Electronic Supplementary Material (ESI) for Chemical Communications.

Activation of $[^{99(m)}TcO_4]^-$ by Phosphonium Cations

Supporting Information

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1 Experimentel Part

1.1 General Information

Caution: ^{99}Tc is a weak β^- emitter. All experiments have to be done in laboratories approved for working with low-level radioactive materials.

All reactions were carried out under an inert N_2 atmosphere. $(NH_4)[^{99}TcO_4]$ (Oak Ridge) and all other chemicals were of reagent grade and used without further purification. Bis(3,5-dimethyl-1*H*-pyrazol-1-yl)acetic acid (Hbpza*)[1], 1,1',1''-methanetriyltris(3,5-dimethyl1*H*-pyrazole) (tpzm*)[2], as well as 1,3,5-trimethyl-1,3,5-triazacyclohexane (Me_3tach)[3] have been prepared according to literature procedures. FT-IR spectra were measured as KBr pellets on a Perkin Elmer Spectrum Two spectrophotometer. The ^{1}H NMR spectra of $[^{99}TcO_3$(tpzm*)]Br was recorded on a Varian Mercury 200 MHz spectrometer. ^{1}H, ^{13}C, ^{31}P, and ^{99}Tc NMR spectra of $[^{99}TcO_3(Me_3$tach)][$^{99}TcO_4]$ were recorded on a Bruker DRX500 500 MHz. ^{13}C NMR spectra were proton decoupled. Chemical shifts of ^{99}Tc are referenced relative to the signal of a 0.1 M solution of $(NH_4)[^{99}TcO_4]$ in CD_3OD ($\delta = 0$). HPLC analyses were performed on a Merck Hitachi LaChrom L 7100 pump coupled to a Merck Hitachi LaChrom L7200 tunable UV detector and a radiodetector, separated by a Teflon tube, which causes about a 0.4 – 0.7 min delay compared to Uv/vis detection. Uv/vis detection was performed at 250 nm. The detection of radioactive ^{99m}Tc complexes was performed with a Berthold LB506 radiodetector equipped with a BGO-X gamma cell. Separations were achieved on a Macherey-Nagel C18 reversed-phase column (Nucleosil 10 µm, 250 4 mm) using a gradient MeCN/50 mM TEAP as eluent, and flow rates of 0.5 mL/min. Gradient: t = 0 – 3 min: 0% MeCN; 3 – 3.1 min: 0 – 25% MeCN; 3.1 – 9 min: 25% MeCN; 9 – 9.1 min: 25 – 34% MeCN; 9.1 – 12 min: 34% MeCN; 12. – 12.1 min: 34 – 100% MeCN, 12.1 – 15 min: 100% MeCN; 15 – 15.1 min: 100 – 0% MeCN; 15.1 – 18 min: 100% MeCN.

1.2 Syntheses of ^{99}Tc complexes

1.2.1 Synthesis of $[^{99}TcO_3$(bipy)Br]

$(Bu_4N)[TcO_4]$ (40 mg, 0.1mmol), PPh_3Br_2 (42 mg, 0.1 mmol) and bipy (16 mg, 0.1mmol) were dissolved in dry acetonitrile (3 mL), and the solution was stirred for 30 min at ambient temperature. The product precipitated from the reaction solution as a yellow powder. Yield: 31 mg (82%).

IR(KBr): 3104(w), 3056(w), 1597(m), 1495(m), 1471(m), 1443(m), 1311(m), 1248(w), 1226(w), 1174(w), 1156(w), 1072(w), 1063(w), 904(vs), 884(vs), 773(m), 728(m), 666(w), 656(w), 648(w) 452(w) and 421(w) cm^{-1}. Data are in agreement with literature values.

1.2.2 Synthesis of [^{99}TcO$_3$(bpza*)]

(Bu_4N)[TcO_4] (36 mg, 0.09mmol), PPh_3Br_2 (39 mg, 0.09 mmol) and Hbpza* (23 mg, 0.09 mmol) were dissolved in dry acetonitrile (3 mL), and the solution was stirred for 2 h at ambient temperature. The product precipitated from the reaction solution as a yellow powder. Yield: 33 mg (93%).
IR (KBr): 1699(vs), 1675(vs), 1558(w), 1463(m), 1364(m), 1332(w), 1314(w), 1260(w), 1083(w), 1049(m), 904(vs), 896(vs), 821(w), 810(w), 765(w), 756(w), 715(w), 664(w), 651(w), 636(w), 484(w), 464(w), 426(w) cm^{-1}. Data are in agreement with literature values.

