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Synthesis and Structural Characterization of Complexes of a DO3A-Conjugated Triphenylphosphonium Cation with Diagnostically Important Metal Ions

Chang-Tong Yang¹, Yongxin Li², and Shuang Liu^{1,*}

¹ School of Health Sciences, Purdue University, West Lafayette, Indiana, USA

² School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore

Abstract

To understand the coordination chemistry of a DO3A-conjugated triphenylphosphonium (TPP) cation, triphenyl(4-((4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)phosphonium (DO3A-xy-TPP), with diagnostically important metal ions, In(DO3A-xy-TPP)⁺, Ga(DO3A-xy-TPP)⁺ and Mn(DO3A-xy-TPP) were prepared by reacting DO3A-xy-TPP with one equivalent of the respective metal salt. All three complexes have been characterized by elemental analysis, IR, ESI-MS, NMR methods for In(DO3A-xy-TPP)⁺ and Ga(DO3A-xy-TPP)⁺, and X-ray crystallography. Results from HPLC concordance experiments show that ¹¹¹In(DO3A-xy-TPP)⁺ and In(DO3A-xy-TPP)⁺ have the same composition. The solid state structures of In(DO3A-xy-TPP)⁺ and Mn(DO3A-xy-TPP) are very similar with DO3A being heptadentate in bonding to In(III) and Mn(II) in a monocapped octahedral coordination geometry. Because of the smaller size of Ga(III), the DO3A in Ga(DO3A-xy-TPP)⁺ is only hexadentate with four amine-N and two carboxylate-O atoms bonding to Ga(III). One carboxylic acid group in DO3A is deprotonated to in order balance the positive charge of Ga(III). The coordination geometry of Ga(DO3A-xy-TPP)⁺ is best described as a distorted octahedron. The NMR data shows that the coordinated DO3A in In(DO3A-xy-TPP)⁺ and Ga(DO3A-xy-TPP)⁺ is symmetrical in aqueous solution. There is no dissociation of the acetate chelating arms in In(DO3A-xy-TPP)⁺ and Ga(DO3A-xy-TPP)⁺, providing indirect evidence for the high solution stability of ¹¹¹In(DO3A-xy-TPP)⁺ and ⁶⁸Ga(DO3A-xy-TPP)⁺.

INTRODUCTION

Alteration in the electric component or mitochondrial membrane potential ($\Delta\Psi_m$) is an important characteristic of cancer caused directly by mitochondrial dysfunction, such as DNA mutation and oxidative stress.^{1–4} It has been reported that the mitochondrial transmembrane potential in carcinoma cells is significantly higher than that in normal epithelial cells.^{5–9} For example, the difference in $\Delta\Psi_m$ between the CX-1 colon carcinoma cells and the control green monkey kidney epithelial cell line was approximately 60 mV (163 mV in tumor cells vs. 104 mV in normal cells). The observation that the enhanced mitochondrial transmembrane potential is prevalent in tumor cell phenotype provides the conceptual basis for development of mitochondrial targeting diagnostic and therapeutic pharmaceuticals.^{1–3, 10–13}

Measurement of mitochondrial transmembrane potential ($\Delta\Psi_m$) provides the most comprehensive reflection of mitochondrial bio-energetic function primarily because it depends

* To whom correspondence should be addressed. School of Health Sciences, Purdue University, 550 Stadium Mall Drive, West Lafayette, IN 47907. Phone: 765-494-0236; Fax 765-496-1377; Email: lius@pharmacy.purdue.edu.

directly on the proper integration of diverse metabolic pathways that converge at mitochondria. Since the plasma and mitochondrial transmembrane potentials are negative, delocalized cationic molecules with appropriate structural features are driven electrophoretically through these membranes and tend to accumulate inside the energized mitochondria.^{1–4, 11} For example, lipophilic cations, such as rhodamine-123 and ³H-tetraphenylphosphonium (³H-TPP), have been widely used to measure mitochondrial potentials in tumor cells.^{1, 14–16} According to the Nernst equation, the 60 mV difference in $\Delta\Psi_m$ between carcinoma and control epithelial cell is theoretically sufficient to account for a 10-fold greater accumulation of cationic compounds in carcinoma mitochondria than in normal cells.^{1–4, 11} In addition, the plasma membrane potential (30 – 90 mV) also pre-concentrates cationic species relative to the external medium, thus affecting the cytoplasmic concentration of these compounds and their availability for mitochondrial uptake.

Recently, several groups reported the use of radiolabeled triphenylphosphonium (TPP) cations, such as 4-(¹⁸F-benzyl)triphenylphosphonium (Figure 1: ¹⁸F-BzTPP), as positron emission tomography (PET) potential radiotracers for tumor and heart imaging.^{17–25} Even though ³H-tetraphenylphosphonium (Figure 1: ³H-TPP) was reported to have a better tumor uptake than ^{99m}Tc-Sestamibi, its tumor selectivity is very poor with the tumor/heart ratio being <0.2.^{19, 23} In addition, ³H-TPP is not suitable for imaging purposes. The high uptake of ¹⁸F-BzTPP in the heart and liver may also impose a significant challenge for its clinical applications in diagnosis of cancer in the chest and abdominal regions. Thus, there is an urgent need for new radiotracers that have high tumor-selectivity, and are able to provide information of mitochondrial bio-energetic function in tumors by monitoring mitochondrial potential in a noninvasive fashion.

Previously, we reported several ⁶⁴Cu-labeled triphenylphosphonium (TPP) cations, such as ⁶⁴Cu(DO3A-xy-TPP) (Figure 1: DO3A-xy-TPP = triphenyl(4-((4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzyl)phosphonium), as new radiotracers for imaging tumor by positron emission tomography (PET).²⁶ The TPP moiety acts as the “mitochondrion-targeting biomolecule” to carry ⁶⁴Cu into tumor cells.²⁶ DO3A is used as the bifunctional chelator since it is able to form highly stable radiometal chelates with radionuclides, such as ⁶⁴Cu and ⁶⁸Ga for PET, ¹¹¹In for single photon emission computed tomography (SPECT), ⁹⁰Y and ¹⁷⁷Lu for radiotherapy. Biodistribution and microPET imaging studies have demonstrated that the ⁶⁴Cu-labeled TPP cations are able to localize in tumors with high tumor uptake (2 – 3.5 %ID/g) and high tumor selectivity (tumor/heart ratio $\approx$ 5:1 at 2 h postinjection as compared to tumor/heart ratio being <0.2 during the 2 h study period for ^{99m}Tc-Sestamibi). The high tumor selectivity of the ⁶⁴Cu-labeled TPP cations is related to their low lipophilicity.²⁶ The *in vitro* assay data show that ⁶⁴Cu(DO3A-xy-TPP) is able to localize in mitochondria of U87MG glioma cells. The ¹¹¹In-labeled TPP cations also have high tumor uptake; but their tumor selectivity is not as good as that of their ⁶⁴Cu analogs.²⁷

