtained by cooling the CH_3CN solution in the fridge for several days. Crystals were washed with CH_2Cl_2. Required for $C_9H_{21}AlCl_3N_3 \cdot 0.2CH_2Cl_2$: C, 34.4; H, 6.7; N, 13.1. Found: C, 34.2; H, 7.2; N, 13.9. ^1H NMR (CD_2Cl_2, 298 K): δ 3.23 (m, [6H], tacn-CH_2), 2.86 (s, [9H], CH_3), 2.67 (m, [6H], tacn-CH_2). IR (Nujol, ν/cm^{-1}): 389, 375 (Al–Cl).

$[AlF_3(Me_3\text{-tacn})] \cdot xH_2O$

Method 1. $AlF_3 \cdot 3H_2O$ (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 °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 $C_9H_{21}AlF_3N_3\cdot 3H_2O$: C, 34.9; H, 8.8; N, 13.6. Found: C, 34.3; H, 8.9; N, 14.7%. ^{1}H NMR (CD_3CN, 298 K): δ 2.84–2.76 (m, [6H], tacn-CH_2), 2.72–2.65 (m, [6H], tacn-CH_2), 2.55 (s, [9H], CH_3), 2.19 (s, H_2O). IR (Nujol, ν/cm^{-1}): 3438 br (H_2O), 1668 (H_2O), 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 [$AlCl_3$(Me_3-tacn)] (0.100 g, 0.33 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.

[$AlCl_3$($BzMe_2$-tacn)]. Method as for [$AlCl_3$(Me_3-tacn)] but using $AlCl_3$ (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 $C_{15}H_{25}A1Cl_3N_3$: C, 47.3; H, 6.6; N, 11.0. Found: C, 47.0; H, 6.6; N, 11.2. ^{1}H NMR (CD_2Cl_2, 298 K): δ 7.31 (m, [5H], ArH), 4.58 (s, [2H], Ar-CH_2), 3.54 (m, [2H], tacn-CH_2), 3.29 (m, [4H], tacn-CH_2), 2.92 (s, [6H], CH_3), 2.65 (m, [4H], tacn-CH_2), 2.28 (m, [2H], tacn-CH_2). IR (Nujol, ν/cm^{-1}): 398, 385 (Al–Cl).

[AlF_3($BzMe_2$-tacn)]. Method as for [AlF_3(Me_3-tacn)]$\cdot x H_2O$ above, using [$AlCl_3$($BzMe_2$-tacn)] and aqueous KF. ^{1}H NMR (CD_3CN, 298 K): δ 7.62 (m, [5H], ArH), 4.26 (s, [2H], Ar-CH_2), 3.01 (m, [4H], tacn-CH_2), 2.89 (m, [4H], tacn-CH_2), 2.85 (s, [6H], CH_3), 2.74 (m, [4H], tacn-CH_2), 1.53 (br s, H_2O). IR (Nujol, ν/cm^{-1}): 3392 br (OH), 1665 (H_2O), 1639 (Bz aromatic CC), 635, 601 (Al–F).

[$GaCl_3$(Me_3-tacn)]. Me_3-tacn (0.09 g, 0.52 mmol) was added to a solution of $GaCl_3$ (0.088 g, 0.50 mmol) in anhydrous CH_2Cl_2 (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 $C_9H_{21}Cl_3GaN_3$: C, 31.1; H, 6.1; N, 12.1. Found C, 31.2; H, 5.9; N, 12.1%. ^{1}H NMR (CD_2Cl_2, 298 K): δ 3.2 (br m, [6H], tacn-CH_2), 2.85 (br s, [9H], Me), 2.6 (br m, [6H], tacn-CH_2). IR (Nujol, ν/cm^{-1}): 290, 275 (Ga–Cl).

[GaF_3(Me_3-tacn)]$\cdot x H_2O$

Method 1. [$GaCl_3$(Me_3-tacn)] (0.1 g, 0.28 mmol) was added to CH_2Cl_2 (8 mL) and stirred for *ca.* 15 min, the solid mostly dissolved to give a clear solution. [N^{n}Bu$_4$]F in thf (1 mol dm^{-3}, 0.84 mL, 0.84 mmol) was added to the mixture *via* syringe and the reaction was stirred for *ca.* 10 min, giving a clear, colourless solution. The solution was filtered and the filtrate was taken to dryness *in vacuo*. The resulting colourless solid was re-dissolved in CH_2Cl_2, the solution was filtered and the CH_2Cl_2 was left to evaporate, giving a colourless solid product. Yield: 50%. Required for $C_9H_{21}F_3GaN_3\cdot 3H_2O$: C, 30.7; H, 7.7; N, 11.9. Found: C, 30.6; H, 6.9; N, 11.0%. ^{1}H NMR (CD_2Cl_2, 298 K): δ 2.85–2.94 (br m, [6H], tacn-CH_2), 2.67 (s, [9H], Me), 2.55–2.61 (br m, [6H], tacn-CH_2, 2.17 (s, H_2O)). IR (Nujol, ν/cm^{-1}): 3481, 3429 (H_2O), 1648 (H_2O), 530, 492 (Ga–F). Colourless crystals were grown from the CH_2Cl_2 solution of the product upon slow evaporation.

Method 2. [$GaCl_3$(Me_3-tacn)] (0.05 g, 0.15 mmol) was suspended in 5 mL anhydrous CH_2Cl_2. The suspension was treated with [NMe_4]F (0.042 g, 0.45 mmol) and stirred at room temperature for 1 h. The [NMe_4]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: 0.037 g, 74%. Spectroscopic data as for Method 1.

