

## Activation of $[^{99(m)}\text{TcO}_4]^-$ by phosphonium cations<sup>†</sup>

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**Phosphonium salts in solution or bound to solid phase supports interact with the robust  $[^{99(m)}\text{TcO}_4]^-$  anion in neutral water. This activated form of  $[^{99(m)}\text{TcO}_4]^-$  represents a source for complexes with the  $\text{fac}\{-^{99m}\text{Tc}^{\text{VII}}\text{O}_3\}^+$  core, which can be synthesized in high yields and purity.**

Technetium (Tc) is the lightest artificial element, environmentally present in minute quantities resulting from spontaneous fission of uranium. Large amounts of the long-lived  $\beta^-$  emitter  $^{99}\text{Tc}$  ( $2.13 \times 10^5$  years half-life) are produced in nuclear power plants.<sup>1</sup>  $^{99}\text{Tc}$  is isolated from spent fuels as highly water soluble  $[\text{NH}_4]^{99}\text{TcO}_4$ . To assess the hazard potential after an accidental release of  $[\text{TcO}_4]^-$  into the environment, it is essential to elucidate parameters leading to the activation of  $[\text{TcO}_4]^-$  at the tracer level. The nuclear isomer  $^{99m}\text{Tc}$  is a commonly used radio-nuclide in nuclear medicine.<sup>2–5</sup> Low valent  $^{99m}\text{Tc}$  complexes comprising the  $\text{fac}\{-^{99m}\text{Tc}^{\text{I}}(\text{CO})_3\}^+$  core are currently investigated for molecular imaging purposes.<sup>2,3,6</sup> To extend the available building blocks for labeling chemistry, we introduced high-valent and water stable  $^{99(m)}\text{Tc}$  complexes based on the  $\text{fac}\{-^{99(m)}\text{Tc}^{\text{VII}}\text{O}_3\}^+$  core.<sup>7–10</sup> Their cycloaddition reactivities towards alkenes led to a new labeling strategy: conjugation of a targeting molecule to the  $^{99m}\text{Tc}$  complex at the ligand and not at the metal.<sup>7,8</sup> Reminiscent of  $[\text{OsO}_4]$ , the  $\text{fac}\{-^{99(m)}\text{Tc}^{\text{VII}}\text{O}_3\}^+$  core reacts with alkenes by a (3+2)-cycloaddition (vic. *cis*-dihydroxylation – alkene–glycol interconversion).<sup>11</sup>

Pertechnetate is a robust anion. It can be “activated” by reduction or by strong Brønsted acids (e.g.  $\text{H}_2\text{SO}_4$  or  $\text{HCl}$ ) in dry, organic solvents. *In situ* formed  $(\text{H}^{99}\text{TcO}_4)$  is a reactive, moisture sensitive and volatile compound from which a series of  $\text{fac}\{-^{99}\text{Tc}^{\text{VII}}\text{O}_3\}^+$  complexes were prepared.<sup>12–16</sup> Alternatively,  $[\text{TcO}_4]^-$  is activated

by Lewis-acids (LA). LAs form reactive, mixed anhydrides of the  $\{\text{O}_3^{99}\text{Tc}^{\text{VII}}\text{O}\text{-LA}\}$  type.<sup>9,17</sup> The  $\{\text{O-LA}\}$  group is then replaced by tridentate ligands, yielding  $\text{fac}\{-^{99}\text{Tc}^{\text{VII}}\text{O}_3(\text{L}^3)\}^+$  type complexes. Due to moisture sensitivity of Lewis acids, these reactions generally require organic solvents.