1.2.3 Synthesis of [^{99}TcO$_3$(tpzm*)]Br

(Bu_4N)[TcO_4] (36 mg, 0.09mmol), PPh_3Br_2 (39 mg, 0.09 mmol), and tpzm* (27 mg, 0.09 mmol) were dissolved in dry acetonitrile (3 mL) and the solution was stirred for 3 h at ambient temperature. The product was precipitated from the reaction solution by the addition of ether as a yellow powder. Yield: 38 mg (81%).
IR(KBr): 3118(w), 2971(w), 1564(m), 1462(m), 1413(m), 1391(m), 1303(m), 1262(m), 1049(m), 905(vs), 895(vs), 858(m), 808(m), 788(w), 704(m), 668(w), 629(w), 533(w), 521(w), 493(w) cm^{-1}.
^{1}H-NMR (CD_3CN, 200 MHz): $\delta = 7.79$ (s, 1 H, CH), 6.30 (s, 3 H, Hpz), 2.83 (s, 9 H, CH_3) 2.54 ppm (s, 9 H, CH_3). Data are in agreement with literature values.

1.2.4 Synthesis of [^{99}TcO$_3$(Me$_3$tach)][^{99}TcO$_4$] ([**3**][^{99}TcO$_4$])

[^{99}TcO$_3$(Me$_3$tach)][^{99}TcO$_4$] was synthesized in an inert nitrogen atmosphere (glove box, Schlenck technique is possible, but with lower yield).
(Bu_4N)[TcO_4] (40 mg, 0.1 mmol) and an excess Me$_3$tach (25 mg, 0.19 mmol) was dissolved in 1 ml of dry THF. PPh_3Br_2 (22 mg, 0.05 mmol) was suspended in 1 ml dry THF and the suspension was added to the reaction mixture. The reaction mixture immediately changed color from colorless to orange-brown and a yellow solid precipitated. The reaction mixture was filtered quickly to avoid the formation of side products. The yellow powder was washed with 2 x 0.2 ml dry diethylether and was dried under vacuum. The obtained crude product still contained small amounts of PPh_3Br_2. Because of the high moisture sensitivity of [**3**][^{99}TcO$_4$], no further purification steps have been performed. Consequently, no yield (%) and technetium content can be given. Yield: 13 mg. IR(KBr): 3440(m), 3372(m), 2981(m), 2955(m), 1616(w), 1465(m), 1414(w), 1381(w), 1260(m), 1172(w), 1104(s), 1003(m), 917(vs), 902(vs), 839(m), 721(w), 694(w), 541(w), 525(w), 509(w), 473(w) cm^{-1}. ^{1}H NMR (500 MHz, MeCN-D$_3$): $\delta = 4.20$ (s, 6 H, CH_2), 3.07 ppm (s, 9 H, CH_3). ^{13}C NMR (125 MHz, MeCN-D$_3$): $\delta = 40.27$ (CH_3), 67.60 ppm (CH_2). ^{99}Tc (113 MHz, MeCN-D$_3$): $\delta = 362$ ($\nu_{1/2} = 913$Hz), 0 ppm ($\nu_{1/2} = 52$ Hz).

1.3 Synthesis of [$^{99m}TcO_3(tacn)]^+$

1.3.1 Polymer synthesis

Triphenylphosphine, polymer bound (0.5 g, loading: ≈ 3 mmol / g, Sigma-Aldrich) was suspended in DMF 6 ml and swollen for 3 h. The solvent was filtered and a solution of benzyl bromide (7.5 mmol, 0.9 ml) in DMF (6 ml) was added. The resulting suspension was reacted for 24 h. The suspension was filtered and washed with CH_2Cl_2 three times. The obtained orange powder was dried in vacuo.

1.3.2 [$^{99m}TcO_3(tacn)]^+$

Method a) A vial containing 10 mg methyltriphenylphosphonium iodide, polymer bound, 200-400 mesh (Sigma-Aldrich) was tightly closed and flushed with N_2 for 10 min. 1,4,7-triazacyclononane trihydrochloride (15 mg, 0.06 mmol) was dissolved in 1 ml [$^{99m}TcO_4]^-$ 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: 64%, radiochemical purity ≥ 97%.

Method b) A vial containing 10 mg benzyltriphenylphosphonium bromid, polymer bound, was tightly closed and flushed with N_2 for 10 min. 1,4,7-triazacyclononane trihydrochloride (15 mg, 0.06 mmol) was dissolved in 1 ml [$^{99m}TcO_4]^-$ 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%.

1.3.3 [$^{99m}TcO(O_2styrSO_3)(tacn)$] synthesis ("one-pot")

A vial containing 10 mg benzyltriphenylphosphonium bromid, polymer bound, was tightly closed and flushed with N_2 for 10 min. 1,4,7-triazacyclononane trihydrochloride (15 mg, 0.06 mmol) and 4-vinylbenzenesulfonate (5 mg, 0.02 mmol) were dissolved in 1 ml [$^{99m}TcO_4]^-$ 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: 40%, radiochemical purity > 93%.