In our previous report,²⁶ we described the synthesis of Cu(DO3A-xy-TPP) as part of the characterization of ⁶⁴Cu-labeled TPP cations. However, we were not able to obtain crystals of Cu(DO3A-xy-TPP) suitable for structural determination by X-ray crystallography. In order to understand the coordination chemistry of DO3A-conjugated TPP cations with diagnostically important metals and the impact of radiometal chelates on biological properties of the radiolabeled TPP cations, we prepared In(III), Ga(III) and Mn(II) complexes of DO3A-xy-TPP. We are interested in Ga(III) and In(III) complexes because of their potential applications as PET (⁶⁸Ga) and SPECT (⁶⁷Ga and ¹¹¹In) radiotracers. The Mn(II) complex is of our particular interest for its potential as a magnetic resonance imaging (MRI) contrast agent and its similarity to that of its Cu(II) analog with respect to molecular charge. In this report, we present the synthesis and structural characterization of M(DO3A-xy-TPP)⁺ (M = Ga and In) and Mn(DO3A-xy-TPP). The main objective of this study is to determine their structures in

both solid state and solution. Biodistribution and imaging data for ^{64}Cu -labeled TPP cations has been described previously.²⁶ Biological evaluation for the ^{111}In -labeled TPP cations will be reported as a separate account.²⁷

EXPERIMENTAL SECTION

Materials and Instruments

Chemicals were obtained from *Sigma/Aldrich* (St. Louis). 1,4,7,10-Tetraazacyclododecane-4,7,10-tris(*t*-butyl acetate) ($\text{DO3A}(\text{O}i\text{Bu}-t)_3$) was purchased from Macrocyclics Inc. (Dallas, TX). NMR (^1H , ^{13}C , ^{31}P , ^1H - ^1H COSY, HMQC, HSQC, HMBC, NOESY) data were obtained using a Bruker DRX 300 MHz and a Bruker Avance 500 MHz FT NMR spectrometer. Chemical shifts are reported in ppm relative to TMS. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer. Mass spectra were collected using positive mode on a Finnigan LCQ classic mass spectrometer, School of Pharmacy, Purdue University. Elemental analysis was performed by Dr. H. Daniel Lee using a Perkin-Elmer Series III analyser, Department of Chemistry, Purdue University.

HPLC Method

The HPLC method used equipped with a UV/vis detector ($\lambda = 254 \text{ nm}$), a β -ram IN-US detector and a Zorbax Rx-C18 column (4.6 mm $\times$ 150 mm, 300 Å pore size). The flow rate was 1 mL/min with the mobile phase being isocratic with 80% solvent A (10 mM ammonium acetate) and 20% solvent B (acetonitrile) at 0 – 5 min, followed by a gradient mobile phase going from 20% B at 5 min to 60% B at 20 min.

In(DO3A-xy-TPP)(OAc)

DO3A-xy-TPP was prepared according to the procedure described in our previous report.²⁶ DO3A-xy-TPP (71.1 mg, 0.1 mmol) and $\text{In}(\text{OAc})_3$ (29.1 mg, 0.1 mmol) were dissolved in 0.2 mL NH_4OAc buffer (0.5 M, pH = 6.0). The mixture was stirred and heated at 100 °C for 30 min. After filtration, the filtrate was transferred into a clean 5 mL vial. Slow diffusion of acetone into the reaction mixture produced colorless crystals suitable for X-ray crystallography. The solid was separated by filtration and dried under vacuum overnight before being submitted for elemental analysis. The yield was 52.2 mg (~63.5 %). A sample was analyzed by HPLC. The HPLC retention time was 14.7 min with the purity >95%. IR (cm^{-1} , KBr pellet): 1629.6 (s, $\nu_{\text{C=O}}$) and 3435.2 (bs, $\nu_{\text{O-H}}$). ESI-MS: $m/z = 823.16$ for $[\text{M} + \text{H}]^+$ (823.60 calcd. for $[\text{C}_{40}\text{H}_{45}\text{InN}_4\text{O}_6\text{P}]^+$). The ^1H and ^{13}C NMR data are listed in Table 1. ^{31}P NMR (D_2O , 500 Hz, 25 °C): 19.5 (s, 1P). Anal. Calcd. for $\text{C}_{42}\text{H}_{48}\text{InN}_4\text{O}_8\text{P} \cdot (\text{CH}_3)_2\text{CO} \cdot 3\text{H}_2\text{O}$: C, 54.32; H, 6.03; N, 5.63. Found: C, 54.68; H, 6.19; N, 5.76.

Ga(DO3A-xy-TPP)(NO₃)

$\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3)$ was prepared using $\text{Ga}(\text{NO}_3)_3\text{H} \cdot 2\text{O}$ (27.3 mg, 0.1 mmol) according to the same procedure for $\text{In}(\text{DO3A-xy-TPP})(\text{OAc})$. Slow diffusion of acetone into the reaction mixture produced colorless crystals suitable for X-ray crystallography. The solid was separated and dried under vacuum overnight before being submitted for elemental analysis. The yield was 64.4 mg (~67.6 %). The HPLC retention time was 14.8 min with the purity >95%. IR (cm^{-1} , KBr pellet): 1632.7 (s, $\nu_{\text{C=O}}$), 1726.6 (s, $\nu_{\text{C=O}}$) and 3441.3 (bs, $\nu_{\text{O-H}}$). ESI-MS: $m/z = 777.02$ for $[\text{M} + \text{H}]^+$ (778.50 calcd. for $[\text{C}_{40}\text{H}_{45}\text{GaN}_4\text{O}_6\text{P}]^+$). ^1H and ^{13}C NMR data are listed in Table 1. ^{31}P NMR (D_2O , 300 Hz, 25 °C): 26.3 (s, 1P). Anal. Calcd. For $\text{C}_{40}\text{H}_{46}\text{GaN}_5\text{O}_9 \cdot (\text{CH}_3)_2\text{CO} \cdot 3\text{H}_2\text{O}$: C, 54.16; H, 6.06; N, 7.35. Found: C, 54.42; H, 5.93; N, 7.02.

