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Water-stable *fac*-$\{TcO_3\}^+$ Complexes – A New Field of Technetium Chemistry

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Abstract: The development of technetium chemistry has been lagging behind that of its heavier congener rhenium, primarily because the inherent radioactivity of all Tc isotopes has limited the number of laboratories that can study the chemistry of this fascinating element. Although technetium is an artificial element, it is not rare. Significant amounts of the isotope ^{99}Tc are produced every day as a fission byproduct in nuclear power plants. Therefore, a fundamental understanding of the chemistry of ^{99}Tc is essential to avoid its release into the environment. In this article the chemistry of technetium at its highest oxidation state (+VII) is reviewed with a special focus on recent developments which make water-stable complexes of the general type $[TcO_3(tacn\text{-}R)]^+$ (tacn-R = 1,4,7-triazacyclononane or derivatives) accessible. Complexes containing the *fac*-$\{TcO_3\}^+$ core display a unique reactivity. In analogy to $[OsO_4]$ and $[RuO_4]$, complexes containing the *fac*-$\{TcO_3\}^+$ core undergo with alkenes metal-mediated, vicinal *cis*-dihydroxylation reactions (alkene-glycol interconversion) in water *via* a (3+2)-cycloaddition reaction. Therefore, water-stable *fac*-$\{^{99m}TcO_3\}^+$ complexes pave the way for a new labeling strategy for radiopharmaceutical applications, based on (3+2)-cycloaddition reactions. This new concept for the labeling of biomolecules with small $[^{99m}TcO_3(tacn\text{-}R)]^+$-type complexes by way of a (3+2)-cycloaddition with alkenes is discussed in detail. The herein reported developments in high-valent technetium chemistry create a new field of research with this artificial element. This demonstrates the potential of fundamental research to provide new impetus of innovation for the development of new methods for radiopharmaceutical applications.

Keywords: Alkenes · (3+2)-Cycloaddition · Labeling · Radiopharmacy · Technetium

1. Introduction

Technetium is a fascinating element, located in the middle of the periodic table (element 43). Apart from the fact that it does not have even one stable isotope, it can be characterized as a typical second row transition metal. Technetium is not a member of the natural decay series of uranium and thorium, therefore, it is often referred to as a 'man-made' element. Although technetium is an artificial element, it is not rare. Technetium is a fission byproduct in nuclear power plants. It was estimated that a typical pressurized water reactor (PWR), which is one of two types of light water reactors, produces about 9.3 kg of the isotope technetium-99 (^{99}Tc) per gigawatt$_{(elect)}$ year.[1] Based on this estimation and the amount of energy supplied by nuclear power plants worldwide,[2,3] it can be calculated that today approximately 9.5 kg of ^{99}Tc are produced every day. ^{99}Tc is separated from used nuclear fuel in a reprocessing method known as the Plutonium-Uranium Extraction process (PUREX process). This leads to a current ^{99}Tc 'production' of over three tonnes per year. Fig. 1 shows the estimated ^{99}Tc production worldwide from 1970 until 2009 based on the capacity of all nuclear power plants.[2,3] Furthermore, it shows the possible development of ^{99}Tc production (low and high estimate) until 2050 based on calculations for needs of energy, electricity and nuclear power made by the International Atomic Energy Agency (IAEA).[2] This should demonstrate the abundance of this radioactive artificial element today and in the near future.

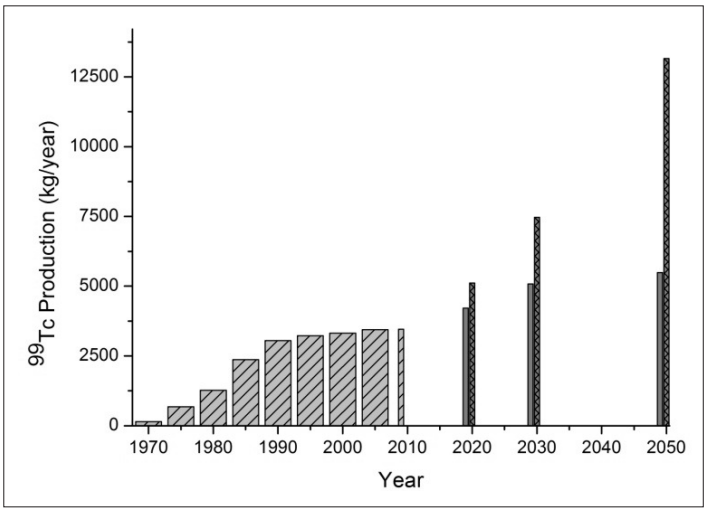

Fig. 1. Estimated ^{99}Tc production per year from 1970 to 2050 based on the capacity of all nuclear power plants worldwide.[2,3]