Method 3. [$GaCl_3$(Me_3-tacn)] (0.05 g, 0.15 mmol) was suspended in anhydrous MeCN (5 mL). A solution of KF (0.026 g, 0.45 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.

Method 4. $GaF_3\cdot 3H_2O$ (0.150 g, 0.83 mmol) was suspended in freshly distilled water (7 mL). Me_3-tacn (0.142 g, 0.83 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 yellow-brown solution 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: 0.21 g, 84%. ^{1}H NMR (CD_3CN, 298 K): δ 2.84 (m, [6H], tacn-CH_2), 2.72 (m, [6H], tacn-CH_2), 2.63 (s, [9H], CH_3). IR (Nujol, ν/cm^{-1}): 529, 492 (Ga–F).

[$GaCl_3$($BzMe_2$-tacn)]. Method as for [$GaCl_3$(Me_3-tacn)] but using $BzMe_2$-tacn (0.125 g, 0.50 mmol) and $GaCl_3$ (0.088 g, 0.50 mmol). White solid. Yield: 0.089 g, 42%. Required for $C_{15}H_{25}Cl_3GaN_3$: C, 42.5; H, 6.0; N, 9.9. Found C, 42.2; H, 6.0; N, 9.6%. ^{1}H NMR (CD_2Cl_2, 298 K): δ 7.30 (br m, [5H], ArH), 4.71 (s, [2H], Ar-CH_2), 3.67 (br, [2H], tacn-CH_2), 3.20 (br, [2H], tacn-CH_2), 2.92 (br s, [6H], CH_3), 2.75 (br m, [2H], tacn-CH_2), 2.62 (br m, [2H], tacn-CH_2), 2.40 (br m, [2H], tacn-CH_2). IR (Nujol, ν/cm^{-1}): 301, 280 (Ga–Cl).

[GaF_3($BzMe_2$-tacn)]$\cdot x H_2O$

Method 1. [$GaCl_3$($BzMe_2$-tacn)] (0.05 g, 0.10 mmol) was suspended in 5 mL anhydrous CH_2Cl_2. The suspension was treated with [NMe_4]F (0.03 g, 0.30 mmol) and stirred at room temperature for 1 h. The [NMe_4]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: 0.035 g, 80%. Required for $C_{15}H_{25}F_3GaN_3\cdot 4H_2O$: C, 40.4; H, 8.8; N, 8.6. Found C, 40.9; H, 8.8; N, 8.6%. ^{1}H NMR (D_2O, 298 K): δ 7.30 (m, [5H], ArH), 4.73 (s, [2H], Ar-CH_2), 3.17 (m, [4H], tacn-CH_2), 2.88 (m, [4H], tacn-CH_2), 2.73 (s, [6H], CH_3), 2.36 (m, [4H], tacn-CH_2), 2.25 (s, H_2O). IR (Nujol, ν/cm^{-1}): 3390, 1654 (H_2O), 526, 515 (Ga–F).

Method 2. As described for [GaF_3(Me_3-tacn)] Method 3, using [$GaCl_3$($BzMe_2$-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.

[$InCl_3$(Me_3-tacn)]. Method as for [$GaCl_3$(Me_3-tacn)], but using Me_3-tacn (0.086 g, 0.50 mmol) and $InCl_3$ (0.110 g, 0.50 mmol). White solid. Yield: 0.113 g, 57%. Required for $C_9H_{21}Cl_3InN_3$: C, 27.5; H, 5.4; N, 10.7. Found C, 27.8; H, 5.4; N, 10.9%. ^{1}H NMR ($CDCl_3$, 298 K): δ 3.1 (br m, [6H], tacn-CH_2), 2.8 (br m, [15H], Me and tacn-CH_2). IR (Nujol, ν/cm^{-1}): 287, 269 (In–Cl).

[$InF_3(Me_3$-tacn)]·xH_2O

Method 1. [$InCl_3(Me_3$-tacn)] (0.214 g, 0.54 mmol) was added to CH_2Cl_2 (8 mL) and stirred for *ca.* 15 min, this gave a cloudy suspension. [N^nBu_4]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 $C_9H_{21}F_3InN_3\cdot H_2O$: C, 29.9; H, 6.4; N, 11.6. Found: C, 29.9; H, 6.1; N, 11.5%. ^{1}H NMR (CD_2Cl_2, 298 K): δ 3.09–3.15 (br m, [6H], tacn-CH_2), 2.93 (m, [9H], Me), 2.72–2.82 (br m, [6H], tacn-CH_2), 2.19 (s, H_2O). IR (Nujol, ν/cm^{-1}): 3392 br (H_2O), 1669 (H_2O), 479, 462, 443 (In–F). Colourless crystals were grown from the CH_2Cl_2 solution of the product upon slow evaporation.

Method 2. [$InCl_3(Me_3$-tacn)] (0.060 g, 0.17 mmol) was suspended in 5 mL anhydrous CH_2Cl_2. The suspension was treated with [NMe_4]F (0.047 g, 0.51 mmol) and stirred at room temperature for 1 h. The [NMe_4]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), $InF_3\cdot 3H_2O$ (0.200 g, 0.90 mmol) and Me_3-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.