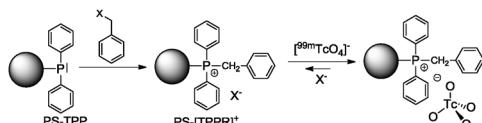
A direct synthesis from  $[\text{TcO}_4]^-$  in water would be desirable and would open an alternative and more applicable pathway to new high-valent building blocks for molecular imaging. Herein, we report that phosphonium cations, albeit not “typical” Lewis acids, activate  $[\text{TcO}_4]^-$  at the tracer level and enable the synthesis of  $[\text{^{99m}TcO}_3(\text{taen})]^+$  (taen = 1,4,7-triazacyclononane,  $[\mathbf{1}]^+$ ) directly in neutral water. The same strategy in organic solvents leads to  $[\text{^{99}TcO}_3(\text{Me}_3\text{tach})]^+$  ( $\text{Me}_3\text{tach}$  = 1,3,5-trimethyl-[1,3,5]triaxinane). Previously,  $[\mathbf{1}]^+$  was accessible in low yields from  $[\text{^{99m}TcO}_4]^-$  and in the presence of triphenyl-phosphine (TPP) at low pH values ( $< 2$ )<sup>7,8</sup> where TPP is protonated to  $(\text{HTPP})^+$  ( $\text{pK}_a = 2.73$ ).<sup>18–20</sup> We hypothesized that this phosphonium cation, generated *in situ*, may activate  $[\text{^{99m}TcO}_4]^-$ . To support this assumption,  $[\text{^{99m}TcO}_4]^-$  and taen were reacted in water at neutral pH in the presence of a series of phosphonium salts, such as  $(\text{PPh}_3\text{Me})\text{Br}$ ,  $(\text{PPh}_3\text{Bz})\text{Br}$ ,  $(\text{PPh}_3\text{Et})\text{Br}$ ,  $(\text{P}^{\text{t}}\text{Bu}_4)\text{Br}$ ,  $(\text{PPh}_4)\text{Br}$  and  $(\text{PPh}_2\text{Me}_2)\text{I}$  (Table S2.1.1, ESI<sup>†</sup>). All did activate  $[\text{^{99m}TcO}_4]^-$  with ultimate formation of  $[\mathbf{1}]^+$  in 19–35% yields, demonstrating that phosphonium cations do interact with  $[\text{^{99m}TcO}_4]^-$  in water and at elevated temperatures. The fate of *e.g.*  $[\text{PPh}_4]^-$  is not known. Most likely, it forms an oxy-anion  $[\text{PPh}_4\text{O}]^-$  from which  $[\text{PPh}_4]^+$  is regenerated after protonation and water cleavage. No product at all was obtained in the absence of phosphonium cations. Even sterically crowded cations, such as  $(\text{P}^{\text{t}}\text{Bu}_4)^+$  or  $(\text{PPh}_4)^+$  lead to product formation, albeit in low yields.

For applications, dissolved phosphonium salts are not desirable for toxicity reasons. Immobilization on solid phase supports would elegantly circumvent this concern. Polystyrene beads with covalently bound methyl-triphenyl-phosphonium cations ( $\text{PS-TPPR}^+$ ) or neutral triphenylphosphine ( $\text{PS-TPP}$ ) groups are commercially available. On the latter resin, cations can be generated by quaternization of the phosphine groups with the respective alkyl halides (Scheme 1).

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<sup>†</sup> Electronic supplementary information (ESI) available: Ligand and complex synthesis including IR data, NMR data as well as crystallographic details. CCDC 976753. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00718b



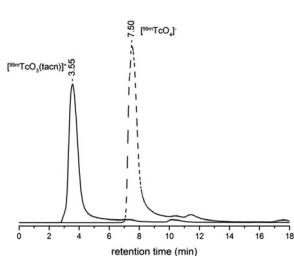


**Scheme 1** Extraction and activation of  $[^{99m}\text{TcO}_4]^-$  from saline with polystyrene bound quaternary phosphines.

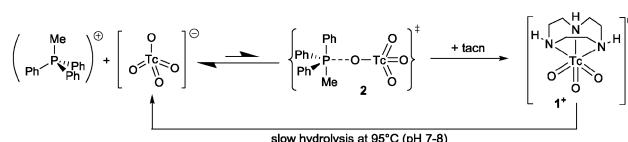
These phosphonium derivatized polystyrene beads PS-[TPPP] $^+$  are potent anion exchangers. Even from standard saline solution (0.9% NaCl,  $\sim 0.15$  M),  $[^{99m}\text{TcO}_4]^-$  ( $10^{-6}$ – $10^{-8}$  M) is extracted using a few mg of resin within minutes and in  $>98\%$  yield. Exposure of such resins with  $[^{99m}\text{TcO}_4]^-$  as a counter ion to a neutral solution of tacn gave better  $[^{99m}\text{TcO}_3(\text{tacn})]^{+}$  yields than the homogeneous reactions. As a beneficial side effect, unreacted  $[^{99m}\text{TcO}_4]^-$  remained bound to the resin. Consequently, cationic  $\text{Tc}^{VII}$  complexes such as  $[1]^{+}$  are obtained in very high radiochemical purity and in one single step. For instance, the reaction of PS-[PPh<sub>3</sub>Me] $^+$  with  $[^{99m}\text{TcO}_4]^-$  in the presence of tacn gave  $[1]^{+}$  in 64% yield (3% residual  $[^{99m}\text{TcO}_4]^-$  in solution), after 1 h at 95 °C and pH = 7. The “missing” 33%  $[^{99m}\text{TcO}_4]^-$  remained resin bound (Fig. S2.2.1, ESI $^\ddagger$ ). This remarkable reaction is now a generally applicable approach to obtain  $^{99m}\text{Tc}^{VII}$  complexes without soluble phosphonium salts and at neutral pH.