^{99}Tc is a weak β^--emitter (emission of electrons, E_{max} = 293 keV), but there is a potential hazard because of its long half-life of $2.13 \cdot 10^5$ years, which brings severe problems for nuclear waste management. Therefore, a fundamental understanding of the chemistry of ^{99}Tc is essential to avoid its release into the environment. Furthermore, profound insights into fundamental and environmental chemistry of ^{99}Tc are important to gain a broad knowledge of potential mobilization mechanisms, distribution pathways and hazards after accidental release. The development of technetium

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chemistry has been lagging behind that of its heavier congener rhenium, primarily because the inherent radioactivity of all Tc isotopes has limited the number of laboratories that can study the chemistry of this fascinating element. Good examples for these curious gaps in fundamental technetium chemistry are the recent preparations of the simple trivalent technetium halides $TcBr_3$ and $TcCl_3$,[4,5] and the binary halide $TcCl_2$.[6]

Most current studies with technetium focus on the development of novel compounds for radiopharmaceutical diagnostics in nuclear medicine.[7–12] Radioactivity remains one of the most sensitive methods for non-invasive imaging, where the nuclear isomer of ^{99}Tc, technetium-99m (^{99m}Tc), plays a prominent role. An estimated 90% of all diagnostic procedures in nuclear medicine, carried out worldwide involve ^{99m}Tc compounds.[13] Because of its nearly ideal nuclear properties and widespread availability at modest cost, ^{99m}Tc is said to be the 'workhorse' for nuclear medicine. The availability of the isotope from generators, in combination with the short physical half-life time (6 h) and the emission of low energy γ-rays (140.5 keV) make ^{99m}Tc a very convenient and practical isotope. Nevertheless, a site-specific conjugation of a metalloradionuclide like ^{99m}Tc to a targeting vector in a manner in which the product retains the affinity of the parent biomolecule is challenging.

To address this issue, one can take advantage of the rich coordination chemistry of technetium. Coordination of radiometals to an appropriate and strong chelator, conjugated to a targeting biomolecule (peptides, oligonucleotides or small molecules) is the most frequently applied labeling strategy and known as the bifunctional chelator (BFC) approach[14] (Fig. 2).

The BFC approach conveniently enables screening of a large number of targeting molecules with one particular metal core for which the chelator is designed. In the field of technetium chemistry, Tc^{V} and Tc^{I} cores have been widely explored to prepare molecular imaging probes.[7–10]

In the future, fundamental chemistry of Tc and applied radiopharmacy have to be pushed forward due to their importance for society. Therein, synergy plays an important role. On one hand, knowledge gained by radiopharmaceutical developments can draw a detailed picture of the biological profile (stability and distribution) of technetium compounds *in vivo* and can help to gain an understanding of its biological impact. On the other hand fundamental research with ^{99}Tc is essential to understand the (coordination) chemistry of technetium. This could lead to the creation of new Tc synthons, which again creates opportunities to develop new and effective imaging probes that overcome the challenges of introducing a metal complex into a vector. Our research is a recent example for this synergetic effect.

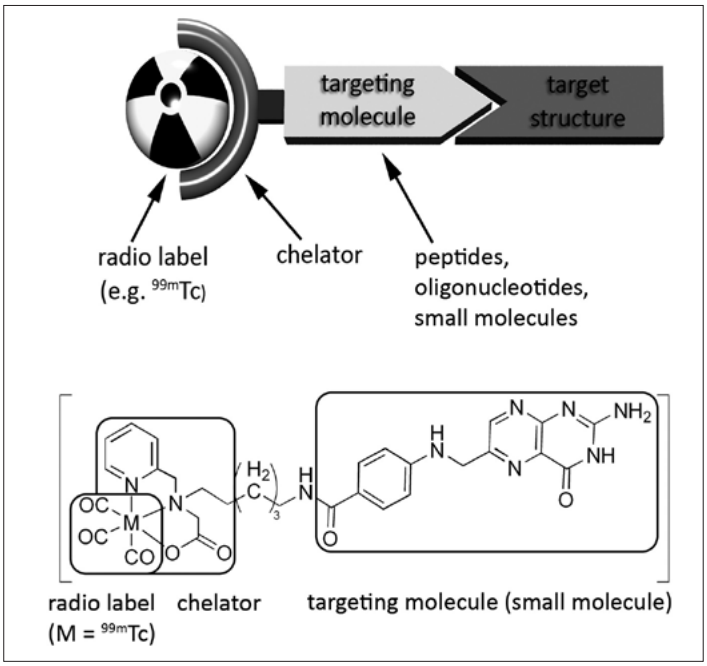


Fig. 2. The general bifunctional chelator concept (BFC) for the site specific conjugation of a metalloradionuclide to a targeting vector and an example for its translation into ^{99m}Tc chemistry (labeling of a pteroate derivative).[15]