Mn(DO3A-xy-TPP)— $\text{Mn}(\text{DO3A-xy-TPP})$ was prepared using MnCl_2 (12.5 mg, 0.1mmol) according to the same procedure for $\text{In}(\text{DO3A-xy-TPP})(\text{OAc})$. Slow diffusion of methanol into

the reaction mixture afforded colorless crystals suitable for X-ray crystallography. The solid was separated and dried under vacuum before being submitted for elemental analysis. The yield was 61.7 mg (~ 71.2 %). A sample was analyzed by HPLC. The retention time was 16.8 min with the purity >95%. IR (cm^{-1} , KBr pellet): 1637.1 (s, $\nu_{\text{C=O}}$) and 3429.3 (bs, $\nu_{\text{O-H}}$). ESI-MS: $m/z = 764.09$ for $[\text{M} + \text{H}]^+$ (763.72 calcd. for $[\text{C}_{40}\text{H}_{45}\text{MnN}_4\text{O}_6\text{P}]$). Anal. Calcd. for $\text{C}_{40}\text{H}_{45}\text{MnN}_4\text{O}_6\text{P} \cdot 4\text{H}_2\text{O} \cdot \text{CH}_3\text{OH}$: C, 54.46; H, 7.03; N, 5.72. Found: C, 54.24; H, 6.71; N, 5.70.

$^{111}\text{In}(\text{DO3A-xy-TPP})^+$

To a clean 3 mL plastic vial were added 0.5 mL NH_4OAc buffer (0.1 M, pH = 6.9) containing 50 μg of the DO3A-xy-TPP and 0.10 mL of $^{111}\text{InCl}_3$ solution (0.2 –2.0 mCi) in 0.05 N HCl. The mixture was heated at 100 $^\circ\text{C}$ for 30 min. After cooling to room temperature, a sample of the resulting solution was analyzed by radio-HPLC. The HPLC retention time was 14.7 min. The HPLC concordance experiment was performed by injecting the HPLC-purified $^{111}\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{In}(\text{DO3A-xy-TPP})^+$ sequentially under the same chromatographic conditions.

X-ray Crystallographic Analysis

Crystallographic data for $\text{In}(\text{DO3A-xy-TPP})(\text{OAc}) \cdot 7.5\text{H}_2\text{O} \cdot (\text{CH}_3)_2\text{CO}$, $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3) \cdot 6\text{H}_2\text{O} \cdot (\text{CH}_3)_2\text{CO}$ and $\text{Mn}(\text{DO3A-xy-TPP}) \cdot 4\text{H}_2\text{O} \cdot \text{CH}_3\text{OH}$ were collected on a Nonius Kappa CCD diffractometer, and are listed in Table 2. Crystals were mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed using graphite monochromated Mo K_α radiation ($\lambda = 0.71073 \text{ \AA}$). Cell constants for data collection were obtained from least-squares refinement, using the setting angles of 23636 reflections in the range $2 < \lambda < 25^\circ$ for $\text{In}(\text{DO3A-xy-TPP})(\text{OAc}) \cdot 7.5\text{H}_2\text{O} \cdot (\text{CH}_3)_2\text{CO}$. A total of 23636 reflections were collected and 9031 reflections were unique. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 5.6 cm^{-1} for Mo K_α radiation. An empirical absorption correction using SCALEPACK²⁸ was applied. The structure was solved by direct methods using Charge Flipping²⁹ in PLUTON³⁰. There are eight oxygen atom positions of water molecules found in $\text{In}(\text{DO3A-xy-TPP})(\text{OAc}) \cdot 7.5\text{H}_2\text{O} \cdot (\text{CH}_3)_2\text{CO}$, seven of which have full occupancies while one has fractional occupancy. For $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3) \cdot 6\text{H}_2\text{O} \cdot (\text{CH}_3)_2\text{CO}$, cell constants for data collection were obtained from least-squares refinement, using the setting angles of 18858 reflections in the range $3 < \lambda < 27^\circ$. The refined mosaicity from DENZO/SCALEPACK²⁸ was 0.34° indicating good crystal quality. A total of 18858 reflections were collected, of which 8697 were unique. Frames were integrated with DENZO-SMN.²⁸ Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 7.0 cm^{-1} for Mo K_α radiation. An empirical absorption correction using SCALEPACK²⁸ was applied. The structure was solved by direct methods using SIR2004.³¹ Refinement was performed on a LINUX PC using SHELX-97.³² There were six O atom positions of lattice water molecules found in $\text{Ga}(\text{DO3A-xy-TPP})^+$. No hydrogen atom was included for these oxygen atoms for which only the isotropic thermal parameter was refined. Crystallographic drawings were done using programs ORTEP,³³ and PLUTON.³⁰ For $\text{Mn}(\text{DO3A-xy-TPP}) \cdot 4\text{H}_2\text{O} \cdot \text{CH}_3\text{OH}$, the cell constants for data collection were obtained from least-squares refinement, using the setting angles of 26583 reflections in the range $2 < \lambda < 26^\circ$. A total of 26583 reflections were collected and 6443 reflections were unique. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 4.1 cm^{-1} for Mo K_α radiation. An empirical absorption correction using SCALEPACK²⁸ was applied. The structure was solved by direct methods using SIR2004.³¹ Refinement was performed on a LINUX PC using SHELX-97.³² Crystallographic drawings were done using programs ORTEP.³³

RESULTS

Synthesis

In this study, we prepared $\text{Ga}(\text{DO3A-xy-TPP})^+$, $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Mn}(\text{DO3A-xy-TPP})$ by reacting DO3A-xy-TPP with one equivalent of the respective metal salt in 0.5 M ammonium acetate buffer (pH = 6). Heating was needed to complete the reaction. $\text{Ga}(\text{DO3A-xy-TPP})^+$ and $\text{In}(\text{DO3A-xy-TPP})^+$ were designed as model compounds for $^{67/68}\text{Ga}(\text{DO3A-xy-TPP})^+$ and $^{111}\text{In}(\text{DO3A-xy-TPP})^+$, respectively. $\text{Mn}(\text{DO3A-xy-TPP})$ was prepared due to its potential as a MRI contrast agent, and its similarity to that of the Cu(II) analog with respect to molecular charge and lipophilicity.²⁶ Both $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$ were isolated as the complex cations with acetate and nitrate as counter ions, respectively. $\text{Mn}(\text{DO3A-xy-TPP})$ was obtained as the Zwitterion salt. All three compounds have been characterized by IR, ESI-MS, HPLC, elemental analysis and X-ray crystallography. $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$ have also been studied by NMR spectroscopic methods (^1H , ^{13}C , ^{31}P , ^1H - ^1H COSY, HSQC, HMQC, HMBC, NOESY) in order to determine their solution structures.