The role of the phosphonium cation is dual: (i) trapped  $[^{99m}\text{TcO}_4]^-$  on the resin leads to a much higher, “local” concentration and, thus, to faster reactions and (ii)  $[^{99m}\text{TcO}_4]^-$  is polarized and thereby activated. Both factors lead to improved yields and purities of *e.g.*  $[1]^{+}$ , and are crucial features for radiopharmaceuticals. The nature of the phosphonium cation has a distinct influence on product yields, *i.e.* the reactivity can be tuned by altering the 4th group on the quaternary phosphonium. From a functionality screen, the benzyl group PS-[PPh<sub>3</sub>Bz] $^+$  emerged as the most favourable; yields up to 88% with less than 0.5% residual  $[^{99m}\text{TcO}_4]^-$  were achieved in one step (Fig. 1). $^{21}$  Since conditions are neutral,  $[1]^{+}$  can directly be subjected to further reactions such as cycloaddition with alkenes to yield  $\text{Tc}^V$  glycolato complexes. This has been shown by the synthesis of the model compound  $[^{99m}\text{TcO}(\text{tacn})(\text{O}_2\text{styrSO}_3)]$  (Fig. S2.3.1, ESI $^\ddagger$ ). $^{7,8}$

In the preparation of  $^{99m}\text{Tc}$ -based molecular imaging agents, microwave assisted heating is an alternative to thermal heating. $^{22-24}$  The reaction of  $[^{99m}\text{TcO}_4]^-$  with tacn in the presence of PS-[PPh<sub>3</sub>Me] $^+$  in a microwave reactor at 120 °C for 10 min gave 78%  $[1]^{+}$  (64% thermal, 1 h, Fig. S2.2.2, ESI $^\ddagger$ ) and still 7% at 50 °C



**Fig. 1** HPLC trace before (dashed line) and after the reaction (solid line) of  $[^{99m}\text{TcO}_4]^-$  with PS-[PPh<sub>3</sub>Bz] $^+$  and tacn (1 h, 95 °C, pH 7). Yield: 88%.



**Scheme 2** Synthesis of  $[^{99m}\text{TcO}_3(\text{tacn})]^{+}$  via the mixed anhydride  $\{\text{PPh}_3\text{Me}-\text{O}-^{99m}\text{TcO}_3\}$  (2).

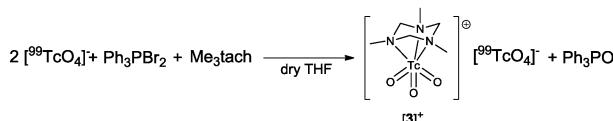
after 1 h (microwave and thermal heating). The superiority of PS-[PPh<sub>3</sub>Bz] $^+$  over  $[^{99m}\text{TcO}_4]^-$  activation was evident since about 30%  $[1]^{+}$  was obtained under these conditions (50 °C).