2. High-valent Technetium Compounds

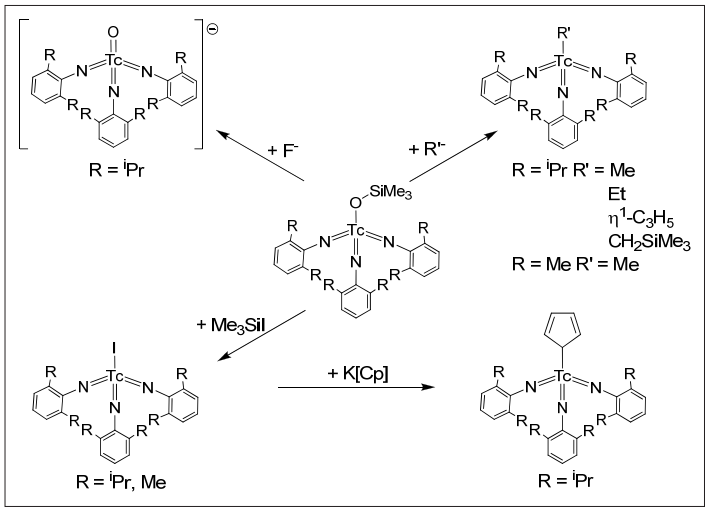
Technetium (^{99}Tc) is obtained as pertechnetate ($[TcO_4]^-$) from the PUREX process. Therefore $[TcO_4]^-$ is the only starting material for technetium chemistry. This compound contains the metal in its highest oxidation state +VII. Although pertechnetate contains formally only 16 e^-, it is extremely stable. In most cases, reduction is the key step for further conversion to other complexes. Complexes such as $[TcNCl_4]^-$ (Tc^{VI}), $[TcOCl_4]^-$ (Tc^{V}), $[TcCl_6]^{2-}$ (Tc^{IV}), and $[Tc(CO)_3Cl_3]^{2-}$ (Tc^{I}) are common precursors for ^{99}Tc chemistry. However, a direct activation of $[TcO_4]^-$ is a question of permanent interest since it could induce possibilities for the synthesis of new starting compounds. Moreover, it could answer the question of a biological activation after its accidental release into the environment.

Besides $[TcO_4]^-$, only a relatively small number of high-valent Tc-complexes are known. This can be rationalized by the lack of a suitable precursor complex for the synthesis of Tc^{+VII} complexes. $[Tc_2O_7]$ is a very prominent compound. It can be prepared by oxidizing Tc metal in a stream of oxygen at 400–600 °C. Chemically it behaves as if it was built of $[TcO_4]^-[TcO_3]^+$. $[Tc_2O_7]$ can therefore be heterolytically cleaved by strong ligands such as CH_3^-.[16] In contrast to the homologous binary metal oxide, $[Re_2O_7]$, which exhibits an infinite polymeric solid-state structure, $[Tc_2O_7]$ has a discrete molecular composition.[17] Due to its molecular character, $[Tc_2O_7]$ is volatile. This fact and the moisture sensitivity of $[Tc_2O_7]$ make this compound an inconvenient precursor for the synthesis of high-valent Tc complexes. As an alternative, pertechnetic acid ($HTcO_4$) was used. $HTcO_4$ can be prepared *in situ* by the addition of strong Brønsted acids (*e.g.* H_2SO_4 or HCl) to a solution of $[TcO_4]^-$ in dry organic solvents. However, $HTcO_4$ is volatile as well and thereby not a suitable precursor due to radioprotection restrictions. Beside the lack of a suitable precursor complex for high-valent Tc chemistry, a (water) stable metal core, such as the *fac*-$\{Tc(CO)_3\}^+$ core for low-valent Tc chemistry, that could act as a building block is not available. Only compounds containing the *fac*-$\{Tc(NAr)_3\}^+$ or *fac*-$\{TcO_3\}^+$ core have so far been found to be sufficiently resistant to reduction and hydrolysis.

The reaction of the moisture-sensitive $[TcO_3(OSiMe_3)]$[18] with 2,6-diisopropylphenylisocyanate or 2,6-dimethylphenylisocyanate leads to elimination of the CO_2 and the formation of tris-imido complexes $[Tc(NAr)_3(OSiMe_3)]$ (Ar = 2,6-diisopropylphenyl or 2,6-dimethylphenyl).[19] $[Tc(NAr)_3(OSiMe_3)]$ is the precursor complex for a variety of new Tc^{+VII} complexes of the general formula $[Tc(NAr)_3X]^{0/-}$ (X = alkyl, I, η^1-Cp) (Scheme 1).[19,20]

Surprisingly, this interesting metal core was not a subject of further studies and no syntheses for corresponding ^{99m}Tc complexes were developed. Water-stable *fac*-$\{^{99m}Tc(NAr)_3\}^+$ complexes such as the $[Tc(NAr)_3Cp]$ could have interesting properties for potential radiopharmaceutical applications.

