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Review

Technetium and Rhenium - Coordination Chemistry and Nuclear Medical Applications

Ulrich Abram*[*,a] and Roger Alberto[b]

[a]*Freie Universität Berlin, Institute of Chemistry and Biochemistry, Fabeckstraße 34-36, D-14195 Berlin, Germany*

[b]*Institute of Inorganic Chemistry, University of Zürich, Winterthurerstraße 190, CH-8057 Zürich, Switzerland*

Compostos de coordenação do elemento radioativo tecnécio são empregados para diagnóstico em medicina nuclear, sendo vários complexos do nuclídeo emissor de radiação γ ^{99m}Tc usados rotineiramente na obtenção de imagens de órgãos. As tendências modernas da química radiofarmacêutica concentram-se na marcação de moléculas biologicamente ativas tais como peptídeos, esteróides ou outras espécies com receptor específico. Por esta razão é necessário conhecer melhor a química de coordenação deste metal de transição artificial, especialmente no que diz respeito às esferas de coordenação estáveis ou inertes que possibilitam o acoplamento a biomoléculas, de acordo com a estratégia de formação de bioconjugados. O papel dominante dos compostos de tecnécio nos procedimentos de diagnóstico sugere o uso dos isótopos do rênio emissores de radiação β, ^{186}Re e ^{188}Re, para fins terapêuticos em medicina nuclear. O isótopo ^{188}Re é facilmente obtido a partir do isótopo ^{188}W, e as abordagens sintéticas empregadas na química do tecnécio podem ser investigadas para a obtenção dos complexos de rênio.

Coordination compounds of the radioactive element technetium are well established in diagnostic nuclear medicine, and various complexes of the γ-emitting nuclide ^{99m}Tc are routinely used for organ imaging. Modern trends in the radiopharmaceutical chemistry of technetium focus on the 'labeling' of biologically active molecules such as peptides, steroids or other receptor-seeking units. This requires more knowledge about the coordination chemistry of the artificial transition metal, particularly with regard to stable or kinetically inert coordination spheres, which allow couplings to biomolecules following a bioconjugate approach. The dominant role of technetium compounds in diagnostic procedures recommends the β$^-$-emitting rhenium isotopes ^{186}Re and ^{188}Re for applications in nuclear-medical therapy. ^{188}Re is readily available from an ^{188}W/^{188}Re radionuclide generator system and general synthetic approaches can be adopted from the established technetium chemistry.

Keywords: technetium, rhenium, coordination chemistry, nuclear medicine, bioconjugates

1. Introduction

As members of group 7 of the Periodic Table, the elements with the atomic numbers 43 (technetium) and 75 (rhenium) possess a rich coordination chemistry. This covers eight different oxidation states and various ligand systems reaching from almost pure electron donors, such as oxo or imido ligands to systems with pronounced back-donating properties such as carbonyls or isocyanides.[1,2] The organometallic chemistry of the two elements is well established as well as the chemistry of compounds with metal-metal bonds.[3]

Despite the fact that technetium has no stable isotopes (see Scheme 1) the chemistry of this artificial element is relatively well explored. The recent progress in the development of the coordination chemistry of technetium is directly related with the extended use of Tc compounds in diagnostic nuclear medicine and the permanent quest for new compounds with improved chemical and pharmaceutical properties. Two nuclides play an outstanding role: ^{99}Tc and its metastable nuclear isomer ^{99m}Tc.

The long-lived isotope ^{99}Tc (half-life time 2.12×10^5 years) is a β$^-$-emitter without accompanying γ-radiation. It is formed as one of the major fission products in nuclear reactors. The fission yield of ^{99}Tc is about 6.1%.[1] This means that a 100 MeV reactor produces about 2.5 g ^{99}Tc *per* day. The total amount of technetium currently on earth is estimated to be in the range of 2,000 kg, and, thus, this isotope is available in macroscopic amounts for chemical studies and allows the preparation and structural analysis

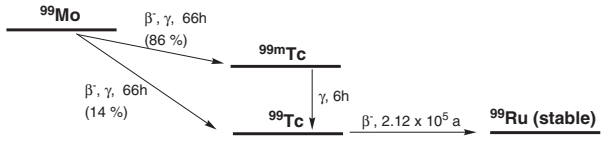
*e-mail: abram@chemie.fu-berlin.de

^{96}Ru Stable (5.52%)	^{97}Ru 2.9 d ec, γ	^{98}Ru Stable (1.88%)	^{99}Ru Stable (12.7%)	^{100}Ru Stable (12.6%)	^{101}Ru Stable (17.0%)	^{102}Ru Stable (31.6%)	^{103}Ru 39.4 d β$^-$, γ	^{104}Ru Stable (18.7)
^{95}Tc 60 d β$^+$, γ	^{96}Tc ^{96}Tc 52 m γ | ^{96}Tc 4.3 d ec, γ	^{97}Tc ^{97m}Tc 91 d γ | ^{97g}Tc 3 10^6 a ec	^{98}Tc 4.2 10^6 a β$^-$, γ	^{99}Tc ^{99m}Tc 6 h γ | ^{99g}Tc 2?10^5 β$^-$	^{100}Tc 15.8 s β$^-$, γ	^{101}Tc 14.2 m β$^-$, γ	^{102}Tc 4.3 m β$^-$, γ	^{103}Tc 54.2 s β$^-$, γ
^{94}Mo Stable (9.25%)	^{95}Mo Stable (15.92%)	^{96}Mo Stable (16.68%)	^{97}Mo Stable (9.55%)	^{98}Mo Stable (24.1%)	^{99}Mo 66.0 h β$^-$, γ	^{100}Mo Stable (9.63 %)	^{101}Mo 14.6 m β$^-$, γ	^{102}Mo 11.2 m β$^-$, γ

Scheme 1.

of technetium compounds applying conventional chemical and spectroscopic methods including X-ray diffraction. The weak β$^-$-emission of ^{99}Tc (E_{max} = 0.3 MeV) permits the handling of milligram amounts of ^{99}Tc in normal glassware, since the β$^-$-particles are effectively shielded by the glass walls and secondary X-rays (bremsstrahlung) become important only with larger amounts of ^{99}Tc. Nevertheless, gloves and safety glasses are essential when working with radioactive materials and particular care must be taken to avoid any ingestion or inhalation, since (although being a weak β$^-$-emitter) ^{99}Tc may cause serious damages to biological tissue, when incorporated. Almost all our chemical and structural knowledge about technetium and its compounds derived from studies performed with ^{99}Tc.