2 Supporting Information

2.1 Homogenous [^{99m}TcO$_3$(tacn)]$^+$ formation

Table ESI 2.1.1: Comparison of the [^{99m}TcO$_3$(tacn)]$^+$ formation by using different phosphonium salts to activate [^{99m}TcO$_4$]$^-$.

Phosphonium salt	**Yield of [^{99m}TcO$_3$(tacn)]$^+$**
(PPh$_3$Me)Br	35%
(PPh$_3$Bz)Br	35%
(PPh$_3$Et)Br	25%
(P^{n}Bu$_4$)Br	20%
(PPh$_4$)Br	19%
(PPh$_2$Me$_2$)I	19%
(PPh$_3$BzCOOMe)Br	20%
(PPhF$_3$Me)I	20%

2.2 Heterogeneous [^{99m}TcO$_3$(tacn)]$^+$ formation

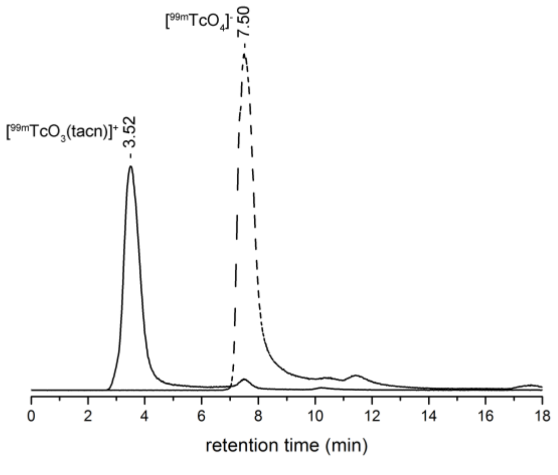

Figure ESI 2.2.1: HPLC trace (TEAP gradient) of the reaction solution before (dashed line) and after the reaction (solid line) of [^{99m}TcO$_4$]$^-$ with PS-[PPh$_3$Me]I and tacn (1 h, 95°C, pH = 7). Yield: 64% (3% [TcO$_4$]$^-$ remained in solution).

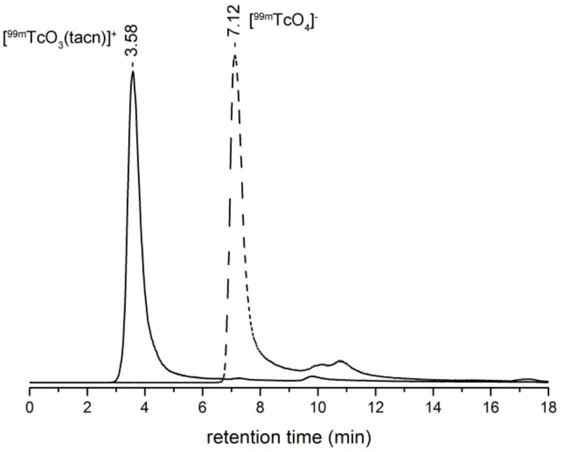

Figure ESI 2.2.2: HPLC trace (TEAP gradient) of the reaction solution before (dashed line) and after the reaction (solid line) of $[^{99m}TcO_4]^-$ with PS-$[PPh_3Me]I$ and tacn (10 min, 120°C, pH = 7, microwave reaction.). Yield: 78% (0.5% $[TcO_4]^-$ remained in solution).

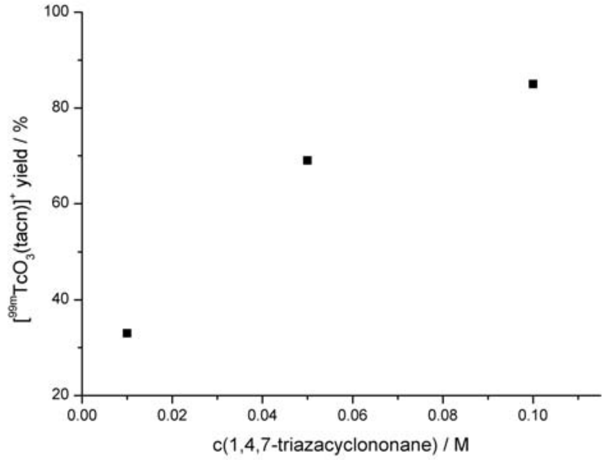

Figure ESI 2.2.3: $[^{99m}TcO_3(tacn)]^+$ yield vs. 1,4,7-triazacyclononaen concentration. Reaction conditions: 1 ml $[^{99m}TcO_4]^-$ eluat, 15 mg PS-$[PPh_3Me]I$, 1 h at 95°C (thermal heating).