IR and ESI-MS

The IR spectrum of $\text{In}(\text{DO3A-xy-TPP})(\text{OAc})$ shows a strong and broad band at 3435 cm^{-1} due to $\nu_{\text{O-H}}$ of crystallization water molecules, and a strong band at 1630 cm^{-1} from the coordinated carboxylate groups. Upon coordination, stretching frequencies from the carboxylic groups ($\nu_{\text{C=O}} \sim 1730\text{ cm}^{-1}$) undergo a significant “red-shift” ($\sim 100\text{ cm}^{-1}$). The IR spectra of complexes $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3)$ and $\text{Mn}(\text{DO3A-xy-TPP})$ also show broad bands at 3441 cm^{-1} and 3429 cm^{-1} , respectively, due to crystallization water molecules, a strong band at 1633 cm^{-1} for $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3)$ and 1637 cm^{-1} for $\text{Mn}(\text{DO3A-xy-TPP})$ due to the coordinated carboxylate groups. A strong band at 1727 cm^{-1} was observed for the uncoordinated carboxylate group in $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3)$. Two strong bands at 1300 cm^{-1} and 1412 cm^{-1} are typical of non-coordinating NO_3^- counter ions in $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3)$. The ESI-MS of $\text{In}(\text{DO3A-xy-TPP})(\text{OAc})$ shows a molecular ion at $m/z = 823.16$ for $[\text{M}+\text{H}]^+$ while the ESI-MS of $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3)$ has the molecular ion at $m/z = 777.02$ for $[\text{M}+\text{H}]^+$. $\text{Mn}(\text{DO3A-xy-TPP})$ displays the molecular ion at $m/z = 764.09$ for $[\text{M}+\text{H}]^+$ in its ESI mass spectrum.

HPLC analysis

The same HPLC method was used to determine relative lipophilicity of $\text{Ga}(\text{DO3A-xy-TPP})^+$, $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Mn}(\text{DO3A-xy-TPP})$. Figure 2 illustrates their representative HPLC chromatograms. The presence of a single peak in the region of interest suggests that they exist in solution as a single or “averaged” species under the chromatographic conditions used in this study. The HPLC retention times for $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$ are almost identical (14.5 and 14.7 min, respectively); but they are significantly shorted than that of $\text{Mn}(\text{DO3A-xy-TPP})$ (16.8 min). Obviously, $\text{Ga}(\text{DO3A-xy-TPP})^+$ and $\text{In}(\text{DO3A-xy-TPP})^+$ with the +1 overall molecular charge are more hydrophilic (shorter HPLC retention time) than $\text{Mn}(\text{DO3A-xy-TPP})$ in the Zwitterion form. The HPLC retention time of $\text{Mn}(\text{DO3A-xy-TPP})$ is very close to that of $\text{Cu}(\text{DO3A-xy-TPP})$ (17.2 min) under identical chromatographic conditions.²⁶

HPLC Concordance Experiment

The HPLC concordance experiment was performed using the HPLC-purified $^{111}\text{In}(\text{DO3A-xy-TPP})$ and $\text{In}(\text{DO3A-xy-TPP})$. Figure 3 shows HPLC chromatograms of $\text{In}(\text{DO3A-xy-TPP})^+$ (top) and $^{111}\text{In}(\text{DO3A-xy-TPP})^+$ (bottom) under the same chromatographic conditions. Since

they share almost identical HPLC retention times, we believe that $^{111}\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{In}(\text{DO3A-xy-TPP})^+$ have the same composition at both tracer and macroscopic levels.

Structure of $\text{In}(\text{DO3A-xy-TPP})^+$

Figure 4 illustrates an ORTEP view of $\text{In}(\text{DO3A-xy-TPP})^+$. There are two $\text{In}(\text{DO3A-xy-TPP})$ (OAc) molecules in each unit cell, along with eight crystallization water molecules and one acetone surrounding each $\text{In}(\text{DO3A-xy-TPP})^+$. DO3A acts as a heptadentate ligand in bonding to $\text{In}(\text{III})$ with four amine-N, three carboxylate-O donor atoms. The coordination geometry in $\text{In}(\text{DO3A-xy-TPP})^+$ is best described as the monocapped octahedron in which three amine-N atoms, N(1), N(4), N(10), and three oxygen atoms, O(41), O(71), O(101), from the carboxylate groups. The atom N(7) caps the triangular face formed by N(4), N(10) and O(71). $\text{In}(\text{DO3A-xy-TPP})^+$ has a symmetry plane that is defined by four atoms: N(1), In(51), N(7) and O(71). The structure of $\text{In}(\text{DO3A-xy-TPP})^+$ is very similar to that of $\text{Na}[\text{In}(\text{L1})](\text{NO}_3)(\text{H}_2\text{O})(\text{C}_2\text{H}_5\text{OH}) \cdot 2.65\text{H}_2\text{O}$ ($\text{H}_3\text{L1}$ = tris(2'-hydroxybenzylaminoethyl)amine),³⁴ and $[\text{In}(\text{DO3A})] \cdot 2\text{H}_2\text{O} \cdot \text{MeOH}$.³⁵

Table 3 lists selected In-N and In-O bond distances and selected bond angles in $\text{In}(\text{DO3A-xy-TPP})^+$. The average In-N bond length is 2.374 Å (In(51)-N(1): 2.375(4), In(51)-N(4): 2.399(4), In(51)-N(10): 2.327(4) Å, In(51)-N(7): 2.395(4) Å), which is close to that (average In-N distance = 2.356 Å) of $\text{In}(\text{DO3A}) \cdot 2\text{H}_2\text{O} \cdot \text{MeOH}$,³⁵ and is slightly shorter than that (average In-N distance = 2.430 Å) of $\text{In}(\text{DOTA-AA})$ (DOTA-AA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid mono(*p*-aminoanilide)) due to its smaller coordination number.³⁶ The average In-O bond length is 2.174 Å (In(51)-O(41): 2.159(3) Å, In(51)-O(71): 2.162(3) Å, and In(51)-O(101): 2.202(3) Å), which is comparable to that observed in $\text{In}(\text{DO3A}) \cdot 2\text{H}_2\text{O} \cdot \text{MeOH}$ (average In-O distance = 2.181 Å),³⁵ but it is shorter than that of $\text{In}(\text{DOTA-AA})$ (average In-O distance = 2.2191 Å).³⁶ The N(7) amine-nitrogen atom caps the triangular face formed by N(4), N(10) and O(71), leading to the enlarged triangular face (O(71)-In(51)-N(4) = 114.19(13)°, N(10)-In(51)-N(4) = 120.38(14)°, O(71)-In(51)-N(10) = 103.51(14)°) and the reduced triangular face formed by N(1), O(41) and O(101) (O(41)-In(51)-N(1) = 86.06(13)°, O(101)-In(51)-N(1) = 86.55(13)° and O(41)-In(51)-O(101) = 84.51(12)°). The In(51)-N(7) bond distance is 2.395(4) Å, which is significantly shorter than that (In(1)-N(7) = 2.752(4) Å) in $\text{Na}[\text{In}(\text{L1})](\text{NO}_3)(\text{H}_2\text{O})(\text{C}_2\text{H}_5\text{OH}) \cdot 2.65\text{H}_2\text{O}$.³⁴