[$InCl_3(BzMe_2$-tacn)]. Method as for [$GaCl_3(Me_3$-tacn)], but using $BzMe_2$-tacn (0.125 g, 0.50 mmol) and $InCl_3$ (0.110 g, 0.50 mmol). White solid. Yield: 0.093 g, 40%. Required for $C_{15}H_{25}Cl_3InN_3$: C, 38.5; H, 5.4; N, 9.0. Found C, 38.8; H, 5.8; N, 8.7%. ^{1}H NMR (CD_3CN, 298 K): 7.2–7.4 (m, [5H], ArH), 4.37 (s, [2H], Ar-CH_2), 3.45 (br, [2H], tacn-CH_2), 3.10 (br, [2H], tacn-CH_2), 2.80 (s, [6H], CH_3), 2.75 (br m, [2H], tacn-CH_2), 2.60 (br m, [2H], tacn-CH_2), 2.40 (br m, [2H], CH_2). IR (Nujol, ν/cm^{-1}): 289, 271 (In–Cl). Crystals formed from the CH_2Cl_2 solution of the product stored in the freezer at −18 °C.

[$InF_3(BzMe_2$-tacn)]·xH_2O. [$InCl_3(BzMe_2$-tacn)] (0.06 g, 0.10 mmol) was suspended in 5 mL anhydrous CH_2Cl_2. The suspension was treated with [NMe_4]F (0.03 g, 0.30 mmol) and stirred at room temperature for 1 h. The [NMe_4]Cl by-product was removed by filtration. The resulting colourless filtrate was treated with 5 mL anhydrous hexane, forming in a white precipitate which was isolated by filtration, washed with hexane and dried *in vacuo*. Yield: 0.02 g, 48%. $C_{15}H_{25}F_3InN_3\cdot 3H_2O$: C, 38.1; H, 6.6; N, 8.9. Found C, 37.6; H, 5.2; N, 8.6%. ^{1}H NMR (CD_3CN, 298 K): 7.37 (m, [5H], ArH), 4.37 (s, [2H], Ar-CH_2), 3.08 (m, [6H], CH_3), 2.91 (m, [4H], tacn-CH_2), 2.80 (m, [4H], tacn-CH_2), 2.64 (m, [4H], tacn-CH_2). IR (Nujol, ν/cm^{-1}): 3450 v br (H_2O), 1651 (H_2O), 481, 463 (In–F).

F-18 radiolabelling of [$GaCl_3(BzMe_2$-tacn)]

Experiments were analysed on a Gilson 322 HPLC system with a Gilson 156 UV detector. Dionex Chromeleon 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 [$GaCl_3(BzMe_2$-tacn)] (0.001 g, 2.36 μmol) was dissolved in a mixture of MeCN (0.5 mL) and H_2O (0.1 mL). This solution was added to 0.4 mL of an aqueous solution containing [^{18}F]–KF (100 to 500 MBq) and [^{19}F]–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 ($^{18}F^-$). 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/NH_4OAc): found *m*/*z* = 354 [$GaF_2(BzMe_2$-tacn)]$^+$; 391 [$GaF_3(BzMe_2$-tacn) + NH_4]$^+$. 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 (N_2 cryostream) or a Bruker-Nonius FR591 rotating anode diffractometer fitted with confocal mirrors and with the crystal held at 120 K (N_2 cryostream). Mo-K_α X-radiation (λ = 0.71073 Å). Structure solution and refinement were generally routine,[20,21] except as described below, with hydrogen atoms on C added to the model in calculated positions and using the default C–H distance. For [$AlCl_3(Me_3$-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 [$InCl_3(BzMe_2$-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, $MF_3 \cdot 3H_2O$, 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.[10] Notable exceptions include *mer*-[GaF_3(pyridine)$_3$] (prepared by prolonged refluxing of the constituents in thf),[22] [GaF_3{1,4,7-tris(2-amino-3,5-di-butylbenzyl)-1,4,7-triazacyclononane}],[23] and direct reaction of $InF_3 \cdot 3H_2O$ with 2,2′-bipy or 1,10-phen (L–L) forms the distorted octahedral species [InF_3(L–L)(H_2O)].[24] Diimine and amine complexes of MF_3 (M = Al, Ga, In) have been obtained using hydrothermal syntheses at elevated temperature (~180 °C),[25] while reaction of AlN or InN and NH_4F in supercritical ammonia (400 °C) forms [$AlF_3(NH_3)_2$] and [$InF_2(NH_2)(NH_3)$] respectively.[26]

Direct reaction of $AlF_3 \cdot 3H_2O$ and Me_3-tacn under hydrothermal conditions (180 °C, 15 h) led to formation of [AlF_3(Me_3-tacn)]$\cdot 4H_2O$ as a white solid in good yield. The IR spectrum shows two bands in the far-IR region attributed to the a_1 and e stretching modes from the *facial* MF_3 unit of a distorted octahedron (C_{3v}). There is also clear evidence for H-bonded H_2O, which turn out to be an important feature of these complexes and is described in more detail below. The ^{1}H NMR spectrum (CD_3CN) is characteristic of *facially* coordinated Me_3-tacn. NMR spectroscopic measurements in D_2O also confirm the stability of the trifluoro species in aqueous solution. The ^{27}Al [$I = 5/2$, 100% abundance, $Q = 0.149 \times 10^{-28}$ m^2, $R_C = 1170$] and ^{19}F{^{1}H} 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 Me_3-tacn ligand and three *fac* F^- ligands (Fig. 1(a)).