The main motivation for most of these studies is related to practical applications of its γ-emitting isomer ^{99m}Tc, which is the workhorse of nuclear medicine.[5] The unstable parent isotope of ^{99m}Tc is ^{99}Mo, which is a β$^-$-emitter and disintegrates with a half-life time of 66 h (Scheme 2) to ^{99}Tc. This decay proceeds with a high percentage *via* the metastable ^{99m}Tc. The transition between ^{99m}Tc and its ground state is nuclear-spin-forbidden and therefore relatively slow. The resulting half-life time of 6 h is in the optimal range for studies in diagnostic medicine and the related γ-energy of 140 keV is sufficiently low to prevent a high dose burden to the patient, but sufficiently high to penetrate biological tissues and emerge from internal organs. The distribution of ^{99m}Tc can be monitored externally by scintillation counters.

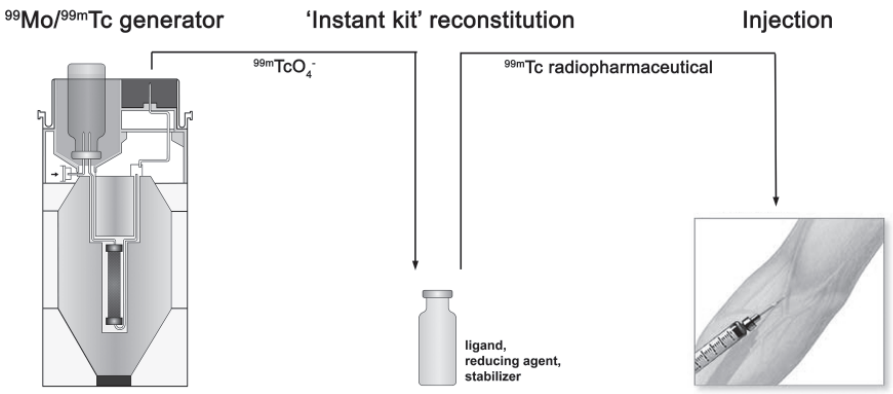


Scheme 2.

Differences in the chemical properties of molybdenum and technetium allow the chemical separation of the daughter nuclide ^{99m}Tc from its parent ^{99}Mo in so-called 'isotope generators'. The heart of almost all commercially available ^{99}Mo/^{99m}Tc-generators is an alumina chromatography column, which tightly binds the doubly negative MoO_4^{2-} ions, while the product of the nuclear decay, TcO_4^-, can readily be eluted by saline solutions. Such a procedure provides an almost continuous supply of the daughter radionuclide for a time period of some physical half-lifes of the parent. This guarantees the permanent availability of $Na^{99m}TcO_4$ solutions at clinical sites and is responsible for the widespread use of technetium compounds for nuclear-medical imaging.

In a similar way, the β$^-$-emitter ^{188}Re ($t_{1/2}$ = 16.9 h, E_{max} = 2.1 MeV) can be obtained from a generator system applying the beta decay of ^{188}W ($t_{1/2}$ = 69 d). With its ready availability and favourable nuclear properties, ^{188}Re is one of the two rhenium isotopes, which are extensively under study for the development of future radiotherapeutic pharmaceuticals. The second one is ^{186}Re ($t_{1/2}$ = 89.2 h, E_{max} = 1.1 MeV). Both β$^-$-emitters possess physical properties which allow an effective energy transfer to cancer tissue.

The preparation of technetium or rhenium radiopharmaceuticals from the permetallate ions obtained from the different nuclide generators (^{99m}Tc or ^{188}Re) or from reactor-irradiated targets (^{186}Re) is very similar. In all instances, the metal ions must be reduced by an appropriate reducing agent and coordinated by ligand systems, which (*i*) stabilize the lower oxidation states of the metals and (*ii*) significantly determine the biological distribution patterns of the pharmaceuticals. Such procedures are commonly done in so-called 'instant kits', that means that appropriate amounts of the radioactive $^{99m}TcO_4^-$ or $^{186,188}ReO_4^-$ solutions are added to pre-manufactured mixtures of the corresponding ligands, reductants, and stabilizers and catalysts (see Scheme 3). This type of reaction must be optimized and the expected yields and purities of the products should be reproducible at >95%. The resulting pharmaceuticals should be ready for injection after chromatographic quality control preferably without further purification steps.



Scheme 3.

The quest for technetium or rhenium complexes with desired *in vivo* distributions and the development of appropriate 'kit-like' synthetic procedures require exact knowledge of the chemistry of these transition metals. This includes basic chemistry and redox behaviour as well as coordination chemistry with biologically relevant ligands. In the following sections, an overview of important classical Tc radiopharmaceuticals will be given together with recent trends and future prospects, as a guide to the labelling of bioactive molecules with ^{99m}Tc or ^{186,188}Re. In the latter context, some coordination chemistry is reported, which is currently done in the laboratories of the authors and is directed towards the labeling of peptides or proteins via a bioconjugate approach.