Structure of $\text{Ga}(\text{DO3A-xy-TPP})^+$

Figure 5 shows the ORTEP view of $\text{Ga}(\text{DO3A-xy-TPP})^+$. In each unit cell, there are four $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3)$ molecules, along with six crystallization water molecules and one acetone surrounding each $\text{Ga}(\text{DO3A-xy-TPP})(\text{NO}_3)$. The coordinated DO3A is hexadentate with four amine-N, two carboxylate-O donor atoms bonding to $\text{Ga}(\text{III})$ due to its smaller size than that of $\text{In}(\text{III})$. The remaining acetic acid group is uncoordinated and deprotonated to balance the positive charge of $\text{Ga}(\text{III})$. The coordination geometry around the $\text{Ga}(\text{III})$ is best described as a distorted octahedron with N(4), N(10), O(41) and O(101) forming the equatorial plane, N(1) and N(7) occupying the remaining two axial positions. The structure of $\text{Ga}(\text{DO3A-xy-TPP})^+$ is very similar to that reported for $\text{Ga}(\text{DOTA-D-PheNH}_2)$ (DOTA-D-PheNH₂ = 1,4,7,10-Tetraazacyclododecane-4,7,10-tricarboxymethyl-1-yl-acetyl-D-Phe-NH₂),³⁷ $\text{Ga}(\text{HDOTA}) \cdot 5.5\text{H}_2\text{O}$ (DOTA = 1,4,7,10-tetraazacyclododecane-4,7,10-triacetic acid),³⁸ $[\text{Ga}(\text{Brbad})]\text{ClO}_4 \cdot \text{DMSO}$ (H_2Brbad = 1,10-bis(2-hydroxy-5-bromobenzyl)-1,4,7,10-tetraazadecane),³⁹ and $[\text{Ga}(\text{HL3})]\text{Cl} \cdot \text{CHCl}_3$ ($\text{H}_3\text{L3}$ = tris(5'-bromo-2'-hydroxybenzylaminoethyl)amine).³⁴ There is a symmetry plane that is defined by N(1), Ga(1) and N(7), divide s the coordinated DO3A moiety into two identical part. As a result, the bond angle N(10)-Ga(1)-N(7) (83.35(11)°) is almost identical to that of N(4)-Ga(1)-N(7) (83.52(12)°) while the bond angle N(10)-Ga(1)-N(1) (82.72(11)°) is very close to the angle N(4)-Ga(1)-N(1) (83.10(12)°).

Table 4 lists the selected bond distances and bond angles in $\text{Ga}(\text{DO3A-xy-TPP})^+$. The average Ga-N bond length is 2.127 Å (Ga(1)-N(4): 2.115(3) Å, Ga(1)-N(10): 2.122(3) Å, Ga(1)-N(7): 2.125(3) Å, Ga(1)-N(1): 2.147(2) Å), which is very similar to that of $\text{Ga}(\text{HDO3A})\cdot 5.5\text{H}_2\text{O}$ (average Ga-N distance = 2.123 Å),³⁸ $[\text{Ga}(\text{Brbad})]\text{ClO}_4\cdot\text{DMSO}$ (average Ga-N distance = 2.112 Å),³⁹ $[\text{Ga}(\text{HL3})]\text{Cl}\cdot\text{CHCl}_3$ (average Ga-N distance = 2.113 Å)³⁴ and is slightly shorter than that of $\text{Ga}(\text{DOTA-D-PheNH}_2)$ (average Ga-N distance = 2.141 Å). The equatorial Ga-N bonds (2.125(3) Å and 2.147(2) Å) are slightly longer than the axial ones (2.115(3) Å and 2.122(3) Å). The average Ga-O bond length is 1.930 Å (Ga(1)-O(41): 1.926(2) Å, Ga(1)-O(101): 1.934(3) Å), which is very close to that of $\text{Ga}(\text{HDO3A})\cdot 5.5\text{H}_2\text{O}$ (1.935 Å),³⁸ and slightly longer than that of $[\text{Ga}(\text{Brbad})]\text{ClO}_4\cdot\text{DMSO}$ (1.913 Å),³⁹ $[\text{Ga}(\text{HL3})]\text{Cl}\cdot\text{CHCl}_3$ (1.901 Å)³⁴ and $\text{Ga}(\text{DOTA-D-PheNH}_2)$ (1.918 Å).³⁷

Structure of $\text{Mn}(\text{DO3A-xy-TPP})$

A representative ORTEP view of $\text{Mn}(\text{DO3A-xy-TPP})$ is shown in Figure 6. Crystallization water molecules and hydrogen atoms are omitted for the sake of clarity. In general, there are four $\text{Mn}(\text{DO3A-xy-TPP})$ molecules in each unit cell, along with four crystallization water molecules and one methanol molecule surrounding each $\text{Mn}(\text{DO3A-xy-TPP})$. Like that in $\text{In}(\text{DO3A-xy-TPP})^+$, DO3A is heptadentate with all four amine-N, three carboxylate-O atoms bonding to the Mn(II). There is a symmetry plane defined by N(1), Mn, N(7) and O(71) in the coordinated DO3A. The coordination geometry of $\text{Mn}(\text{DO3A-xy-TPP})$ is very similar to that of $\text{In}(\text{DO3A-xy-TPP})^+$. Three amine-N atoms, N(1), N(4) and N(10), and three carboxylate-O, O(43), O(73) and O(103), form the distorted octahedron. The remaining amine-N atom, N(7), caps the triangular face formed by N(4), N(10) and O(73).