The asymmetric unit contains four H_2O molecules as well as one [AlF_3(Me_3-tacn)] molecule. The water molecules are involved in an array of H-bonding interactions both with the F atoms in the [AlF_3(Me_3-tacn)], as well as between the H_2O molecules themselves, giving $H_2O\cdots F1 = 2.806(3)$, $H_2O\cdots F2 = 2.701(3)$, $H_2O\cdots F3 = 2.688(3)$, $H_2O\cdots F1 = 2.802(4)$ Å. This gives rise to the extensively H-bonded array illustrated in Fig. 1(b).

The GaF_3 analogue, [GaF_3(Me_3-tacn)]$\cdot 4H_2O$, obtained and characterised similarly, also crystallises as a tetrahydrate (below). These [MF_3(Me_3-tacn)]$\cdot 4H_2O$ species are remarkably stable in the solid and also in solution in H_2O, CH_2Cl_2, 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 [MF_3(Me_3-tacn)] (M = Al, Ga or In), by virtue of the M–F bonds formed being stronger than those involving the heavier halides.[10]

In order to test this idea, the complexes, *fac*-[MX_3(Me_3-tacn)] (M = Al, Ga, In; X = Cl, Br) and [MX_3($BzMe_2$-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 MX_3 with the triaza macrocycle in anhydrous CH_2Cl_2 or MeCN. Confirmation of their identities follows from microanalyses, IR and ^{1}H NMR spectroscopic data and from crystal structures of representative examples.

Multinuclear solution ^{27}Al, ^{71}Ga and ^{115}In 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 ^{27}Al and ^{71}Ga [$I = 3/2$, 39.6% abundance, $Q = 0.112 \times 10^{-28}$ m^2, $R_C = 322$] nuclei. This is consistent with the proposed distorted six-coordinate geometry with local C_{3v} symmetry, leading to the electric field gradient (EFG) being close to zero, and hence relatively sharp lines.[27] The ^{115}In NMR spectra were less informative due to the much larger quadrupole moment, which sometimes led to the resonance not being observed for [InX_3(R_3-tacn)] (X = Cl or Br) [^{115}In: $I = 9/2$, 95.7% abundance, $Q = 1.16 \times 10^{-28}$ m^2, $R_C = 1920$]. 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 1 Multinuclear NMR spectroscopic data

Complex	δ^{27}Al/^{71}Ga/^{115}In/ppm; ($w_{1/2}$/Hz)	δ^{19}F{^{1}H} (ppm)	Solvent
[AlF_3(Me_3-tacn)]	19.0 (60); 18.5 (52)	−176.1; −169.9	MeCN; D_2O
[$AlCl_3$(Me_3-tacn)]	34.5 (30)	—	CH_2Cl_2
[$AlBr_3$(Me_3-tacn)]	18.9 (80)	—	CH_2Cl_2
[GaF_3(Me_3-tacn)]	42.0 (q, $^1J_{GaF} \sim 490$ Hz); 44.6 (br q)	−180.9 (two br q); −173 (br)	CH_2Cl_2; D_2O
[$GaCl_3$(Me_3-tacn)]	93.9 (60)	—	CH_2Cl_2
[$GaBr_3$(Me_3-tacn)]	−29.3 (180)	—	MeCN
[InF_3(Me_3-tacn)]	64 (q, $^1J_{InF} \sim 600$ Hz); n.o.	−215 (br); −192.5 (br)	MeCN; D_2O
[$InCl_3$(Me_3-tacn)]	268 (750)	—	CH_2Cl_2
[$InBr_3$(Me_3-tacn)]	n.o.[a]	—	MeCN
[AlF_3($BzMe_2$-tacn)]	19.8 (100)	−161.5 (F), −161.7 (2F)	MeCN
[$AlCl_3$($BzMe_2$-tacn)]	36.5 (45)	—	CH_2Cl_2
[$AlBr_3$($BzMe_2$-tacn)]	20.1 (35)	—	CH_2Cl_2
[GaF_3($BzMe_2$-tacn)]	44.9 (q $^1J_{GaF} \sim 445$Hz)	−172.8 (br)	D_2O
[$GaCl_3$($BzMe_2$-tacn)]	92.8 (360)	—	MeCN
[InF_3($BzMe_2$-tacn)]	n.o.[a]	−220 (br)	MeCN
[$InCl_3$($BzMe_2$-tacn)]	265 (2200)	—	MeCN

[a] n.o. = not observed.