2. Classical Organ Imaging with the 'First Generation' of ^{99m}Tc Radiopharmaceuticals

^{99m}Tc imaging started in 1961 with the use of $^{99m}TcO_4^-$ to image the thyroid. The accumulation of pertechnetate in the thyroid gland is prompted by the presumed similarity between TcO_4^- and thyroid-essential iodide. This was the first so-called technetium essential agent, in which the biodistribution was based on the physical properties of the complex (charge, size, lipophilicity etc.). Subsequently, ^{99m}Tc complexes were successfully developed for the imaging of organs such as liver, kidney, bones, heart or brain.

Imaging of the renal and hepatobilary excretion, that means kidney and liver imaging, is a very thoroughly investigated field of ^{99m}Tc radiopharmaceuticals and the first successfully used ligand systems belong to the complexone family. These derivatives of aminoacetic acids (for examples see Figure 1) form negatively charged complexes with technetium, the excretion pathway of which can readily be controlled by modifications of the periphery of the ligand. Thus, the highly hydrophilic technetium complex with DTPA (diethyl-enetriamine pentaacetic acid) is excreted via the renal system, while the more lipophilic EHIDA (N-(2,6-diethylacetanilido) iminodiacetic acid) derivative is excreted *via* the hepatobiliary tract and is used for liver scintigraphy. It is remarkable that the chemical structures of these classical technetium pharmaceuticals, although they have been routinely used for more than 30 years, are still not known. During this time, their compositions have been subject of many investigations and much speculation. On a macroscopic level, some dimeric products have been isolated, which contain the metal atoms in the oxidation states '+3', '+4' or '+5'.[5] It appears, however, extremely likely that the biologically active species have other, monomeric structures, since the concentration of generator-eluted ^{99m}Tc (about 10^{-10} mol L^{-1}) is too low for the formation of significant amounts of dimeric products. Despite the uncertainty of the structures of the ^{99m}Tc-DTPA and ^{99m}Tc-EHIDA derivatives, they are in regular radiodiagnostic use and have been a commercial success for decades.

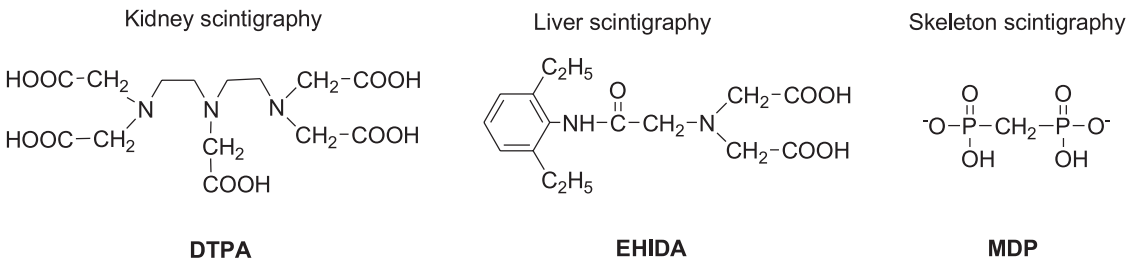


Figure 1. Complexone-type ligands, which are used in classical ^{99m}Tc radiopharmaceuticals for imaging of kidney, liver and bone.

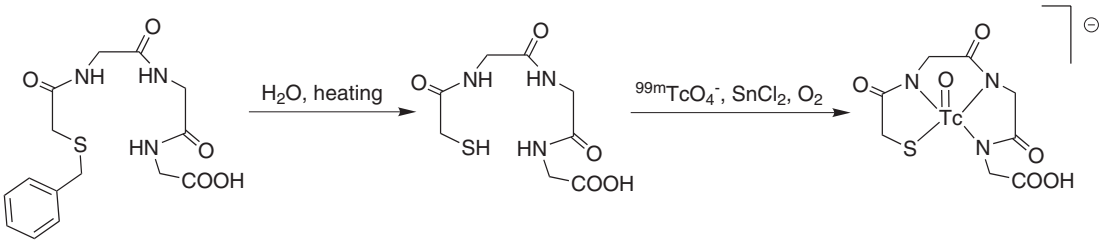
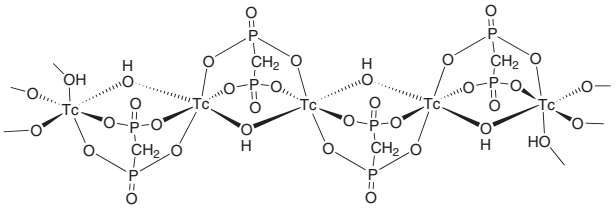


Figure 2. Chemical reactions during the reconstitution of a ^{99m}Tc-MAG3 kit.

Different from the ^{99m}Tc-DTPA agent, the structure and composition of another technetium complex for the imaging of renal excretion, the ^{99m}Tc-MAG3 complex, is well known. It is an anionic oxotechnetium(V) complex with the tetradentate peptide-like ligand mercaptoacetyltriglycine.[6] The ligand is used as its benzyl-protected derivative in order to avoid the formation of considerable amounts of disulphide during reconstitution of the kit. $SnCl_2$ is applied as a reducing agent and finally a hydrophilic oxotechnetium(V) complex is formed. The carboxylic group of the complex is deprotonated at physiological pH making the compound monoanionic (Figure 2). After administration to the patient, the complex binds to a large extend to plasma proteins. These weak interactions allow excretion through tubular secretion and about 50 *per* cent of the radioactivity is excreted after each blood pass through the kidneys.[7] For this excretion, the presence of a non-coordinated carboxylic group seems to be essential in order to be recognized by the corresponding receptors in the kidneys. The commercial introduction of the ^{99m}Tc-MAG3 kit has almost replaced the use of *o*-iodohippuran in diagnostic nuclear medicine.