Table 5 lists selected Mn-N and Mn-O bond distances and selected bond angles in the coordination sphere $\text{Mn}(\text{DO3A-xy-TPP})$. The average Mn-N bond length is 2.426 Å (Mn-N(1): 2.447(3) Å, Mn-N(4): 2.379(3) Å, Mn-N(10): 2.421(3) Å, Mn-N(7): 2.455(3) Å), which is in agreement with those previously reported.^{40, 41} The average Mn-O bond length is 2.182 Å (Mn-O(43): 2.196(3) Å, Mn-O(73): 2.190(3) Å, Mn-O(103): 2.161(3) Å), which is slightly shorter than that of $[\text{Mn}(\text{EDTB})(\text{Ac})](\text{Ac})\cdot\text{C}_2\text{H}_5\text{OH}$ (EDTB = *N, N, N', N'*-tetrakis(2'-benzimidazolylmethyl)-1,2-ethanediamine).⁴¹ The Mn-N(7) bond distance is 2.455(3) Å with N(7) capping the triangular face formed by N(4), N(10), O(73), which leads to an increase of the triangular face (N(4)-Mn-O(73) = 110.85(12)°, N(4)-Mn-N(10) = 116.45(12)°, N(10)-Mn-O(73) = 107.81(12)°) and a decrease of the triangular face formed by N(1), O(43), and O(103) (N(1)-Mn-O(43) = 90.23(12)°, N(1)-Mn-O(103) = 82.34(11)°, O(103)-Mn-O(43) = 87.98(10)°) in the octahedron. The coordination numbers of Mn(II) complexes range from four to eight.⁴⁴ Seven-coordinated Mn(II) complexes normally have the coordination geometry of either monocapped octahedron or a pentagonal bipyramid.^{39–43, 45–47}

NMR for $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$

Since $^{111}\text{In}(\text{DO3A-xy-TPP})^+$ and $^{67/68}\text{Ga}(\text{DO3A-xy-TPP})^+$ are used as radiotracers in biological systems, it is necessary to study their solution properties (structure, isomerism and stability) in aqueous solution. The solution structures of $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$ were elucidated using NMR methods (^1H , ^{13}C , ^1H - ^1H COSY, HSQC, HMQC, HMBC and NOESY) while isomerism and stability were monitored by variable temperature ^1H NMR spectroscopy. Table 1 summarizes ^1H NMR and ^{13}C NMR data for $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$ in D_2O at 25 °C. Assignments of resonance signals from phenyl, *p*-xylene and acetate groups were based on results from the ^1H - ^1H COSY, NOESY, HSQC and HMQC experiments at 25 °C (Figures SI –SVI). The assignment of resonance signals from protons of the cyclen backbone was tentative due to the fact that many of them are superimposed.

Figure 7 shows the aliphatic region of ^1H NMR spectra of $\text{In}(\text{DO3A-xy-TPP})^+$ in D_2O at 5°C (top) and 25°C (bottom). The doublet at 4.73 ppm is assigned to H14 and H14' of the $\text{PCH}_2\text{C}_6\text{H}_4$ moiety. Splitting is caused by coupling from the phosphonium-P. The singlet at 3.96 ppm is from H9 and H9' of the $\text{NCH}_2\text{C}_6\text{H}_4$ moiety. The singlet at 3.53 is from H2a and H2b in the acetate chelating arm attached to N(7). The AB quartet at ~ 3.6 ppm is assigned to H5a, H5b, H5a' and H5b' of the two opposite acetate chelating arms. The multiplets at 3.33 ppm and 3.09 ppm are tentatively assigned to H3a, H3a', H3b and H3b' of the macrocycle. The multiplets at 3.25 ppm and 3.04 ppm are most likely from eight methylene protons (H4, H4', H7 and H7') while the broad peak at 2.69 ppm are probably from the other methylene protons (H8a, H8a', H8b and H8b') of the cyclen macrocycle. As the temperature increases from 5°C to 25°C , all signals become sharper with no significant change in their chemical shifts.

Figure 8 shows the aliphatic region of ^1H NMR spectra of $\text{Ga}(\text{DOTA-xy-TPP})^+$ in D_2O at 25°C (top) and 65°C (bottom). The doublet at 4.78 ppm is assigned to H14 and H14' of the $\text{PCH}_2\text{C}_6\text{H}_4$ moiety. The singlet at 3.92 ppm is from H9 and H9' of the $\text{NCH}_2\text{C}_6\text{H}_4$ moiety. The singlet at 3.49 is assigned to methylene protons (H2a and H2b) in the uncoordinated acetate group. The AB quartet at ~ 3.85 ppm are from four methylene protons (H5a and H5') in the two opposite acetate chelating arms due to the asymmetric nature of $\text{Ga}(\text{DOTA-xy-TPP})^+$. The multiplets at 4.02 ppm and 3.26 ppm are tentatively assigned to methylene protons (H3a, H3a', H3b and H3b') of the cyclen macrocycle. The multiplets at 3.35 ppm and 3.51 ppm are from eight methylene protons (H4, H4', H7 and H7') and the multiplet at 2.89 ppm and 3.39 ppm are from remaining four methylene protons (H8a, H8a', H8b and H8b') on the macrocyclic framework. As the temperature increases from 25°C to 65°C , all proton resonance signals remain the same except the multiplet at 4.0 ppm shifted to 3.9 ppm probably due to rapid inversion of ethylenic groups on the cyclen macrocycle.

DISCUSSION

This report describes synthesis and structural characterization of $\text{Ga}(\text{DO3A-xy-TPP})^+$, $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Mn}(\text{DO3A-xy-TPP})$. The most important finding from this study is that the bonding mode of DO3A depends largely on the size of metal ion. For example, the ionic radius of $\text{In}(\text{III})$ is $0.92 \text{ \AA}$,⁴⁸ and DO3A is heptadentate in $\text{In}(\text{DO3A-xy-TPP})^+$. $\text{Mn}(\text{II})$ has an ionic radius of $0.90 \text{ \AA}$, and the coordination geometry around $\text{Mn}(\text{II})$ in $\text{Mn}(\text{DO3A-xy-TPP})$ is almost identical to that in $\text{In}(\text{DO3A-xy-TPP})^+$ in spite of their charge difference. $\text{Ga}(\text{III})$ has a much smaller ionic radius ($0.62 \text{ \AA}$).⁴⁸ As a result, coordinated DO3A is hexadentate with one acetate group remaining deprotonated in $\text{Ga}(\text{DO3A-xy-TPP})^+$. The overall molecular charge of $\text{Ga}(\text{DO3A-xy-TPP})^+$ is the same as that of $\text{In}(\text{DO3A-xy-TPP})^+$.

The solution structure of $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$ is important for understanding the coordination chemistry of DO3A-conjugated TPP cations with $^{67/68}\text{Ga}$ and ^{111}In at the tracer level. On the basis of HPLC concordance experiments, it is concluded that $^{111}\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{In}(\text{DO3A-xy-TPP})^+$ have the same composition due to their identical HPLC retention times (Figure 3). $\text{In}(\text{DO3A-xy-TPP})^+$ remains symmetrical in aqueous solution. This conclusion is supported by the fact that the proton resonance signals from the $\text{NCH}_2\text{C}_6\text{H}_4$ moiety and the acetate arm attached to N(7) appear as two singlets at 3.96 ppm and 3.53 ppm, respectively. The presence of the AB quartet at ~ 3.62 ppm clearly indicates that all three carboxylate-O donors are firmly bonded to $\text{In}(\text{III})$. If these carboxylate-O donors were dissociated, there would have been three singlets: one from the central acetate group, one from the $\text{NCH}_2\text{C}_6\text{H}_4$ moiety, and one from the two remaining acetate arms.