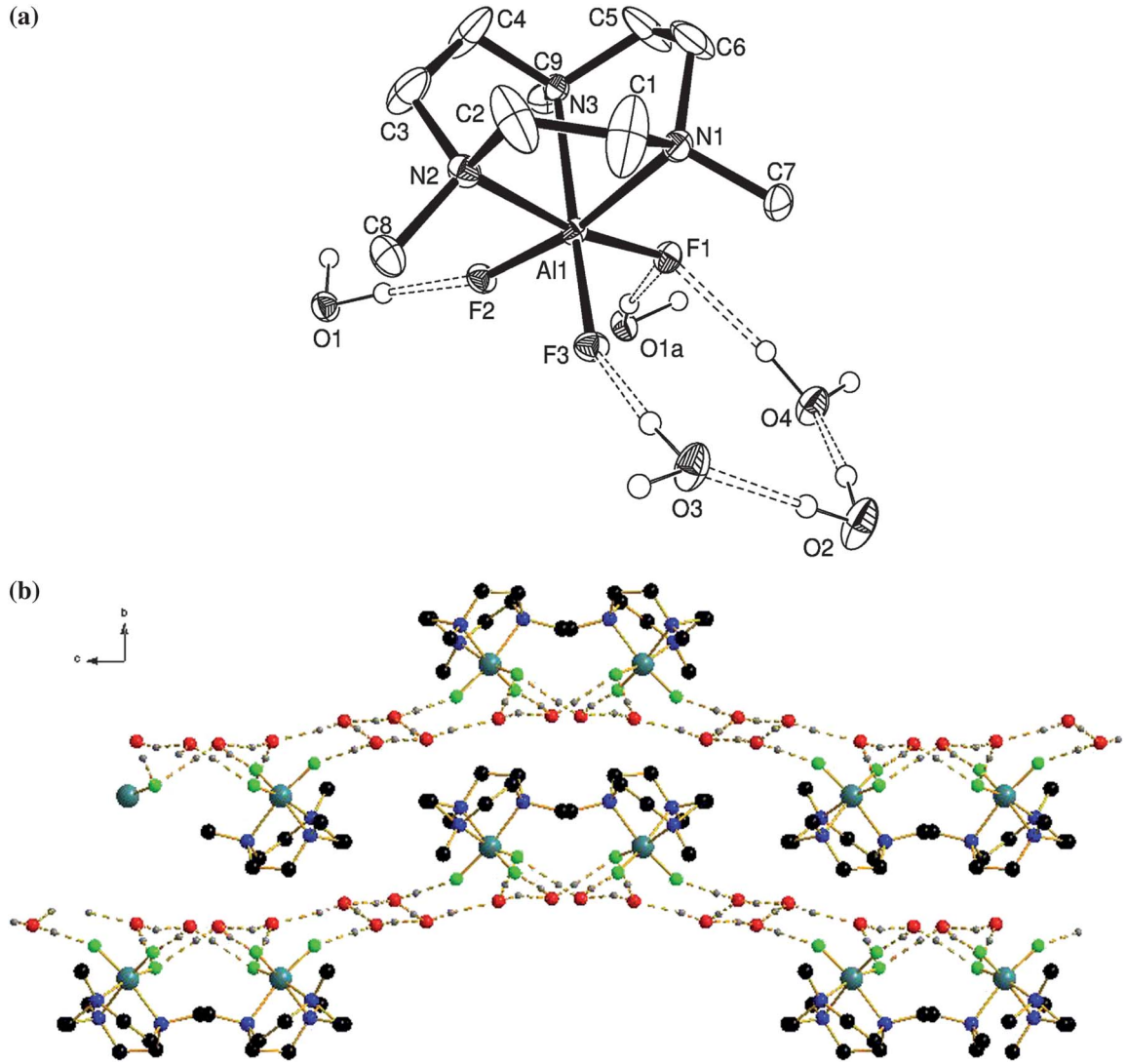


Fig. 1 (a) Structure of $[AlF_3(Me_3\text{-tacn})]\cdot 4H_2O$ showing the atom labelling scheme. Ellipsoids are drawn at the 40% probability level and H atoms bonded to C are omitted for clarity. (b) View along the *a*-axis of the extended structure assembled through intermolecular H-bonding (colour key: teal = Al, green = F, blue = N, red = O, black = C).

complexes are stable in anhydrous CH_2Cl_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 $[GaX_3(Me_3\text{-tacn})]$ (X = Cl or Br) produces the face-sharing bioctahedral dimers $[\{(Me_3\text{-tacn})Ga\}_2(\mu\text{-OH})_3]X_3\cdot 3CH_2Cl_2$, and the crystal structure of the Br derivative was also determined (ESI†). Wieghardt and co-workers have described the hydrolysis of $[InCl_3(Me_3\text{-tacn})]$ 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_3SiF and Me_3SnF are often convenient fluoride sources in synthetic chemistry, *e.g.* $[AlCl_3(py)_n]$ (n = 1 to 3) and Me_3SiF in pyridine affords $[AlF_2(py)_4]Cl$.[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 $Na^{18}F$ (or $K^{18}F$ or $R_4N^{18}F$). 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 $[N^nBu_4]F$ to a suspension of $[MCl_3(R_3\text{-tacn})]$ 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 $^{19}F\{^1H\}$ NMR studies (Table 2) show complete conversion to $[GaF_3(R_3\text{-tacn})]$. 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 ($\delta^{71}Ga = 42.0$, $^1J_{GaF} \sim 490$ Hz – Fig. 2), and although not fully resolved, the $^{19}F\{^1H\}$ NMR spectrum shows a single resonance (−180.0 ppm) with coupling to $^{69/71}Ga$, providing unequivocal evidence for formation of $[GaF_3(Me_3\text{-tacn})]$.