Complexes of ^{99m}Tc with phosphonate ligands are widely used as diagnostic agents for the imaging of metastatic diseases in bones and bone infarction infections. The ligands are generally diphosphonates. One example, methylenediphosphonate (MDP), is shown in Figure 1, but also derivatives such as hydroxymethylenediphosphonate (HMDP), 1-hydroxyethylenediphosphonate (HEDP) or 1-hydroxy-4-aminobutylidene-1,1-diphosphonate (ABP) are in routine use. The corresponding kits commonly contain a standard reductant such as $SnCl_2$ or BH_4^- and are reconstituted by the addition of $^{99m}TcO_4^-$ solution from the generator eluate. Such reactions normally yield mixtures of various technetium



Scheme 4.

complexes, which contain the metal most probably in the oxidation state '+4', but the presence of mixed oxidation states cannot be ruled out.[8] Nevertheless, they are highly effective bone-imaging agents. The presence of uncoordinated phosphonate oxygen atoms allows a mechanism for absorption of the complexes on the surface of newly formed hydroxylapatite. With respect to this fact, such ^{99m}Tc complexes can act as ligands for exposed Ca^{2+} ions on the freshly formed hydroxylapatite during the formation of the mineral components of bone tissue. Despite the fact that many efforts have been undertaken to derive structural features of technetium complexes with phosphonate ligands, there is little structural information available. Most probably, polymeric compounds are formed, the compositions of which vary with the pH and the concentration level.[8] Only one technetium complex with phosphonate ligands, the polymeric $[Tc(OH)(MDP)]_\infty$, has hitherto been isolated and characterized by X-ray crystallography. The compound was prepared by a ligand exchange procedure from the Tc(IV) complex $[TcBr_6]^{2-}$.[9] The coordination spheres of the technetium atoms in this compound are approximately octahedral and each MDP ligand bridges two symmetry-related technetium atoms. An additional bridge is established by an oxygen atom, which most probably belongs to a hydroxo ligand (Scheme 4). Although the crystallographic analysis does not fully allow the assignment of the oxidation state of the metal in this compound, it clearly shows that diphosphonates can act as bidentate ligands and can bridge two transition metal atoms as is the case for their binding to Ca^{2+} in bone. Thus, the above mentioned mechanism of the ^{99m}Tc enrichment in bones is supported.

3. Imaging of Heart and Brain

In the past, the radioactive thallium isotope ^{201}Tl dominated the myocardial imaging as it is taken up by myocytes *via* the Na^+/K^+ ATPase pump. The unfavorable physicochemical properties and the high price of this nuclide, however, led to intense research in order to replace ^{201}Tl by ^{99m}Tc imaging agents. Early studies about structure-activity relationships suggested monocationic technetium complexes to be promising candidates for

myocardial uptake. This was supported by studies on technetium(III) complexes with chelating bis-phosphines and –arsines. Complexes of the type $[TcCl_2(diars)_2]^+$ or $[TcCl_2(DMPE)_2]^+$ (diars = 1,2-bis(dimethylarsino) benzene; DMPE = 1,2-bis(dimethylphosphino) ethane) showed promising heart-uptake result in animal studies, but heart images in humans were poor and the retention rate of the complexes in the myocardium was low, which was assigned to a rapid reduction of the redox-labile compounds in the myocardial cells.[10]

More successful were attempts with isocyanide complexes of technetium(I). Homoleptic, cationic complexes of the composition $[Tc(L)_6]^+$ are kinetically and redox stable. The d^6 electronic situation avoids dissociative ligand loss or associative substitutions by competing ligands in biological systems. They can readily be prepared by the reduction of TcO_4^- with $S_2O_4^{2-}$ ions in the presence of the corresponding isocyanides and a large number of such complexes with various substituents at the isocyanide ligands have been prepared on a macroscopic level and fully characterized structurally.[11] The biological properties of such complexes have been optimized for heart uptake versus blood and organ clearance. An optimum was found when methoxy-isobutylisocyanide (MIBI) was used as ligand. The resulting ^{99m}Tc-MIBI complex (Figure 3A) can conveniently be synthesized in a 'kit-like' preparation from $^{99m}TcO_4^-$ in saline with $SnCl_2$ as a reducing agent. The MIBI ligand is supplied in the form of its cationic copper(I) complex $[Cu(MIBI)_4]^+$.[12] The myocardial uptake of $[^{99m}Tc(MIBI)_6]^+$, although the compound is moncationic, does not occur *via* the Na^+/K^+ channels, but rather by a metabolic process, which involves diffusion of the cations across the membranes. Retention of the agent in the myocytes is provided by partial enzymatic cleavage of the ether functionalities.

Following the general route that was developed for $[^{99m}Tc(MIBI)_6]^+$, a number of other monocationic complexes with peripheral ether functionalities were successfully introduced into studies for myocardial imaging. This also includes complexes with technetium in the oxidation states '+3' and '+5', and ligand systems such as phosphines, Schiff bases or dioximes (see Figure 3). Of particular commercial interest the dioxo-technetium(V) complex B.[13] The compound is structurally derived from the unsuccessfully tested Tc(III) complex $[TcCl_2(DMPE)_2]^+$ (*vide supra*), but is (as a technetium(V) complex) much more resistant to reduction. Together with $[^{99m}Tc(MIBI)_6]^+$, this complex has now largely replaced ^{201}Tl for myocardial imaging.