This symmetrical structure $\text{Ga}(\text{DO3A-xy-TPP})^+$ is also maintained in solution as evidenced by the presence of two singlets at 3.92 ppm and 3.54 ppm from the $\text{NCH}_2\text{C}_6\text{H}_4$ moiety and the acetate arm attached to N(7), respectively. Since the two methylene hydrogens of the

coordinated acetate chelating arms experience different chemical environments, it is not surprising that they appear as the AB quartet at ~3.65 ppm. The two coordinated carboxylate-O donor atoms remain firmly bonded to Ga(III) even at 65 °C (Figure 4), suggesting that $^{68}\text{Ga}(\text{DO3A-xy-TPP})^+$ might have a very high in vivo solution stability as observed for $^{68}\text{Ga}(\text{DOTA-D-Phe-NH}_2)^+$.³⁷

Comparison of the ^1H NMR spectra (Figures 7 and 8) of $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DOTA-xy-TPP})^+$ reveals certain similarities in the splitting patterns for H2, H5, H9 and H14, as well as significant differences in chemical shifts of H3, H4, H7 and H8. The fact that both H3a and H8a have significantly different chemical shifts (Table 1) in the ^1H NMR spectra of $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DOTA-xy-TPP})^+$ strongly suggests that they might have different solution structures as those (Figures 4 and 5) observed in the solid state. It is important to note that the most common coordination number for In(III) is 6 and/or 7 while the coordination number of Ga(III) is predominantly 6 due to its smaller ionic radius.^{34, 35, 38, 39, 48} Therefore, it is reasonable to believe that the solution structure of $\text{Ga}(\text{DOTA-xy-TPP})^+$ is the same as that in the solid state (Figure 5) with one acetate chelating arm being uncoordinated.

CONCLUSION

In conclusion, $\text{Ga}(\text{DO3A-xy-TPP})^+$, $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Mn}(\text{DO3A-xy-TPP})$ have been prepared and characterized by elemental analysis, spectroscopic methods and X-ray crystallography. In the solid state, DO3A uses all of its seven donor atoms (N_4O_3) in bonding to In(III) or Mn(II) while it is only hexadentate in bonding to Ga(III) with four amine-N and only two carboxylate-O donor atoms. The NMR data clearly demonstrate that the coordinated DO3A in $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$ is symmetrical in aqueous solution. The variable temperature ^1H NMR data reveal no dissociation of the two acetate chelating arms in $\text{Ga}(\text{DO3A-xy-TPP})^+$ that remains rigid in aqueous solution even at temperatures over 65 °C.

An important finding from this study is that $\text{Ga}(\text{DO3A-xy-TPP})^+$ and $\text{In}(\text{DO3A-xy-TPP})^+$ are more hydrophilic than $\text{Mn}(\text{DO3A-xy-TPP})$, the HPLC retention time of which is very close to that of $\text{Cu}(\text{DO3A-xy-TPP})$.²⁶ This suggests that $\text{Cu}(\text{DO3A-xy-TPP})$ may also exist in solution as its Zwitterion form as observed in $\text{Mn}(\text{DO3A-xy-TPP})$ despite of their difference in coordination number due to the smaller ionic radius of Cu(II) (0.67 Å) than Mn(II) (0.90 Å).⁴⁸ Since the ionic radius of Cu(II) is very close to that of Ga(III) (0.62 Å),⁴⁸ we believe that the coordinated DO3A in $\text{Cu}(\text{DO3A-xy-TPP})$ most likely hexadentate with one acetate group being deprotonated to balance to cationic charge from the TPP moiety. Evaluation of radiometal chelate and overall molecular charge on biological properties of the radiolabeled TPP cation is still in progress, and the results from these studies will be reported elsewhere.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The DO3A-conjugated TPP analogs and their radiometal complexes useful for imaging tumors.

Figure 2. Representative HPLC chromatograms of $\text{Ga}(\text{DO3A-xy-TPP})^+$, $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Mn}(\text{DO3A-xy-TPP})$.

Figure 3. HPLC concordance for $\text{In}(\text{DO3A-xy-TPP})^+$ (top) and $^{111}\text{In}(\text{DO3A-xy-TPP})^+$ (bottom). Their identical HPLC retention times suggest that $^{111}\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{In}(\text{DO3A-xy-TPP})^+$ have the same composition.

Figure 4. ORTEP drawing of $\text{In}(\text{DO3A-xy-TPP})^+$ (Ellipoids are at 50% probability). Crystallization molecules and hydrogen atoms are omitted for the sake of clarity.

Figure 5. ORTEP drawing of $\text{Ga}(\text{DO3A-xy-TPP})^+$ (Ellipoids are at 50% probability). Crystallization molecules and hydrogen atoms are omitted for the sake of clarity.

Figure 6. ORTEP drawing of Mn(DO3A-xy-TPP) (Ellipoids are at 50% probability). Crystallization water molecules and hydrogen atoms are omitted for the sake of clarity.

Figure 7.
Aliphatic region of the ¹H NMR spectra of In(DOTA-xy-TPP)⁺ in D₂O at 5 °C (top) and 25 °C (bottom).

Figure 8.
Aliphatic region of the ¹H NMR spectra of Ga(DOTA-xy-TPP)⁺ in D₂O at 25 °C (top) and 65 °C (bottom).

Table 1

^1H and ^{13}C NMR Data (500 Hz) for $\text{In}(\text{DO3A-xy-TPP})^+$ and $\text{Ga}(\text{DO3A-xy-TPP})^+$. Both ^1H and ^{13}C NMR spectra were recorded in D_2O at 25°C .

position	$\text{In}(\text{DO3A-xy-TPP})^+$		$\text{Ga}(\text{DO3A-xy-TPP})^+$	
	δ_{H} (mult., J_{HH})	δ_{C}	δ_{H} (mult., J_{HH})	δ_{C}
1		178.2		173.1
2	3.53(s)	60.1	3.54(s)	62.5
3, 3'	3.09(m), 3.33(m)	54.8	3.26(m), 4.02(m)	53.8
4, 4'	3.04(m), 3.25(m)	54.8	3.35(m), 3.51(m)	56.2
5, 5'	3.62(AB quartet)	61.5	3.85(AB quartet)	58.7
6, 6'		177.9		173.0
7, 7'	3.04(m), 3.29(m)	53.5	3.35(m), 3.51(m)	56.5
8, 8'	2.69(m)	49.1	2.89(m), 3.39(m)	53.3
9	3.96(s)	58.9	3.92(s)	63.5
10		132.6		129.9
11, 11'	7.11(d, 9.8 Hz)	134.9	7.20(d, 9.8 Hz)	131.2
12, 12'	7.00(d, 9.8 Hz)	133.7	6.96(d, 9.8 Hz)	130.5
13		131.0		128.2
14	4.78(d, 9.8 Hz)	31.7(d)	4.78(d, 9.8 Hz)	28.6(d)
15, 15', 15''		119.7(d)		116.3
16, 16', 16''	7.65(m)	136.6	7.57(m)	133.3
17, 17', 17''	7.65(m)	132.5	7.57(m)	129.1
18, 18', 18''	7.86(t)	137.7	7.78(m)	134.4
19, 19', 19''	7.65(m)	132.5	7.57(m)	129.1
20, 20', 20''	7.65(m)	136.6	7.57(m)	133.3