However, most stable high-valent tech-



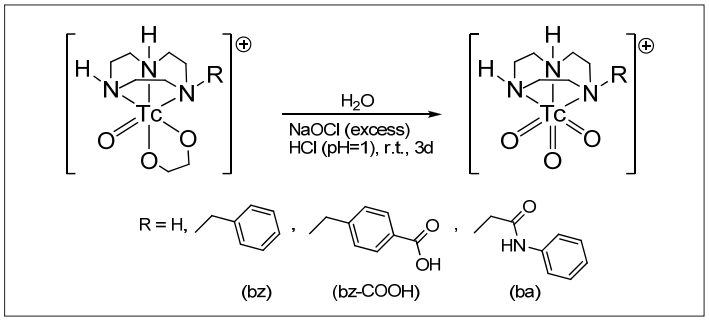
Scheme 1. Reactions of $[Tc(NAr)_3(OSiMe_3)]$ leading to a variety of new Tc^{VII} complexes of the general formula $[Tc(NAr)_3X]^{0/-}$ (X = alkyl, I, η^1-Cp).[19,20]

netium complexes contain the *fac*-$\{TcO_3\}^+$ core. The stability and the unique reactivity of this metal core render these complexes very interesting in the context of our research.

2.1 *The fac-{TcO$_3$}$^+$ Core*

The *fac*-$\{TcO_3\}^+$ core is probably the smallest feasible Tc metal core that can be stabilized by tripodal ligands. Its size is significantly smaller than the *fac*-$\{Tc(CO)_3\}^+$ core and already close to the size of an iodide ion.

Due to the lack of a suitable precursor complex for ligand replacement reactions only two synthetic pathways are available for the synthesis of complexes containing the *fac*-$\{TcO_3\}^+$ core: The direct activation of $[TcO_4]^-$ and the oxidation of stable Tc complexes which contain the metal atom at a lower oxidation state. All known *fac*-$\{TcO_3\}^+$ complexes have been synthesized along these two routes. However, structurally characterized *fac*-$\{TcO_3\}^+$ complexes are relatively rare. Davison *et al.* reported the synthesis of $[^{99}TcO_3(HB(pz)_3]$ (pz = pyrazolyl) through oxidation of $[^{99}TcOCl_2(HB(pz)_3)]$ with nitric acid or from $[HTcO_4]$.[21] *In situ* generated, volatile $HTcO_4$ was the precursor for a variety of *fac*-$\{TcO_3\}^+$ complexes such as $[^{99}TcO_3(bipy)Cl]$, $[^{99}TcO_3(phen)Cl]$,[22] or $[^{99}TcO_3(L^3)]$ (L^3 = Kläui ligand $[(\eta^5\text{-}C_5H_5)Co\{P(OR)_2(=O)\}_3]$.[23,24] Binuclear complexes with bptz and pppz ligands have been prepared along the same route.[25] The very moisture-sensitive compounds $[TcO_3F]$ and $[TcO_3][SO_3F]$ were isolated from pure HF and $[HSO_3F]$.[26,27] Furthermore, $[^{99}TcO_3\{OSn(CH_3)_3\}]$[16] and its silyl analogue are known.[18] Recently the quest for suitable precursor *fac*-$\{TcO_3\}^+$ complexes led to a series of compounds with the general formula $[R_3EOTcO_3]$ (E = C, Si, Ge, Sn, Pb; R = Me, iPr, tBu, Ph).[28] In this context we reported mixed anhydrides $[TcO_3(OCOPh)]$ and $[TcO_3(OBF_3)]^-$.[29] Due to the fact that the activated $[TcO_4]^-$ species, such as $[TcO_3(OBF_3)]^-$, are highly reactive and water sensitive all these reactions were done in organic (dry) solvents. Therefore, a synthesis from water remained unknown until 2006.[30]



Scheme 2. General synthesis of $[TcO_3(tacn\text{-}R)]^+$-type complexes.

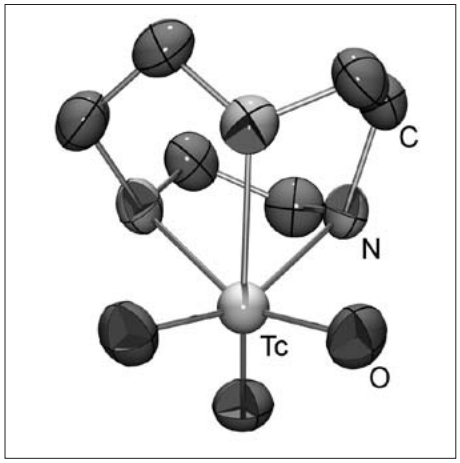


Fig. 3. Crystal structure of $[TcO_3(tacn)]^+$. Hydrogen atoms are omitted for clarity. Bond angles (°): O-Tc-O 106.5(2).[30]

The small tridentate ligand 1,4,7-triazacyclonane and its derivatives form very stable mono oxo Tc^{+V} complexes of the general type $[TcO(glyc)(tacn\text{-}R)]^+$ (glyc = ethylene glycol; tacn-R = 1,4,7-triazacyclononane or derivatives).[30,31] These deep blue complexes are water stable at neutral and basic pH, and only decompose slowly under acidic conditions, accompanied by a color change from deep blue to brown. It is believed that acidic conditions lead to the loss of the glycol ligand, which initiates further decomposition. However, after the addition of a freshly prepared acidic sodium hypochlorite solution (NaOCl) to an aqueous solution of $[TcO(glyc)(tacn\text{-}R)]^+$ a slow color change from blue to yellow can be observed. After evaporation of the solvent $[TcO_3(tacn\text{-}R)]^+$ can be isolated in the form of yellow crystals (Scheme 2).