In addition to the cationic complexes shown in Figure 3, some neutral compounds show significant myocardial uptake and are used in commercially available heart imaging agents. One of them, a seven-coordinate

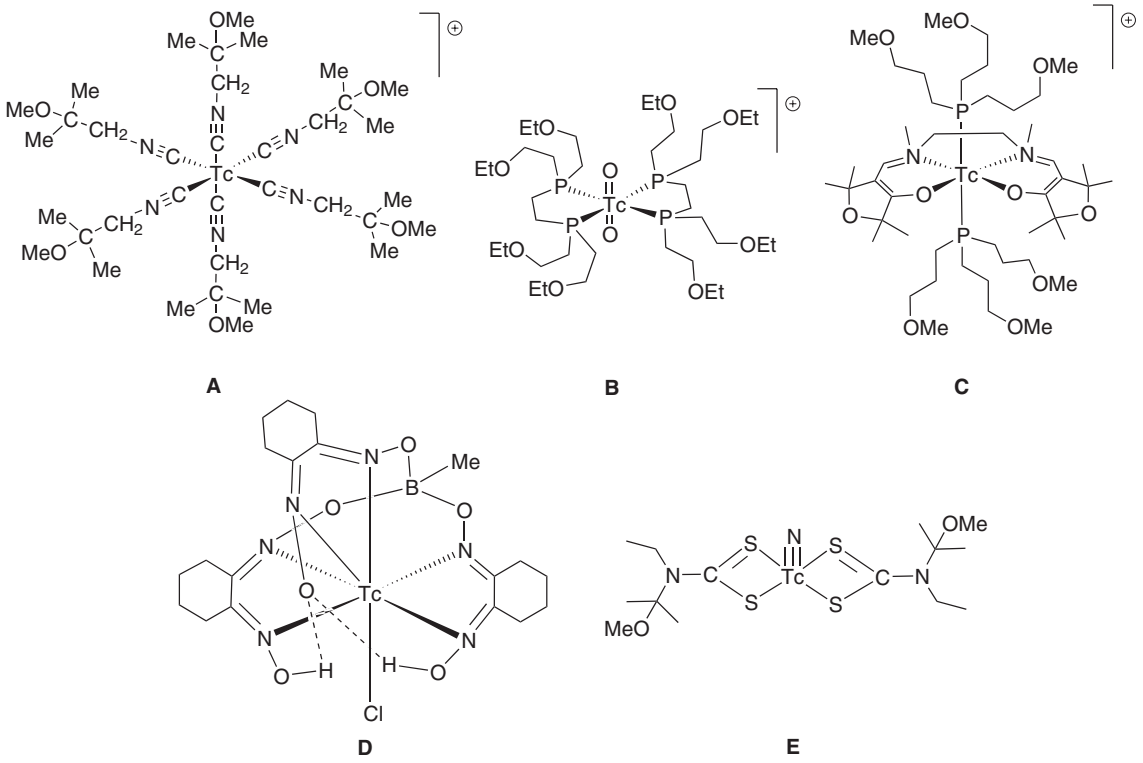


Figure 3. Heart-seeking ^{99m}Tc complexes.

technetium(III) chlatrochelate (Figure 3D) with three dioxime ligands, which are interconnected by a boronic acid building block, will readily exchange its chloro ligand for OH_2 and, thus, may also be regarded as a cationic aqua complex in its physiologically active form.[14] The other one is a nitridotechnetium(V) dithiocarbamato complex (Figure 3E), which can be prepared in high yield and purity from the reaction of $^{99m}TcO_4^-$ with S-methyl-N-methyldithiocarbazate (which establishes the TcN^{3+} core) and subsequent addition of the dithiocarbamato ligand.[15] The *in vivo* behavior of this neutral compound is different from the cationic myocardial imaging agents, showing a slower blood clearance and a faster myocardial washout.

Brain imaging has become a major goal of ^{99m}Tc coordination chemistry, both for perfusion imaging and, more recently, for the labeling of so-called central nervous system (CNS) receptor ligands. These biological ligands target receptors in the brain and are extraordinary important because of their implication in a wide range of mental disorders, such as Alzheimer's and Parkinson's diseases or schizophrenia.

^{99m}Tc-based agents for the assessment of cerebral blood flow still play an important role, although other diagnostic techniques like NMR tomography or ultrasound are strongly competitive. Complexes for such applications must be able to penetrate the intact blood brain barrier by passive diffusion. This is achieved by small, neutral lipophilic molecules. They preferably should provide an intrinsic mechanism, which allows trapping inside the brain and, thus, reduces rapid washout. Such mechanisms can be pH trapping by the protonation of peripheral amines with appropriate pK values in the slightly more acidic brain tissue, or metabolic processes such as ester hydrolysis or partial degradation of the pharmaceutical in the brain. The latter two mechanisms are mainly used in the successfully tested brain imaging agents which are shown in Figure 4. They all belong to the class of five-coordinate technetium(V) oxo complexes with a central $[Tc{=}O]^{3+}$ core. Their equatorial coordination spheres are occupied each by tetradentate, triply deprotonated chelators

In 1983 it was found that a lipophilic complex with a tetradentate amine oxime ligand was able to cross the blood brain barrier quite efficiently, but was not trapped.[16] The required trapping was attempted by varying the positions of peripheral substituents and finally an optimum was found for (RR,SS)-4,8-diaza-3,6,6,9-tetramethyl-undecane-2,10-dione dioxime (HMPAO, the ligand of compound A in Figure 4). The brain retention of this complex is explained by an enzymatic conversion into a more hydrophilic compound, which cannot re-penetrate the blood brain barrier. It is interesting to note that the HMPAO ligand has chiral centers and only its *d,l*-form leads to a technetium complex that is a suitable for clinical brain imaging. Complexes with the meso-form of the ligand show a different biological distribution behavior, particularly they are more resistant against conversion into the hydrophilic species and, therefore, their re-distribution is much faster.[17] This example clearly illustrates the difficulties encountered in the development of new radiopharmaceuticals when there are chiral centers present.