In the homogenous reactions, we did not detect intermediates. It is likely that the cations activate  $[^{99m}\text{TcO}_4]^-$  by forming a mixed anhydride  $\{\text{PPh}_3\text{Me}-\text{O}-^{99m}\text{TcO}_3\}$  which then reacts with tacn to give  $[1]^{+}$  (Scheme 2). The equilibrium in Scheme 2 is on the ion-pair side and the concentration of the mixed anhydride 2 is low. The reaction with  $[1]^{+}$  is therefore slow and yields and rates are strongly tacn concentration dependent (Fig. S2.2.3, ESI $^\ddagger$ ). Stability studies under the applied reaction conditions (saline solution, 95 °C, pH 7–8) disclosed a slow decomposition of complex  $[1]^{+}$  ( $^{99}\text{Tc}$  and  $^{99m}\text{Tc}$ ) to  $[^{99m}\text{TcO}_4]^-$  (S2.5, ESI $^\ddagger$ ). This slow decomposition accounts for reaction yields  $<100\%$ . Adaption of the reaction conditions to  $^{99}\text{Tc}$  is not immediately possible since phosphonium salts of  $[^{99}\text{TcO}_4]^-$  are essentially insoluble in water. Upon adding highly diluted  $[^{99}\text{TcO}_4]^-$  as a carrier to a solution of  $[^{99m}\text{TcO}_4]^-$ , PS-[PPh<sub>3</sub>Bz] $^+$  and tacn,  $^{99}\text{Tc}$  will compete with  $^{99m}\text{Tc}$  in the reaction to give  $[1]^{+}$  ( $^{99}\text{Tc}$  and  $^{99m}\text{Tc}$ ). Since highly diluted,  $[1]^{+}$  ( $^{99}\text{Tc}$ ) is not visible on HPLC, the apparent yield of  $[1]^{+}$  ( $^{99m}\text{Tc}$ ) will be reduced. This was observed, indeed, that increasing amounts of the carrier decreased yields of  $[1]^{+}$  ( $^{99m}\text{Tc}$ , Fig. S2.2.4, ESI $^\ddagger$ ). The conversion of  $[^{99m}\text{TcO}_4]^-$  into defined complexes in water and in the presence of phosphonium cations is remarkable and should be included in the risk assessment of  $[^{99}\text{TcO}_4]^-$ .

To efficiently activate  $[^{99m}\text{TcO}_4]^-$  by phosphonium cations, stronger Lewis acids than  $[\text{PPh}_3\text{R}]^+$  ( $\text{R} = \text{Me, Bz}$ ) are required to shift the equilibrium (Scheme 2) towards the mixed anhydride  $\{\text{Ph}_3\text{RP-O-}^{99}\text{TcO}_3\}$  (2).  $\text{Ph}_3\text{PBr}_2$  is such a strong Lewis acid with distinct affinity for oxygen. In organic solvents,  $\text{Ph}_3\text{PBr}_2$  forms quantitatively the reactive, mixed anhydride  $\{\text{Ph}_3\text{BrP-O-}^{99}\text{TcO}_3\}$  which was observed *in situ* by  $^{99}\text{Tc}$  and  $^{31}\text{P}$  NMR spectroscopy (Fig. S2.4.1/2.4.2, ESI $^\ddagger$ ). The  $^{99}\text{Tc}$  NMR spectrum showed a broad signal ( $\nu_{1/2} = 230$  Hz) at  $\sim 0$  ppm which contrasts the extremely sharp ( $\nu_{1/2} = 2$  Hz) and characteristic  $[^{99m}\text{TcO}_4]^-$  signal at the same chemical shift. Consistently, the  $^{31}\text{P}$  NMR spectrum of the intermediate ( $\{\text{Ph}_3\text{BrP-O-}^{99}\text{TcO}_3\}$ ) showed a broad signal at 27.22 ppm ( $\nu_{1/2} = 110$  Hz).

The mixed anhydride  $\{\text{Ph}_3\text{BrP-O-}^{99}\text{TcO}_3\}$  can be reacted with ligands not compatible with other Lewis acids. Reactions of  $\{\text{Ph}_3\text{BrP-O-}^{99}\text{TcO}_3\}$  with bi- and tridentate ligands, such as 2,2'-bipyridine (bipy), 2,2-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)acetic acid (bpza $^{*}$ ), and tris(3,5-dimethyl-1*H*-pyrazol-1-yl)methane (tpzm $^{*}$ ) gave the corresponding complexes  $[^{99}\text{TcO}_3(\text{bipy})\text{Br}]$ ,  $[^{99}\text{TcO}_3(\text{bpza}^{*})]$  and  $[^{99}\text{TcO}_3(\text{tpzm}^{*})]\text{Br}$  in high yields (S1.2, ESI $^\ddagger$ ).