The isolated *fac*-$\{TcO_3\}^+$ complexes are water stable over a wide range of pH. A common structural feature of all *fac*-$\{MO_3\}^+$ (M = Re, Tc) structures are the large O-M-O angles, which are usually maximized to a nearly ideal tetrahedral angle (Fig. 3).

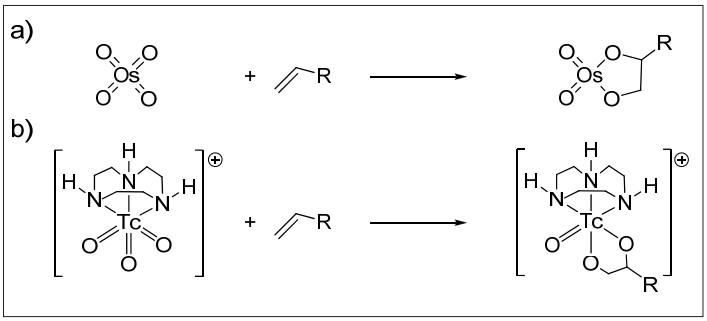
This mirrors the spatial demand of terminal oxo ligands when the metal is in its highest oxidation state +VII. In this case, ligand field effects play a minor role and the terminal oxo ligands assume a minimal energy conformation by minimizing electrostatic repulsion.

Our interest in *fac*-$\{TcO_3\}^+$ complexes is not exclusively based on the possibility to form (water) stable Tc^{VII} complexes but also due to the unique reactivities of *fac*-$\{TcO_3\}^+$ complexes with alkenes.

2.2 *(3+2)-Cycloadditions of fac-{TcO$_3$}$^+$ Complexes with Alkenes*

The *fac*-$\{TcO_3\}^+$ core is compact and can be coordinated to different tripodal ligands as described above. Besides the small size, complexes with the *fac*-$\{TcO_3\}^+$ core display a unique reactivity, particularly in water. In analogy to $[OsO_4]$ and $[RuO_4]$, complexes containing the *fac*-$\{TcO_3\}^+$ core undergo metal-mediated, vicinal *cis*-dihydroxylation reactions (alkene-glycol interconversion) with alkenes *via* a (3+2)-cycloaddition reaction.[32] *Cis*-dihydroxylation reactions with $[OsO_4]$ have been known for a long time,[33,34] with *fac*-$\{TcO_3\}^+$ complexes, however, this reaction type allows for a new way of covalent bond formation between Tc complexes and a substrate, without the need of a ligand replacement reaction (Scheme 3).

In contrast to $[OsO_4]$, $[TcO_3(tacn\text{-}$



Scheme 3. a) *Cis*-dihydroxylation reactions of alkenes with $[OsO_4]$; b) *cis*-dihydroxylation reactions of alkenes with $[TcO_3(tacn)]^+$.

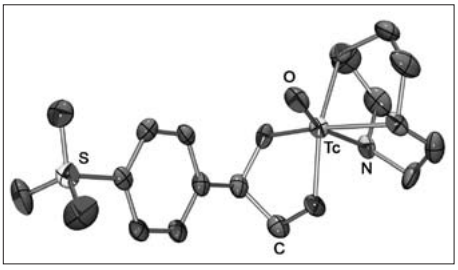


Fig. 4. Crystal structure of $[TcO(styrSO_3)(tacn)]$.[4]

R)]$^+$-type complexes do this reaction in water as shown by the reaction of $[TcO_3(tacn)]^+$ with the water-soluble alkene sodium 4-vinylbenzenesulfonate ($Na(styrSO_3)$). This reaction yields the stable blue complex $[TcO(styrSO_3)(tacn)]$ (Fig. 4). Investigations with a variety of alkenyl-substrates showed that the reaction mechanism is strongly associatively driven and that the rates are highly dependent on the substrate used, but nearly independent of the solvent.[31] Further kinetic studies of the $[^{99}TcO_3(tacn\text{-}R)]^+$ (R = H, bz, bz-COOH) system under pseudo-first-order conditions showed that complexes of monosubstituted tacn-derivatives undergo a faster (3+2)-cycloaddition reaction than in the case with unsubstituted tacn.[31] This observation seems to be of critical importance when taking into account that the rate of the (3+2)-cycloaddition could be tuned by the properties of one or possibly more substituents on the tacn ligand.