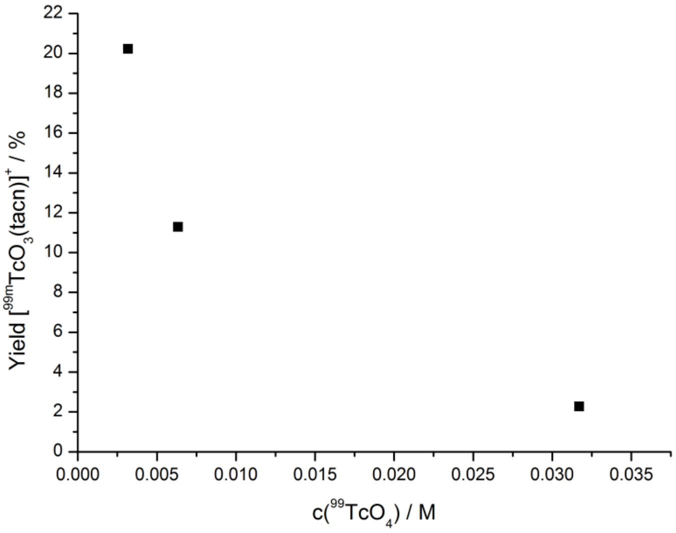

Figure ESI 2.2.4: $[^{99m}TcO_3(tacn)]^+$ yield vs. $[^{99}TcO_4]^-$ concentration. Reaction conditions: 1 ml $[^{99m}TcO_4]^-$ eluat, 13 mg PS-$[PPh_3Bz]Br$, 30 min at 95°C (thermal heating).

2.3 $[^{99m}TcO(O_2styrSO_3)(tacn)]$ ("one-pot")

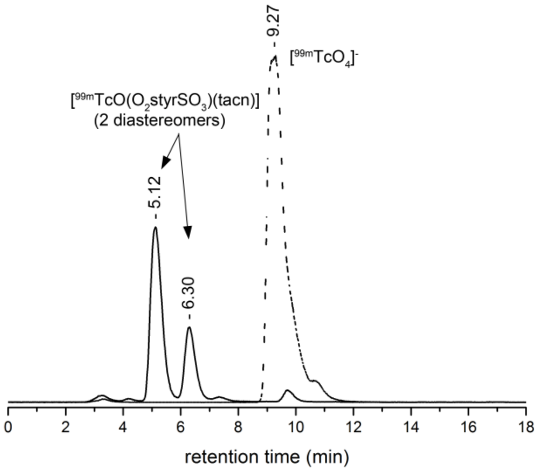

Figure ESI 2.3.1: HPLC trace (γ-detection, TEAP gradient) of the "one-pot" reaction, before (dashed line) and after the reaction (solid line) of $[^{99m}TcO_4]^-$ with PS-$[PPh_3Bz]I$, tacn, and sodium 4-vinylbenzenesulfonate (Na(styrSO$_3$), 1 h, 95°C, pH = 7). Yield: 40% (4% $[^{99m}TcO_4]^-$ and 3% $[^{99m}TcO_3(tacn)]^+$remained in solution). In comparison to other HPLC traces in this report the $[^{99m}TcO_4]^-$ peak shifted to 9 min, because of a new HPLC column,

2.4 ^{99}Tc and ^{31}P NMRs of the [^{99}TcO$_3$(Me$_3$tach)][^{99}TcO$_4$] ([**3**][^{99}TcO$_4$]) synthesis

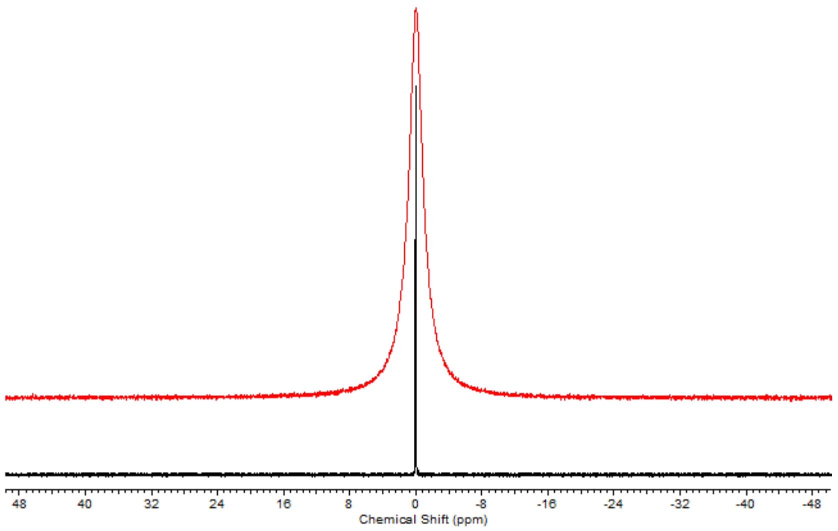

Figure ESI 2.4.1: ^{99}Tc NMR of [^{99}TcO$_4$]$^-$ before (black line, $\nu_{1/2}$ = 5.3 Hz), and after the addition of 1 equivalent of Ph_3PBr_2 (red line, $\nu_{1/2}$ = 229 Hz).