Another compound, which fulfills all the basic requirements of an effective brain-imaging agent is the oxotechnetium(V) complex with the ethylenecysteineester dimer (ECD). The tetradentate ligand belongs to the class of diaminodithiolates, the coordination chemistry of which has been extensively studied.[18] Only one of the two amino groups deprotonates during reactions with common $[TcO]^{3+}$ precursors giving the highly lipophilic, brain-seeking technetium(V) complex, which is shown in Figure 4B. Brain retention is achieved by *in vivo* hydrolysis of the ester side chains, which results in the formation of charged complexes which are trapped in the brain. This hydrolysis also proceeds in the blood stream with that fraction of the injected pharmaceutical that did not pass the blood brain barrier and, thus, provides fast blood clearance. The [$^{99m}TcO(ECD)$] complex is particularly important for the evaluation of patients with ischemic strokes.

Some other neutral and lipophilic technetium compounds were or are under investigation as promising brain-imaging agents. This includes the oxotechnetium(V) complex with the ligand N(2(1-H-pyrolmethyl)N'-(4-pentene-3-one-2)ethane-1,2-diamine (Figure 4C), which shows an excellent brain-uptake and allows a clear

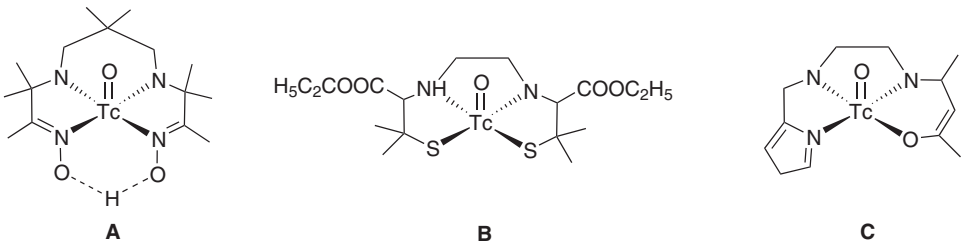


Figure 4. Brain-seeking ^{99m}Tc complexes.

differentiation between gray and white matter,[19] but also clathrochelates of the BATO type (cf. Figure 3D) .[20] Since most representatives of the latter class of compounds are highly lipophilic and the assumed Cl^-/H_2O exchange is slow, a significant fraction of the injected compound is able to cross the blood brain barrier. The obvious lack of a specific trapping mechanism in the brain tissue and the slow blood clearance of such complexes are the main reasons that further developments of BATO-based brain-imaging agents have been terminated.

4. Receptor-Specific and Targeting Molecules

Actual research efforts in technetium- (and rhenium-) based radiopharmaceutical chemistry are in the development of receptor-specific, targeting molecules. Two major approaches have been studied: (*i*) an intrinsic receptor binding by modeling the three-dimensional structure of the metal complexes to meet the topology of the binding motif of a biomolecule (integrated radio-pharmaceutical design), and (*ii*) the bifunctional approach, which couples a receptor-binding organic molecule to a metal chelate *via* a spacer.

The synthesis of transition metal complexes that mimic the binding site of biomolecules is an immense challenge, since not only the topology, but also the distribution of dipole moments and other physico-chemical characteristics of the natural compound, must be presented by the artificial metal compound. Some initial investigations have been performed in order to mimic steroid hormones. In such compounds, the technetium core is incorporated in a carbon skeleton in order to mimic the three-dimensional structure and polarity of the hormone. Metal-oxygen double bonds are often used as surrogates of carbonyl fragments in such compounds. Some examples are shown in Figure 5. They illustrate rhenium complexes, which have been prepared in order to mimic dihydrotestosterone, progesterone and estradiol.[21] Bidentate (Figures 5A and 5B) and tetradentate (Figures 5C and 5D) chelator systems have been used to coordinate the metal atoms, but the compounds with the bidentate ligands show insufficient *in vivo* stabilities. The biological distribution patterns of the more stable complexes with tetradentate amine thiolato bonding sites have been tested with ^{99m}Tc. Despite retaining the overall size and shape, the receptor binding to the estrogen receptor was not encouraging up to now.[22] These first attempts, however, underline the importance to match not only structural features, but also electronic properties of the natural structure.

More successful was the search for neuroreceptor targeting ^{99m}Tc radiopharmaceuticals. Such molecules should have a low molecular mass (< 600), a well-balanced lipophilicity and high specificity and selectivity for the

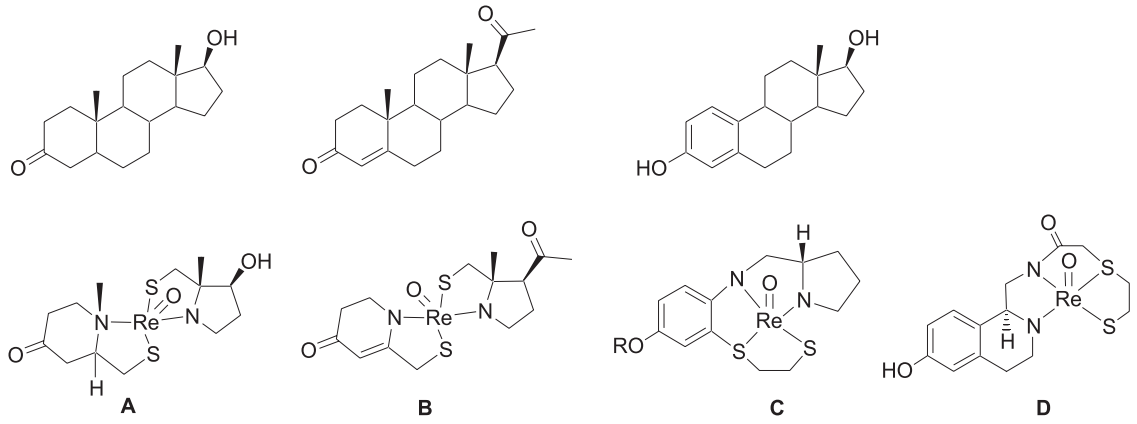


Figure 5. Rhenium complexes, which mimic the structures of the steroids dihydrotestosterone, progesterone and estradiol (upper row).