3. A New Labeling Strategy for Radiopharmaceutical Applications

The knowledge about stability and reactivity gained by the fundamental ^{99}Tc experiments described previously make the *fac*-$\{TcO_3\}^+$ core very attractive as a new synthon for radiopharmaceutical applications. Water-stable *fac*-$\{^{99m}TcO_3\}^+$ complexes would pave the way for a new labeling strategy based on (3+2)-cycloaddition strategies and can provide this research with a new impetus of innovation. In addition to functionalizations *via* cycloaddition, fundamental studies with ^{99}Tc evidence that the tripodal ligand can carry a second, bioactive function. This may present an excellent opportunity for the synthesis of novel bifunctional imaging agents. With this concept, directly transferred to $\{^{99m}TcO_3\}$-labeling procedures, highly versatile, bifunctional radiolabels would become accessible. Whereas today's synthetic strategies for the development of bifunctionalized Tc complexes are based on ligand replacement reactions at the metal core ([2+1], [3+1], [3+2], [4+1] and the HYNIC approaches),[35] *fac*-$\{TcO_3\}^+$ complexes can easily and efficiently be bifunctionalized in a ligand-based fashion (Scheme 4).

This special feature of the *fac*-$\{TcO_3\}^+$ complexes can be used as a creative route to prepare novel molecular imaging probes and can help to overcome limitations given by the coordination chemistry of technetium.

A crucial point for the development of this new labeling strategy was the synthesis of a $[^{99m}TcO_3(tacn)]^+$ complex. In contrast to ^{99}Tc chemistry, ^{99m}Tc chemistry has to be done at high dilution: $[^{99m}TcO_4]^-$ is eluted with a physiological sodium chloride solution from the so-called '^{99m}Tc generator' (^{99}Mo immobilized on an aluminum oxide column) and is obtained in concentrations of 10^{-6}–10^{-9} mol/l. Organic solvents, toxic oxidizing agents and non-pertechnetate starting compounds, make the previously described ^{99}Tc approaches unfeasible for the synthesis of ^{99m}Tc trioxo analogues. For the synthesis of water-stable ^{99m}Tc trioxo complexes ($[^{99m}TcO_3(tacn\text{-}R)]^+$), a new reaction had to be developed starting from the diluted aqueous solution of $[^{99m}TcO_4]^-$ and using phosphines as reagents.[31] The phosphine was conjugated to a solid-phase support (resin), since the resin can easily be filtered after a heterogeneous reaction, which allows for the removal of excess reagents. In the presence of such polymers and a very strong tripodal ligand such as tacn, the corresponding trioxo complex was formed in moderate yield after 1 h at 95 °C as the only product from $[^{99m}TcO_4]^-$ (Scheme 5).

The only suitable analytical method at these low concentrations is a HPLC system which is coupled to a UV- and a radiodetector. In general, the comparison of the HPLC retention times for the new ^{99m}Tc compounds with a corresponding 'cold' standard compound (often the rhenium analog) confirms its identity. In this particular case the corresponding ^{99}Tc compound is the 'cold' standard (Fig. 5).

The synthesis of $[^{99m}TcO(styrSO_3)(tacn)]$ by the reaction of $[^{99m}TcO_3(tacn)]^+$ with sodium 4-vinylbenzenesulfonate ($Na(styrSO_3)$) showed the suitability of

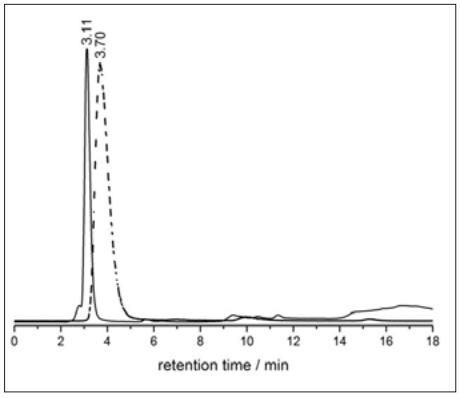
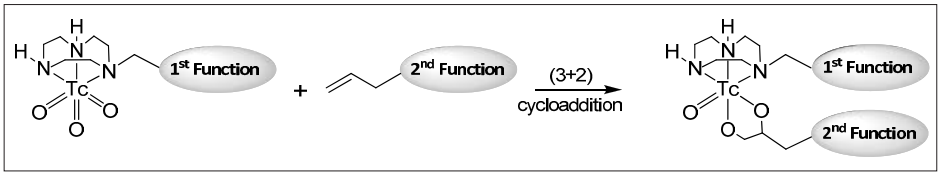
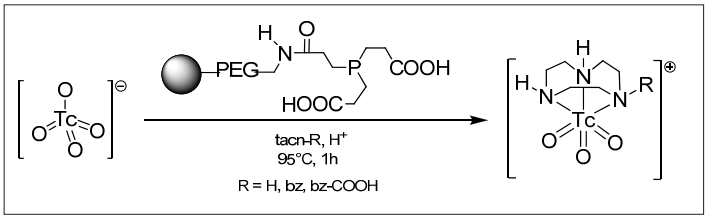