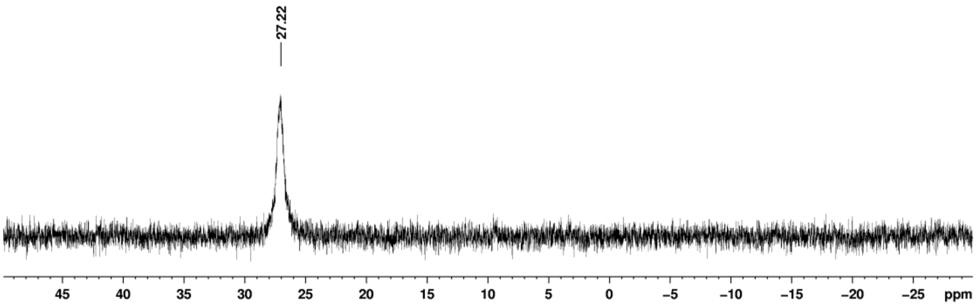

Figure ESI 2.4.2: ^{31}P NMR of the reaction solution (THF) of [^{99}TcO$_4$]$^-$ and 1 equivalent of Ph_3PBr_2 ($\nu_{1/2}$ = 110 Hz).

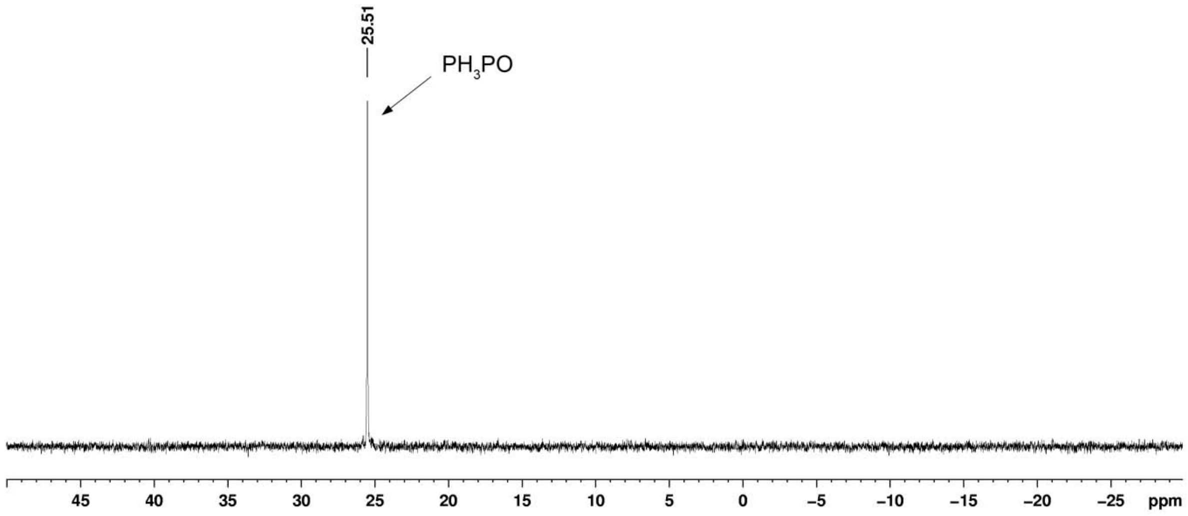

Figure ESI 2.4.3: ^{31}P NMR of the reaction solution (THF) of $[^{99}TcO_4]^-$, 1 equivalent of Ph_3PBr_2, and an excess Me_3tach. The signal at 25.51 ($\nu_{1/2}$ = 9 Hz) can be assigned as Ph_3PO. In this reaction the mixed anhydride $\{Ph_3BrP\text{-}O\text{-}^{99}TcO_3\}$ has been transformed into $[^{99}TcO_3(Me_3tach)][^{99}TcO_4]$ ([**3**]$[^{99}TcO_4]$) and Ph_3PO.