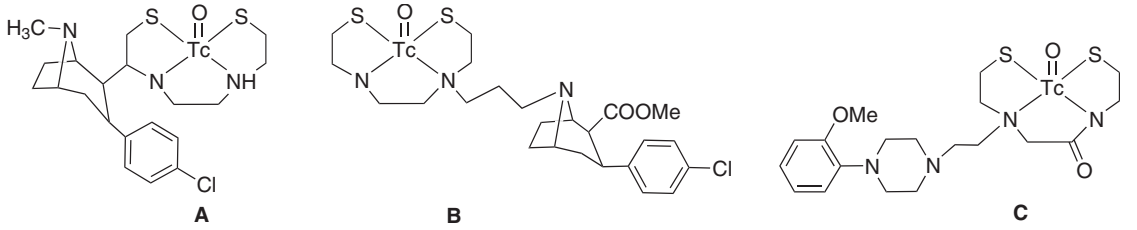


Figure 6. ^{99m}Tc based radiopharmaceuticals for imaging of the neuronal dopamine transporter (A and B) and the serotonergic 5-HT_{1A} ligand WAY (C).

particular receptor. Furthermore, the labeling process should be efficient also at low ligand concentrations in order to prevent saturation of the receptor. Figure 6 depicts the structures of some technetium complexes that have been prepared for imaging of the physiological dopamine transporter system (DAT),[23] and the vector WAY-100635, which is directed towards one of the most thoroughly studied serotogenic receptors.[24] Of particular interest is compound A, which successfully passed all preclinical tests and shows excellent receptor binding. Clinical studies confirm the suggested uptake of the complex in the striatum, which is consistent with the behavior of DAT distribution.[25]

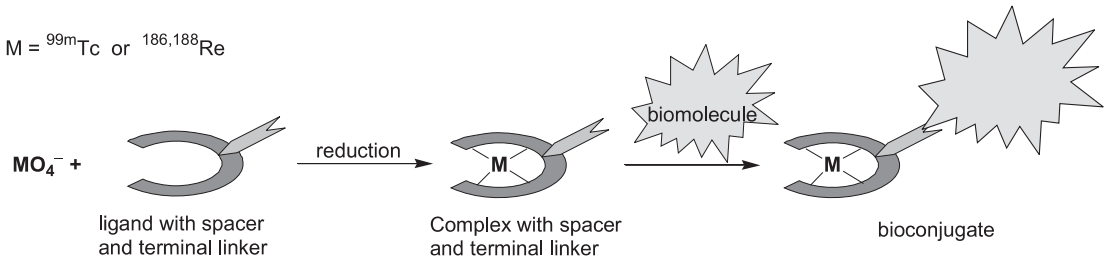
The development of receptor-binding technetium complexes will be one of the major challenges in future radiopharmaceutical chemistry, and the examples above show that there are a number of difficulties to be overcome, which are related to basic biochemical and medical problems. Additionally, stable and/or kinetically inert bonding cores must be developed, which prevent metabolic destruction or reorganization of the coordination sphere of the transition metal ions in such compounds. Particularly, the examples of Figure 6 show that modern trends focus on a bifunctional (or bioconjugate) approach, which keeps the coordination site of the metal apart from the targeting part of the labeled biomolecule.

5. Bifunctional Labeling of Biologically Active Molecules

The labeling of targeting molecules entails the question of tightly binding the metal center to the biologically active molecule without affecting its physiological properties. This means that the metal ion in its particular oxidation state needs to be stabilized and covalently linked to the vector. The connecting functionality to the biomolecule is commonly a carboxylate or an amine group that can conveniently be activated with standard strategies from organic chemistry. The principle of this type of labeling is outlined in Scheme 5.

Labeling of targeting molecules requires a chelator that is strong enough: (*i*) to coordinate to technetium or rhenium at low concentration, (*ii*) to give a single product in high yield, and (*iii*) to stabilize the metal under *in vivo* conditions. The chelator should form an inactive metal complex, that means it should not influence the biological properties of the conjugate. Most of the hitherto explored bioconjugated technetium and rhenium compounds are based on tetradentate ligand systems with amine or amide nitrogen and thiolato sulphur atoms (see also the complexes shown in Figures 3, 4 and 6). The resulting complexes are neutral or anionic depending on the number and type of the nitrogen donor atoms.

Various alternatives to tetradentate N_xS_{4-x} ligands exist. In terms of flexibility, the use of so-called mixed-ligand complexes, that means complexes with ligands of various denticity completing the coordination sphere of a set metal core ($[MO]^{3+}$, $[MN]^{2+}$, $[M(CO)_3]^+$ or M^{3+}) represents an ambitious approach. The combination of ligand systems having various denticity (4+1, 3+1, 3+2 etc.) allows a fine tuning of the coordination site and (depending on the nature of the spacer) it can be placed at different positions of the complex molecule. A collection of such mixed-ligand systems is illustrated in Figure 7. The examples include representatives of the widely used combination of tridentate chelators with a monodentate thiolato ligand (B). This class of compounds, with tridentate thioether dithiolates ligands, appeared to contain promising candidates for a bifunctional labeling of biomolecules, which could readily be added to the coordination sphere of the transition metal by a terminal thiol.[26] The biological properties of such compounds, particularly their insufficient stability in plasma, prevented practical application. More stable and substitution-inert metal-ligand bonds are obtained, when bidentate co-ligands are used or a metal-ligand double bond is established. Compound A of Figure 7 belongs to the latter class of complexes wherein a metal-nitrogen double bond is formed between the metal and 6-hydrazinonicotinic acid (HYNIC, see Figure 8),[27] which can readily be coupled to the amine terminus of a peptide. Although the nature of the resulting complexes (particularly the character of the M=N bond) is not unambiguously clear, this coupling mode became very popular and has been applied for a