Table 2

Selected crystallographic data and structure refinements details for In(DO3A-xy-TPP)(OAc)·7.5H₂O·(CH₃)₂CO, Ga(DO3A-xy-TPP)(NO₃)·6H₂O·(CH₃)₂CO and Mn(DO3A-xy-TPP)·4H₂O·CH₃OH.

formula	C ₄₅ H ₆₉ InN ₄ O _{16.5} P	C ₄₃ H ₆₄ GaN ₅ O ₁₆ P	C ₄₁ H ₅₇ MnN ₄ O ₁₁ P
fw	1075.83	1007.71	867.84
space group	P I (No. 2)	Pca2 ₁ (No. 29)	P2 ₁ /c (No. 14)
λ, (Å)	Mo K _α (0.71073)	Mo K _α (0.71073)	Mo K _α (0.71073)
a, Å	10.7779(9)	28.9585(9)	12.8899(9)
b, Å	16.3040(17)	8.15090(10)	19.1761(10)
c, Å	16.4520(18)	19.6548(6)	17.1960(13)
α, deg	103.482(6)	90	90
β, deg	106.939(6)	90	103.84(4)
γ, deg	104.783(6)	90	90
V, Å ³	2522.0(4)	4639.3(2)	4127.0(5)
Z	2	4	4
d _{calc} , g/cm ³	1.417	1.443	1.397
T, (K)	150	150	150
μ, mm ⁻¹	0.572	0.696	0.406
transmission coeff	0.788, 0.932	0.812, 0.773	0.954, 0.985
R(F _o)	0.056 ^a	0.043 ^a	0.069 ^a
R _w (F _o ²)	0.135 ^b	0.094 ^b	0.161 ^b

^aR = Σ ||F_o| - |F_c|| / Σ |F_o| for F_o² > 2 σ (F_o²).

^bR_w = [Σ w (|F_o² - |F_c²||² / Σ w |F_o²|²)]^{1/2}

Table 3Selected bond distances (Å) and bond angles (°) in $\text{In}(\text{DO3A-xy-TPP})(\text{OAc}) \cdot 7.5\text{H}_2\text{O} \cdot (\text{CH}_3)_2\text{CO}$.

Atom 1	Atom 2	Distance	
In51	O41	2.159(3)	
In51	O71	2.162(3)	
In51	O101	2.202(3)	
In51	N10	2.327(3)	
In51	N1	2.375(3)	
In51	N7	2.395(3)	
In51	N4	2.399(3)	
Atom 1	Atom 2	Atom 3	Angle
O41	In51	O71	87.22(14)
O41	In51	O101	84.51(12)
O71	In51	O101	79.45(13)
O41	In51	N10	152.56(14)
O71	In51	N10	103.51(14)
O101	In51	N10	73.04(13)
O41	In51	N1	86.06(13)
O71	In51	N1	164.99(14)
O101	In51	N1	86.55(13)
N10	In51	N1	77.22(14)
O41	In51	N7	131.71(14)
O71	In51	N7	73.31(15)
O101	In51	N7	131.84(13)
N10	In51	N7	75.72(14)
N1	In51	N7	120.82(14)
O41	In51	N4	75.61(14)
O71	In51	N4	114.19(13)
O101	In51	N4	154.85(14)
N10	In51	N4	120.38(14)
N1	In51	N4	77.00(13)
N7	In51	N4	73.30(14)

Table 4Selected bond distances (Å) and bond angles (°) in Ga(DO3A-xy-TPP)(NO₃)·6H₂O·(CH₃)₂CO.

Atom 1	Atom 2	Distance	
Ga1	O41	1.926(2)	
Ga1	O101	1.934(3)	
Ga1	N4	2.115(3)	
Ga1	N10	2.122(3)	
Ga1	N7	2.125(3)	
Ga1	N1	2.147(2)	
Atom 1	Atom 2	Atom 3	Angle
O41	Ga1	O101	84.95(12)
O41	Ga1	N4	84.17(11)
O101	Ga1	N4	168.95(11)
O41	Ga1	N10	168.13(11)
O101	Ga1	N10	83.25(12)
N4	Ga1	N10	107.67(11)
O41	Ga1	N7	97.49(10)
O101	Ga1	N7	99.82(11)
N4	Ga1	N7	83.52(12)
N10	Ga1	N7	83.35(11)
O41	Ga1	N1	99.95(9)
O101	Ga1	N1	96.91(12)
N4	Ga1	N1	83.10(12)
N10	Ga1	N1	82.72(11)
N7	Ga1	N1	156.76(11)

Table 5Selected bond distances (Å) and bond angles (°) in Mn(DO3A-xy-TPP)·4H₂O·CH₃OH.

Atom 1	Atom 2	Distance	
Mn	O103	2.161(3)	
Mn	O73	2.190(3)	
Mn	O43	2.196(3)	
Mn	N4	2.379(3)	
Mn	N10	2.421(3)	
Mn	N1	2.447(3)	
Mn	N7	2.455(3)	
Atom 1	Atom 2	Atom 3	Angle
O103	Mn	O73	89.64(11)
O103	Mn	O43	87.98(10)
O73	Mn	O43	84.66(11)
O103	Mn	N4	150.19(11)
O73	Mn	N4	110.85(12)
O43	Mn	N4	73.29(11)
O103	Mn	N10	74.55(11)
O73	Mn	N10	107.81(12)
O43	Mn	N10	158.14(11)
N4	Mn	N10	116.45(12)
O103	Mn	N1	82.34(11)
O73	Mn	N1	170.65(11)
O43	Mn	N1	90.23(11)
N4	Mn	N1	74.94(11)
N10	Mn	N1	74.75(11)
O103	Mn	N7	134.40(11)
O73	Mn	N7	71.13(11)
O43	Mn	N7	128.75(11)
N4	Mn	N7	74.43(11)
N10	Mn	N7	72.98(11)