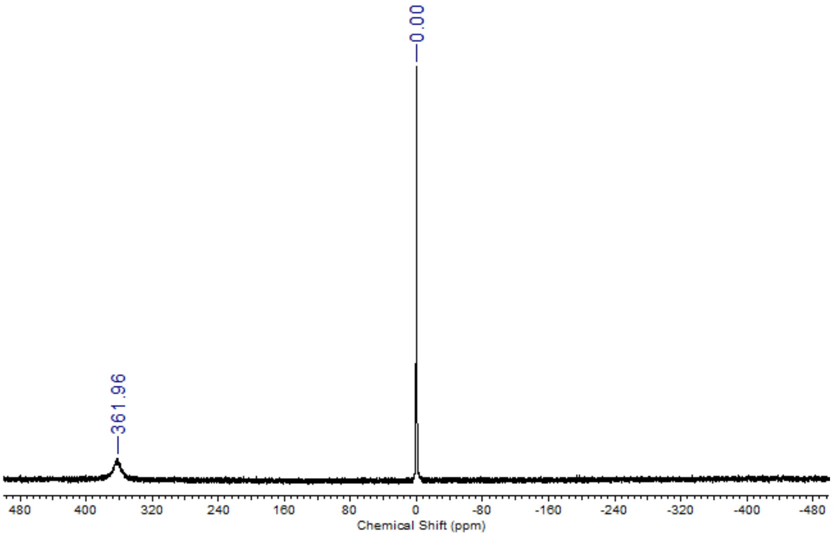

Figure ESI 2.4.4: ^{99}Tc NMR of compound $[^{99}TcO_3(Me_3tach)][^{99}TcO_4]$ ([**3**]$[^{99}TcO_4]$). Integral rate 1:1 ($[^{99}TcO_3(Me_3tach)]^+$: $[^{99}TcO_4]^-$).

2.5 Stability studies of [$^{99(m)}$TcO$_3$(tacn)]$^+$

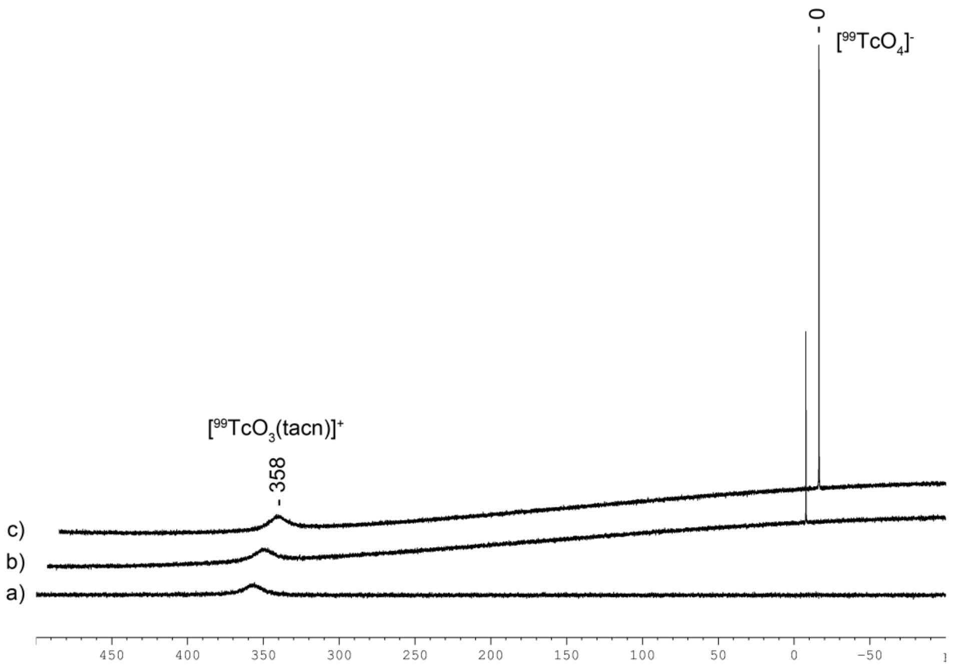

Figure ESI 2.5.1: ^{99}Tc NMRs of a solution of [^{99}TcO$_3$(tacn)]$^+$ dissolved in saline (pH 7, 95°C) at a) t = 0 h, b) t = 4 h, and c) t = 7 h.