To exemplify access to  $[^{99}\text{TcO}_3(\text{L}^3)]^{+}$  type complexes with weakly coordinating ligands  $\text{L}^3$ , we selected the small aliphatic,

Scheme 3 Synthesis of  $[{}^{99m}\text{TcO}_3(\text{Me}_3\text{tach})][{}^{99m}\text{TcO}_4]$  ( $[3][{}^{99m}\text{TcO}_4]$ ).

N-heterocycle 1,3,5-trimethyl-triazacyclohexane ( $\text{Me}_3\text{tach}$ ). High-valent  $\text{Me}_3\text{tach}$  complexes are rare and only  $[\text{ReO}_3(\text{Me}_3\text{tach})]^+$  and  $[\text{Mo}^{\text{VI}}\text{O}_3(\text{R}_3\text{tach})]^0$  are reported.<sup>25,26</sup> Low-valent complexes  $[(\text{Me}_3\text{tach})\text{M}^0(\text{CO})_3]$  ( $\text{M} = \text{Mo, W}$ ) are known<sup>27</sup> and  $[(\text{R}_3\text{tach})\text{CrCl}_3]$  was studied using the Phillips catalyst ( $\text{CrO}_3/\text{SiO}_2$ ).<sup>28–30</sup>

*In situ* prepared  $\{\text{Ph}_3\text{BrP-O-}{}^{99m}\text{TcO}_3\}$  reacts with  $\text{Me}_3\text{tach}$  immediately to give  $\text{Ph}_3\text{PO}$  (Fig. S2.4.3, ESI†) and  $[{}^{99m}\text{TcO}_3(\text{Me}_3\text{tach})][{}^{99m}\text{TcO}_4]$  ( $[3][{}^{99m}\text{TcO}_4]$ ) which is precipitated as a yellow powder (Scheme 3). As solid,  $[3][{}^{99m}\text{TcO}_4]$  can be stored for weeks. It is soluble in dry acetonitrile and  $\text{CH}_2\text{Cl}_2$ .  $[3][{}^{99m}\text{TcO}_4]$  is reactive towards reducing agents such as bromide. Thus, fast separation from the reaction solution is crucial. An X-ray diffraction analysis of single crystals, obtained from slow evaporation of a  $\text{CH}_2\text{Cl}_2$  solution of  $[3][{}^{99m}\text{TcO}_4]$ , gave a structure with two  $[3]^+$  cations, one  $[{}^{99m}\text{TcO}_4]^-$ , and one  $[{}^{99m}\text{TcOBr}_4]^-$  anion. Both cations show identical structural features. Details of data collection and structure calculations are given in the ESI† (Table S3.1). Fig. 2 shows the structure of the  $[3]^+$  cation. The  $\text{Tc-N}$  bond lengths in  $[3]^+$  are elongated (2.265(2)–2.281(2) Å) as compared to the water stable *fac*- $[{}^{99m}\text{TcO}_3]^+$  complex  $[{}^{99m}\text{TcO}_3(\text{tacn})]^+$  (2.239(4) Å).<sup>10</sup> These long bonds are in agreement with the reactivity of  $[3]^+$  and imply the possibility of substituting  $\text{Me}_3\text{tach}$  with other ligands. The highly distorted coordination geometry around the  ${}^{99m}\text{Tc}$  centre ( $d^0$  system) is induced by the strain of the small  $\text{Me}_3\text{tach}$  ligand ( $\text{N-Tc-N}$  angles: 59.85(9)–60.40(9)°). The steric demand of the  $\text{Me}_3\text{tach}$  ligand is significantly smaller than that for  $\text{tacn}$ . The  $\text{O-Tc-O}$  angles in  $[3]^+$  are increased (108.84(12)–109.32(14)°) in comparison to  $[{}^{99m}\text{TcO}_3(\text{tacn})]^+$  (106(2)°) to adopt the favoured tetrahedral conformation.