Table 2 Key structural data for $[MX_3(L)]$

Complex	d(M–X)/Å	d(M–N)/Å	∠(X–M–X)/°	∠(N–M–N)/°
$[AlF_3(Me_3\text{-tacn})]\cdot 4H_2O$	1.740(2), 1.744(2), 1.757(2)	2.098(3), 2.106(3), 2.115(3)	96.65(12), 96.00(11), 95.81(12)	82.20(13), 82.13(13), 82.37(13)
$[AlCl_3(Me_3\text{-tacn})]$	2.267(2), 2.274(2), 2.276(2)	2.111(3), 2.126(4), 2.141(4)	94.03(7), 93.74(6), 94.21(7)	83.03(14), 81.64(14), 81.97(14)
$[GaF_3(Me_3\text{-tacn})]\cdot 4H_2O$	1.851(3), 1.858(3), 1.881(3)	2.126(4), 2.126(4), 2.140(4)	95.81(12), 94.87(13), 94.23(12)	82.2(1), 82.4(2), 81.6(2)
$[GaCl_3(Me_3\text{-tacn})]$	2.3087(5), 2.3177(9), 2.3217(5)	2.1644(13), 2.1755(13), 2.1960(14)	94.38(2), 93.98(2), 94.49(2)	81.90(5), 80.80(5), 80.83(5)
$[InF_3(Me_3\text{-tacn})]\cdot 4H_2O$	2.0318(11), 2.0391(12), 2.0570(11)	2.287(2), 2.289(2), 2.291(2)	96.33(5), 95.04(5), 94.79(5)	78.68(6), 78.91(6), 78.44(6)
$[InBr_3(Me_3\text{-tacn})]\cdot CH_2Cl_2$	2.5987(8), 2.6006(8), 2.6046(8)	2.344(4), 2.345(5), 2.347(4)	96.66(3), 95.06(2), 96.15(3)	76.4(2), 76.8(2), 76.2(2)
$[InF_3(BzMe_2\text{-tacn})]\cdot 1.2H_2O$	2.4443(13), 2.4518(14), 2.4581(14)	2.312(4), 2.342(4), 2.371(4)	96.72(5), 96.72(5), 98.24(5)	77.96(6), 77.14(6), 77.80(6)
$[InCl_3(BzMe_2\text{-tacn})]$	2.4443(13), 2.4518(14), 2.4581(14)	2.312(4), 2.342(4), 2.371(4)	95.32(5), 96.26(5), 98.31(5)	77.1(2), 77.4(2), 76.3(2)

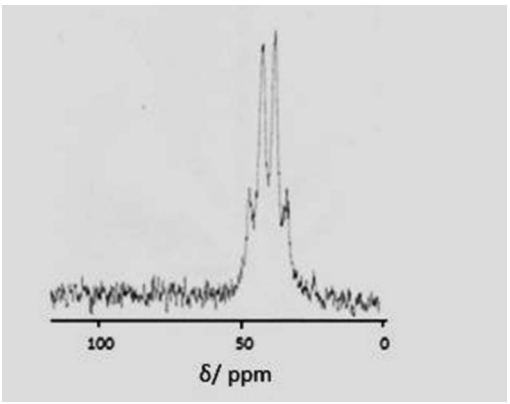


Fig. 2 ^{71}Ga NMR spectrum of $[GaF_3(Me_3\text{-tacn})]$ (CH_2Cl_2) showing the quartet coupling ($^1J_{GaF} \sim 490$ Hz).

Notably, like $[AlF_3(Me_3\text{-tacn})]$, $[GaF_3(Me_3\text{-tacn})]$ also crystallises as a tetrahydrate, $[GaF_3(Me_3\text{-tacn})]\cdot 4H_2O$ (Fig. 3), with an extensive H-bonding array involving intermolecular O···F and O···O interactions.

The $[GaF_3(R_3\text{-tacn})]$ 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_2O.

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 $[N^nBu_4]Cl$). Addition of aqueous KF to a suspension of $[GaCl_3(R_3\text{-tacn})]$ 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 $[InCl_3(R_3\text{-tacn})]$ 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 $[InF_3(Me_3\text{-tacn})]$ shows a well-resolved 1 : 3 : 3 : 1 quartet (Fig. 4) at 64 ppm ($^1J_{InF} \sim 600$ Hz), confirming the complete exchange of Cl^- for F^-.

Both $[InF_3(Me_3\text{-tacn})]\cdot 4H_2O$ (Fig. 5) and $[InF_3(BzMe_2\text{-tacn})]\cdot 1.2H_2O$ (Fig. 6) were also characterised crystallographically. Although none of the $[MF_3(Me_3\text{-tacn})]$ 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 $[InF_3(BzMe_2\text{-tacn})]\cdot 1.2H_2O$, shows the H_2O molecules form significant interactions with F1 and F2, F···H–OH ∼ 2.8 Å.

Unlike the Ga and In analogues, $[AlCl_3(Me_3\text{-tacn})]$ does not react with either $[N^nBu_4]F$ 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 $^{19}F\{^1H\}$ and ^{27}Al NMR spectra for formation of $[AlF_3(Me_3\text{-tacn})]$ 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 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 $[AlCl_3(Me_3\text{-tacn})]$ does lead to clean conversion to form $[AlF_3(Me_3\text{-tacn})]$ at room temperature, the spectroscopic signature of the product matching that formed *via* hydrothermal synthesis from $AlF_3\cdot 3H_2O$ (above). This suggests that the more polar (*cf.* MeCN) H_2O solvent is involved in a solvent assisted substitution mechanism.[30]

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 $[GaCl_3(BzMe_2\text{-tacn})]$ 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 $[GaCl_3(BzMe_2\text{-tacn})]$ in aqueous MeCN, adding 2.99 mol equiv.