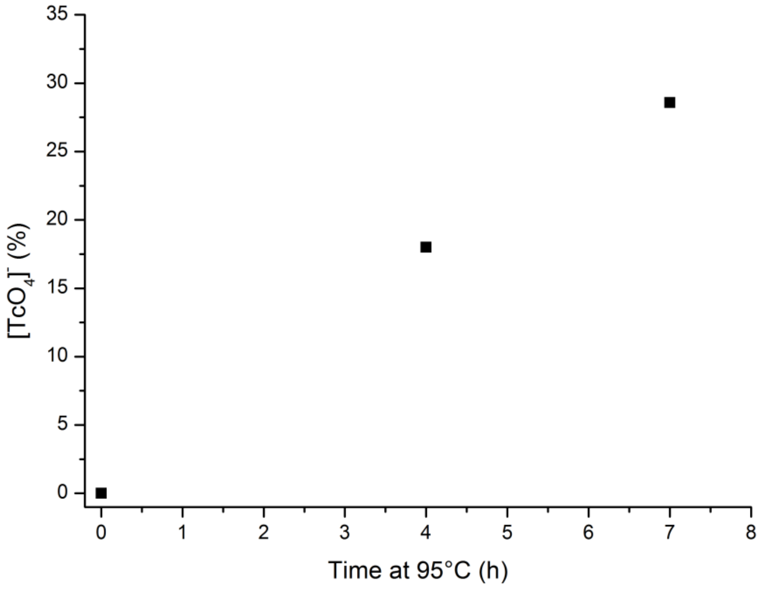

Figure ESI 2.5.2: Formation of [^{99}TcO$_4$]$^-$ in a solution of [^{99}TcO$_3$(tacn)]$^+$ dissolved in saline (pH 7, 95°C), distinguished by integration of the ^{99}Tc NMR signals at t = 0, 4 (18% [^{99}TcO$_4$]$^-$), and 7 h (29% [^{99}TcO$_4$]$^-$).

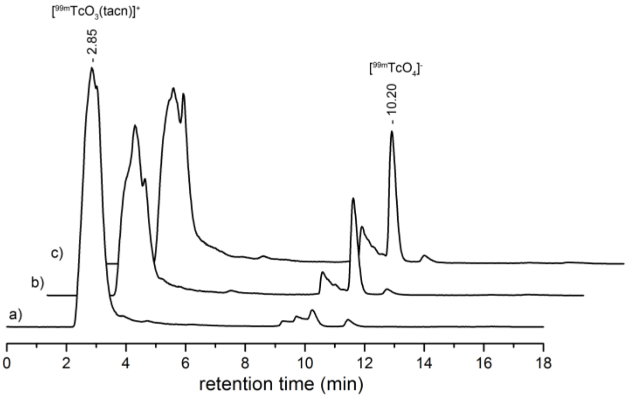

Figure ESI 2.5.3: HPLC traces (γ-detection, TEAP gradient) of the reaction solution of the $[^{99m}TcO_3(tacn)]^+$ synthesis (pH 7, 95°C) at a) t = 0 h, b) t = 1 h, and c) t = 2 h. In comparison to ohter HPLC traces in this report the $[^{99m}TcO_4]^-$ peak got shifted to 10 min, because of a new HPLC column,

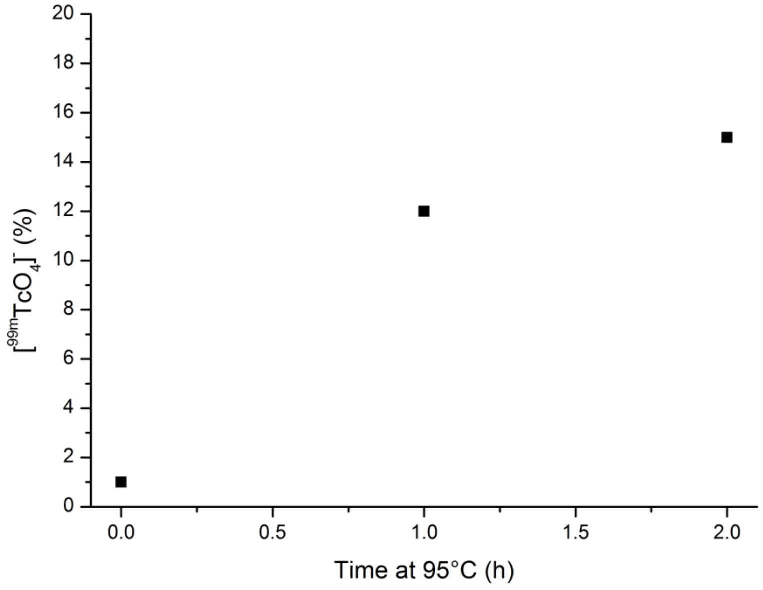

Figure ESI 2.5.4: Formation of $[^{99m}TcO_4]^-$ in the reaction solution of the $[^{99m}TcO_3(tacn)]^+$ synthesis (pH 7, 95°C), distinguished by HPLC at t = 0 (1% $[^{99m}TcO_4]^-$), 1 (12% $[^{99m}TcO_4]^-$), and 2 h (15% $[^{99m}TcO_4]^-$).