The  ${}^{99m}\text{Tc}$  NMR spectrum of  $[3][{}^{99m}\text{TcO}_4]$  exhibits one broad signal at 362 ppm ( $\nu_{1/2} = 913$  Hz), in a similar region as that for  $[{}^{99m}\text{TcO}_3(\text{tacn})]^+$  (358 ppm,  $\nu_{1/2} = 2500$  Hz).<sup>10</sup> An additional sharp signal at 0 ppm represents the  $[{}^{99m}\text{TcO}_4]^-$  counter ion (1 : 1 ratio, Fig. S2.4.4, ESI†). Since the small bite angles of  $\text{Me}_3\text{tach}$  render

its complexes prone to hydrolysis or ligand substitution, trace amounts of water hydrolyse the compound to  $[{}^{99m}\text{TcO}_4]^-$ . The sensitivity of  $[3]^+$  towards hydrolysis was confirmed by  ${}^{99m}\text{Tc}$  NMR studies. In 0.2 ml acetonitrile,  $[3]^+$  is fully converted to  $[{}^{99m}\text{TcO}_4]^-$  within minutes upon the addition of 10  $\mu\text{l}$  of  $\text{H}_2\text{O}$  as evident from the single signal at 0 ppm ( $[{}^{99m}\text{TcO}_4]^-$ ).

The robust  $[{}^{99m}\text{TcO}_4]^-$  anion can be activated in aqueous solution by *in situ* mixed anhydride formation in the presence of quaternary phosphonium cations. Tridentate ligands such as 1,4,7-triazacyclononane ( $\text{tacn}$ ) can replace the  $\{\text{R}_4\text{P-O}\}^-$ -group, thereby forming the water stable  $[{}^{99m}\text{Tc}^{\text{VII}}\text{O}_3(\text{tacn})]^+$  complex. Substituted  $\text{tacn}$  ligands or other ligands are expected to show a similar reactivity pattern. If the phosphonium is bound to a solid phase support, the heterogeneous reaction leads to high purity compounds since residual  $[{}^{99m}\text{TcO}_4]^-$  remains bound to the resin. The overall procedure is carried out at neutral pH, thus, the product can be further directly reacted with *e.g.* alkenes.  $[{}^{99m}\text{TcO}_4]^-$  at the tracer level is transformed into defined complexes in water in the presence of phosphonium cations. In the future, this important finding has to be included in the risk assessment of  $[{}^{99m}\text{TcO}_4]^-$  release into the environment. We are currently studying the highly reactive  $[{}^{99m}\text{TcO}_3(\text{Me}_3\text{tach})]^+$  complex as a source for complexes with the *fac*- $\{{}^{99m}\text{Tc}^{\text{VII}}\text{O}_3\}^+$  core.

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- 21 A vial containing 10 mg benzyltriphenylphosphonium bromide, polymer bound, was tightly closed and flushed with  $\text{N}_2$  for 10 min. 1,4,7-triazacyclononane trihydrochloride (15 mg, 0.06 mmol) was dissolved in 1 ml  $[{}^{99m}\text{TcO}_4]^-$  eluate and neutralized with 1 M NaOH. The solution was added to the polymer and the mixture was heated for 1 h at 95 °C. The reaction solution was cooled and the resin filtered. Yield: 88%, radiochemical purity >99%.

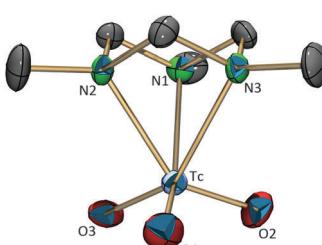


Fig. 2 ORTEP representation<sup>31</sup> of one  $[{}^{99m}\text{TcO}_3(\text{Me}_3\text{tach})]^+$  ( $[3]^+$ ) cation of the  $[3]_2[{}^{99m}\text{TcOBr}_4][{}^{99m}\text{TcO}_4] \cdot \text{CH}_2\text{Cl}_2$  structure (two molecules per asymmetric unit). Thermal ellipsoids represent 50% probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]:  $\text{Tc1-O1}$  1.697(2),  $\text{Tc1-O2}$  1.684(3),  $\text{Tc1-O3}$  1.687(2),  $\text{Tc1-N1}$  2.265(2),  $\text{Tc1-N2}$  2.274(2),  $\text{Tc1-N3}$  2.281(2),  $\text{O1-Tc1-O2}$  109.32(14),  $\text{O1-Tc1-O3}$  108.84(12),  $\text{O2-Tc1-O3}$  109.06(13),  $\text{N1-Tc1-N2}$  60.12(8),  $\text{N1-Tc1-N3}$  60.40(9),  $\text{N2-Tc1-N3}$  59.85(9).



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