Fig. 5. HPLC traces (TEAP gradient) of a co-injection of $[^{99m}TcO_3(tacn)]^+$ and $[^{99}TcO_3(tacn)]^+$: $[^{99}TcO_3(tacn)]^+$ with UV detection (solid line) and $[^{99m}TcO_3(tacn)]^+$ with γ-detection (dashed line). Due to the detector separations, the γ-signal is delayed by 0.6 min compared to the UV-signal.



Scheme 4. Bifunctionalization of $[^{99m}TcO_3(tacn\text{-}R)]^+$ by cycloaddition.



Scheme 5. Synthesis of $[^{99m}TcO_3(tacn\text{-}R)]^+$-type complexes.[31]

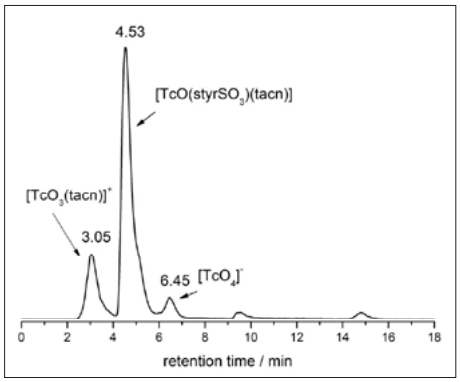
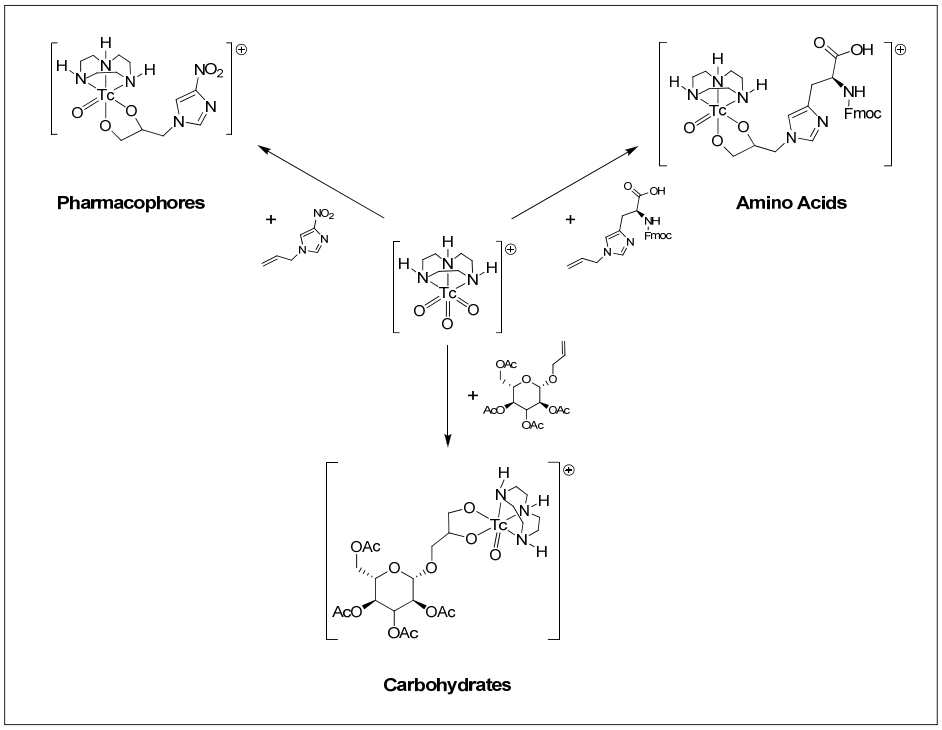


Fig. 6. HPLC γ-trace (TEAP gradient) during the reaction between $(styrSO_3)^-$ and $[^{99m}TcO_3(tacn)]^+$.



Scheme 6. Labeling of 1-allyl-4-nitro-imidazole, 1-allyl-L-histidine and allyl-2,3,4,6-tetra-O-acetyl-β-(D)-glucopyranoside with $[^{99m}TcO_3(tacn)]^+$ *via* (3+2)-cycloaddition.

fac-$\{^{99m}TcO_3\}^+$ complexes as synthons for the new labeling strategy (Fig. 6).