3 Crystallographic Details

Crystallographic data were collected at 183(2) K with Mo Kα radiation (λ = 0.7107 Å) using a graphite monochromator on an Oxford Diffraction Xcalibur system with a Ruby detector. A Suitable crystal was covered with oil (Infineum V8512, formerly known as Paratone N), mounted on top of a glass fiber and immediately transferred to the diffractometer. The program suite CrysAlis Pro was used for data collection, semi-empirical absorption correction, and data reduction.[4] More details on data collection and structure calculations are contained in table ESI2. The structure was solved with direct methods using SIR97[5] and was refined by full-matrix least-squares methods on F^2 with SHELXL-97. The refinement has been done with anisotropic thermal parameters for all non-hydrogen atoms. The positions of the hydrogen atoms have been calculated using the 'riding model' option of SHELXL97.[6]

Table ESI 3.1: Data collection and structure calculation details.

	$[^{99}TcO_3(Me_3tach)]_2[TcOBr_4][TcO4]\cdot CH_2Cl_2$ $[\mathbf{3}]_2[TcOBr_4][TcO4]\cdot CH_2Cl_2$
Formula	$C_{13}H_{32}Br_4Cl_2N_6O_{11}Tc_4$
M_w / g mol^{-1}	1234.95
Space group	$P\bar{1}$
Temperature / K	183
a / Å	10.6731 (3)
b / Å	12.5422 (4)
c / Å	13.5332 (3)
α / °	109.775 (3)
β / °	97.616 (2)
γ / °	96.984 (3)
μ / mm^{-1}	6.65
Z	2
V / Å^3	1662.62 (8)
ρ_{calc} / g cm^{-3}	2.459
Crystal description	orange block
Θ range [°]	2.8 to 30.5
	-15<=h<=15
Index ranges	-17<=k<=17
	-19<=l<=15
Refl collected	34931
Indep refl	10118[R(int) = 0.040]
Refl obs I > 2σ(I)	9012
Compl to theta	99.7% to 30.51°
Max. and min. transm	0.398 and 0.196
Restraints / param	0 / 367
Goodness-of-fit on F^2	1.06
Final diff ρ_{max} (e^-/ Å^3)	1.05 and -1.45
R1[a, c]	0.029
wR2[b, c]	0.069
CCDC	976753

[a] $R1 = |F_o - F_c|/|F_o|$; [b] $wR2 = [w(F_o^2 - F_c^2)^2/(wF_o^2)]^{1/2}$; [c] I > 2 sig(I)

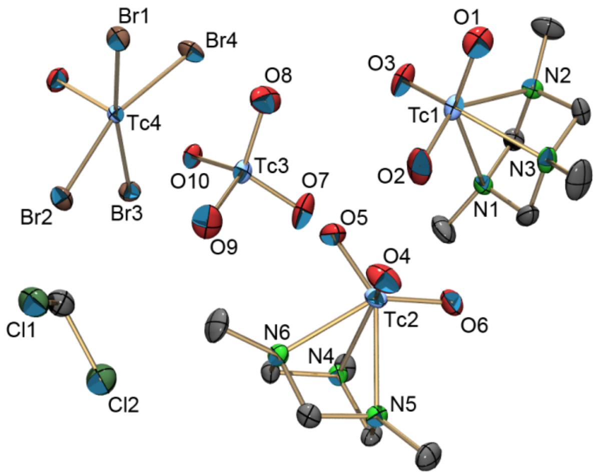

Figure ESI 3.1: Crystal structure of [^{99}TcO$_3$(Me$_3$tach)][TcOBr$_4$][TcO4]·CH$_2$Cl$_2$

Table ESI3:Bond lengths [Å] and angles [°] for [^{99}TcO$_3$(Me$_3$tach)][TcOBr$_4$][TcO4]·CH$_2$Cl$_2$.

Tc1-O1 1.697 (2)	Tc2-O4 1.692 (2)
Tc1-O2 1.684 (3)	Tc2-O5 1.694 (2)
Tc1-O3 1.687 (2)	Tc2-O6 1.700 (2)
Tc1-N1 2.265 (2)	Tc2-N4 2.279 (2)
Tc1-N2 2.274 (2)	Tc2-N5 2.280 (2)
Tc1-N3 2.281 (2)	Tc2-N6 2.276 (2)
O1-Tc1-O2 109.32 (14)	O4-Tc2-O5 109.64 (12)
O1-Tc1-O3 108.84 (12)	O4-Tc2-O6 108.83 (12)
O2-Tc1-O3 109.06 (13)	O5-Tc2-O6 109.62 (11)
N1-Tc1-N2 60.12 (8)	N4-Tc2-N5 59.84(8)
N1-Tc1-N3 60.40 (9)	N4-Tc2-N6 60.18 (8)
N2-Tc1-N3 59.85 (9)	N5-Tc2-N6 60.12 (8)

4 References:

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