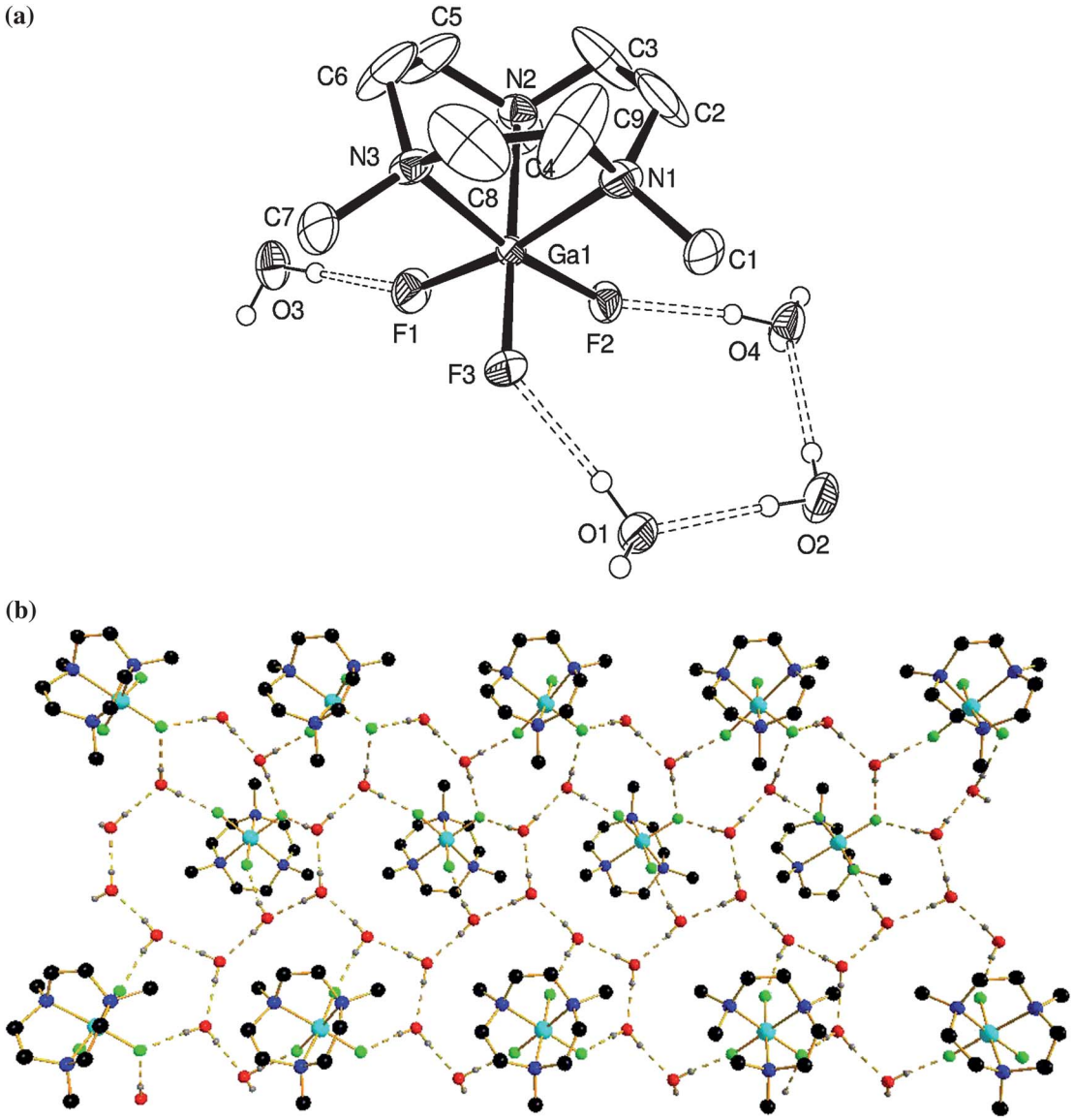


Fig. 3 (a) View of the structure of $[GaF_3(Me_3\text{-tacn})]\cdot 4H_2O$ with numbering scheme adopted. Ellipsoids are shown at the 40% probability level and H atoms (except those on the H_2O molecules) are omitted for clarity. (b) View down the *c*-axis of the extended structure showing the H-bonding interactions (colour key: turquoise = Ga, green = F, blue = N, red = O, black = C).

of aqueous $[^{19}F]$–KF and 0.4 mL of $[^{18}F]$–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 Rt = 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_4OAc–MeCN mobile phase, giving a single peak in the radio-chromatograph at Rt = 6.1 min. ESI^+ mass spectrometric analysis of this species post elution gave an *m*/*z* and isotope pattern consistent with the species $[GaF_3(BzMe_2\text{-tacn}) + NH_4]^+$ (*m*/*z* = 391; 100%) – see ESI.† The presence of associated $[NH_4]^+$ in these species was also confirmed from independent mass spectrometry experiments on the preformed $[GaF_3(BzMe_2\text{-tacn})]$ complex with and without added cation. Thus, introduction of one mol equiv. of $[NH_4][PF_6]$ 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···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 $[Ca(AsF_3)(AsF_6)_2]$, 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 $[AsF_6]^-$ anions).[31]

The purified species was dried under vacuum and treated with phosphate buffered saline (PBS) and ethanol, giving a

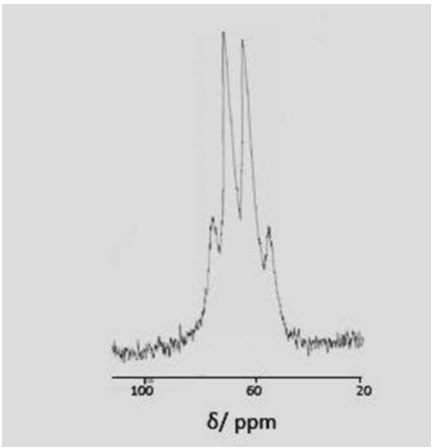


Fig. 4 ^{115}In NMR spectrum of $[InF_3(Me_3\text{-tacn})]$ (MeCN). The splitting pattern arises through the coupling of three equivalent fluorides to the indium centre ($^1J_{InF} \sim 600$ Hz).