In general, the (3+2)-cycloaddition of *fac*-$\{TcO_3\}^+$ complexes with alkenes (except for ethene) will yield two diastereomeres (*exo*- and *endo*-products). The *exo*-product (the product with the larger distance between the substituent of the alkene unit and the Tc-center) is favored over the *endo*-product due to steric repulsion.[32] The formation of two diastereomeres which can hardly be separated by HPLC, rationalizes the broad peak shape of the $[^{99m}TcO(styrSO_3)(tacn)]^+$ in Fig. 6. Nevertheless, if one of the diastereomeres is favored (*e.g.* since it enables the formation of intramolecular hydrogen bonds), the (3+2)-cycloaddition can be stereoselective.[36] This stereoselectivity is a critical point for the development of potential radiopharmaceuticals since the biological profile of diastereomers can be significantly different. Currently, parameters that can influence this stereoselectivity are under intensive investigation.

Very recently the development of the new labeling method was brought to the next level.[36] To characterize the biological profile of $[^{99m}TcO_3(tacn)]^+$ and to evaluate its suitability for preparing bioconjugates *via* cycloaddition reactions, a protocol for the synthesis of $[^{99m}TcO_3(tacn)]^+$ suitable for routine application was developed. The first biodistribution studies of $[^{99m}TcO_3(tacn)]^+$ suggest the stability of this complexes *in vivo* and corroborate the high hydrophilicity of the $[^{99m}TcO_3(tacn)]^+$ building block. Thus, $[^{99m}TcO_3(tacn)]^+$ is a complement to the *fac*-$[Tc(CO)_3(H_2O)_3]^+$ core which binds to blood pool proteins, thereby inhibiting a fast clearance from the body.[37] To explore the potential and general utility of the new bioconjugation strategy, three classes of vectors were bound to the *fac*-$\{^{99m}TcO_3\}^+$ framework *via* a simple (3+2)-cycloaddition: 4-nitro-imidazole as a hypoxia-imaging agent,[38] histidine to create a non-natural amino acid that can be incorporated into peptides and radiolabeled and a simple glucose derivative (Scheme 6). Glucose is a particularly interesting biomolecule due to the search for a ^{99m}Tc-based carbohydrate as a complement to 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG).[11,39,40]

These reactions demonstrate the flexibility and suitability of this new labeling strategy. *In vivo* studies with these new compounds and the preparation of other new radiopharmaceuticals derived from this core are currently under way.

4. Perspectives

The synthesis of new ^{99m}Tc compounds suitable for selective and site-specific targeting (*e.g.* cancer cells) for molecular imaging is the driving force and major objective of today's research with this element. Despite some very promising and innovative new approaches, Tc chemistry is still looking for a new commercial application. This fact is starting to affect research efforts with technetium and the number of young academics working in this important field has dramatically decreased during the last years. New impulses are needed to recall the importance of Tc chemistry and radiochemistry in general. Fundamental chemistry has the unique potential to create new compounds starting at the very beginning. This potential should be used to design compounds with novel properties, which can lead to the development of innovative strategies and applications. The chemistry of high-valent *fac*-$\{TcO_3\}^+$ complexes, including the new concept for the labeling of biomolecules with small $[^{99m}TcO_3(tacn)]^+$ complexes by way of a (3+2)-cycloaddition with alkenes, presented in this article, creates a new field of technetium chemistry. This new field demonstrates the importance of fundamental research and may have the potential to reactivate research efforts on this element in the future.

To develop the high-valent Tc chemistry with *fac*-$\{TcO_3\}^+$ compounds further, multifarious tasks have to be accomplished in the near future. For the synthesis of bifunctional imaging agents, the coordination chemistry of functionalized 1,4,7-triazacyclononane derivatives, which are suitable for coupling reactions, need to be elucidated. Alterations of the tacn ligand itself by extending the ring size from nine to more atoms may provide a very different reactivity pattern and can, in addition, be functionalized at a carbon atom. Furthermore, to make the (3+2)-cycloaddition competitive with today's already established labeling strategies, reaction rates of the (3+2)-cycloadditions have to be optimized. The rate constants of these *cis*-dihydroxylation reactions are highly substrate dependent. Aiming at an understanding of a structure–reactivity correlation, systematic kinetic investigations are necessary. Even more important, a milestone for the convenience and routine applicability of this new labeling technique is the development of a more straightforward $[^{99m}TcO_3(tacn)]^+$ synthesis at neutral pH and ambient conditions. Thereby, the functional group tolerance

of the $[^{99m}TcO_3(tacn\text{-}R)]^+$ synthesis will be increased and make this strategy even more attractive for the labeling of biomolecules.

Finally, it has to be emphasized that the high-valent chemistry of technetium is not only relevant from a radiopharmaceutical point of view, but also with respect to the significant amounts of long-lived ^{99}Tc produced in the world's nuclear power plants. The possibility to bind *fac*-$\{TcO_3\}^+$ compounds *via* (3+2)-cycloaddition covalently to a substrate, such as surface-modified nanoparticles or resins, without a ligand replacement reaction could pave the way for new opportunities in the field of technetium immobilization. Therefore, the direct activation of $[^{99}TcO_4]^-$ and its efficient transformation into water stable *fac*-$\{TcO_3\}^+$ compounds is of great interest.

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