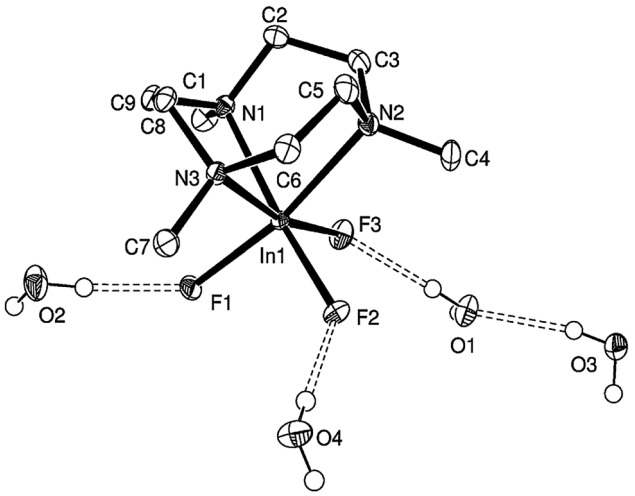


Fig. 5 View of the structure of $[InF_3(Me_3\text{-tacn})]\cdot 4H_2O$ with numbering scheme adopted and showing the F···H–O interactions. Ellipsoids are shown at the 40% probability level and H atoms (except those on the H_2O molecules) are omitted for clarity.

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 $[MX_3(R_3\text{-tacn})]$ 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 $[MX_3(R_3\text{-tacn})]$ were therefore determined for a range of M with X = Cl or Br,

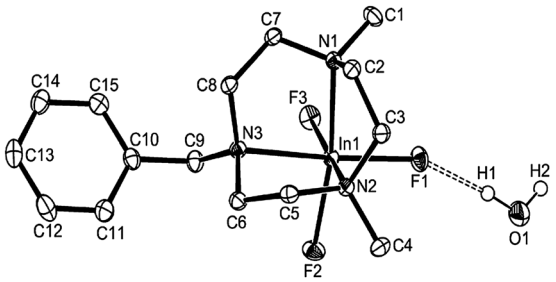


Fig. 6 Structure of $[InF_3(BzMe_2\text{-tacn})]\cdot H_2O$ with atom numbering scheme. Ellipsoids are shown at the 50% probability level and H atoms (except those on O1) are omitted for clarity.

specifically for $[MX_3(Me_3\text{-tacn})]$ (M = Al, X = Cl; M = Ga, X = Cl; M = In, X = Br) – Fig. 7 and ESI, and for $[InCl_3(BzMe_2\text{-tacn})]$ (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–N and M–F distances within the series $[MF_3(Me_3\text{-tacn})]\cdot 4H_2O$ (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 (Al^{3+} = 0.535 Å; Ga^{3+} = 0.62 Å; In^{3+} = 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 $[AlF_3(Me_3\text{-tacn})]\cdot 4H_2O$ with those in $[AlCl_3(Me_3\text{-tacn})]$ reveals a very small increase of only ~0.02 Å, whereas in the Ga systems $[GaF_3(Me_3\text{-tacn})]\cdot 4H_2O$ the Ga–N distances are *ca.* 0.04–0.05 Å shorter than in $[GaCl_3(Me_3\text{-tacn})]$. These observations suggest that the 9-membered triaza

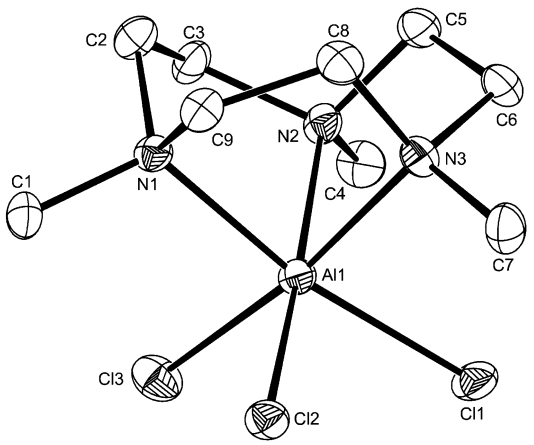


Fig. 7 Structure of $[AlCl_3(Me_3\text{-tacn})]$ with atom numbering scheme. Ellipsoids are shown at the 50% probability level and H atoms are omitted for clarity.

macrocycle 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_2O) 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 angles involving halide ligands are ~94–98°, with no obvious trend with changing X or M. In contrast, the N–M–N angles in the Al^{3+} and Ga^{3+} complexes are essentially invariant (~82°), while those involving In^{3+} are rather more acute, ~77°, reflecting the elongated In–N bond distances.

Conclusions and outlook

This work has shown that direct fluorination of the distorted octahedral Group 13 tacn-based complexes, $[MCl_3(R_3\text{-tacn})]$ (M = Al, Ga, In) occurs cleanly and rapidly at room temperature in aqueous MeCN using KF (as well as in MeCN solution *via* $[NR_4]F$) to produce very stable $[MF_3(R_3\text{-tacn})]$ complexes, all of which are isolated as hydrates. We have also shown that radiolabelling an aqueous solution of $[GaF_3(BzMe_2\text{-tacn})]$ with F-18 doped $[^{19}F]$–KF leads to *ca.* 30% incorporation of F-18, forming $[GaF_3(BzMe_2\text{-tacn})]$ 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[9] 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 $[GaCl_3(Me_2Bz\text{-tacn})]$ complex, whereas McBride *et al.* in their systems[6] 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.

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