Scheme 5.

large number of molecules, including monoclonal antibodies.[28] The labeling is usually carried out by the reaction of the HYNIC-linked biomolecule with $^{99m}TcO_4^-$ or $^{186,188}ReO_4^-$ in the presence of a common reducing agent such as $SnCl_2$ and a co-ligand. Such co-ligands are necessary to complete the coordination sphere of the metal and allow the tuning of basic properties of the resulting complex molecule. Common co-ligands are hydrophilic compounds such as ethylenediamine diacetic acid (as in complex A of Figure 7), glucoheptonate or tricine (compounds B and C in Figure 8). The stability of most of such preparations, however, is relatively low, but can be improved by the addition of ternary ligands such as water-soluble phosphines or amines.[29] Some examples of HYNIC derivatives are shown in Figure 8. The main advantage of this approach to label biomolecules with radioactive technetium or rhenium isotopes is the high labeling efficiency and the possibility of fine-tuning the physico-chemical properties of the labeled biomolecules.

The stability of HYNIC complexes, when the right ternary ligands have been chosen, makes this procedure one of the modern labeling methods, at least when hydrophilic biomolecules such as chemotactic peptides or somatostatin analogues are subjects of the studies. More present trends are outlined in the following Section.

6. Present Trends and Future Prospectives

Fundamental technetium and rhenium chemistry plays an essential role in the development of future diagnostic and therapeutic radiopharmaceuticals. Although a number of reliable techniques for high yield and high stability labeling of targeting biomolecules exist, the possibility of variations is still limited. The metal complex plays an important role in the biological behavior of a radiopharmaceutical and is decisive for success or failure. This implies that more efforts have to be undertaken in the field of basic coordination chemistry of these elements, which is essentially limited to applications in order to develop novel moieties and compounds that allow a convenient and reliable labeling of biomolecules, while considering the other limitations

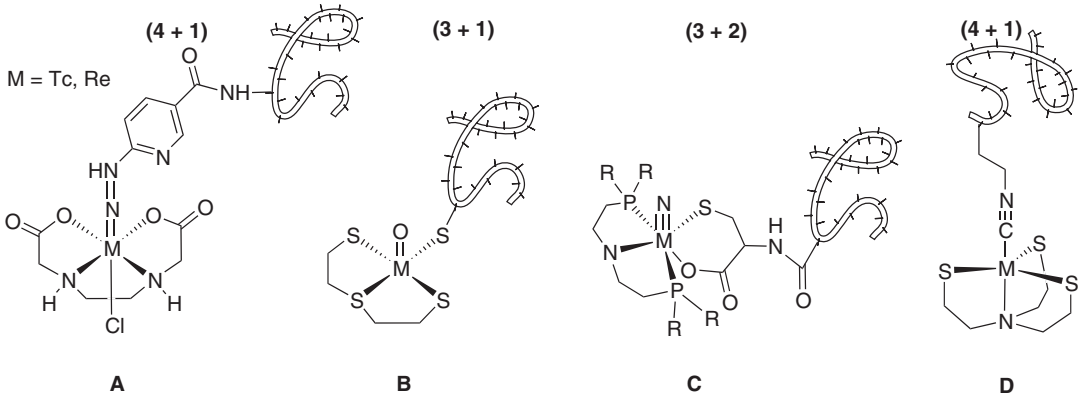


Figure 7. Examples of mixed-ligand complexes of technetium and rhenium for the labelling of biomolecules.

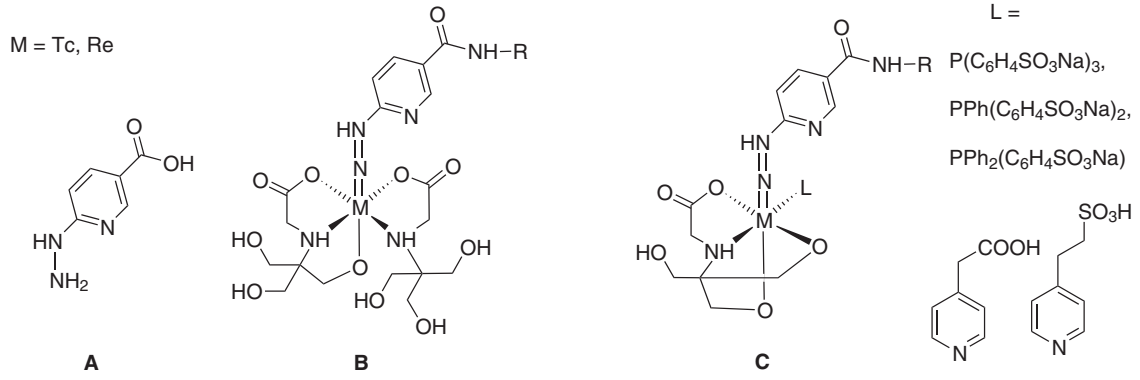
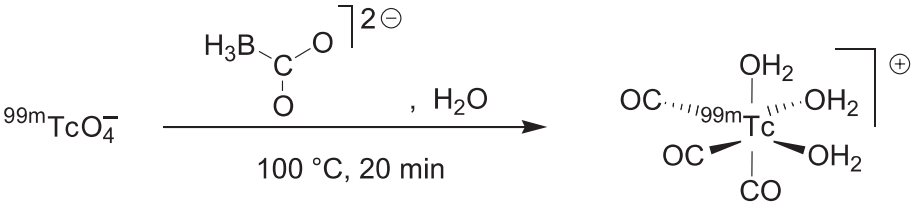


Figure 8. 6-Hydrazinonicotinic acid (A) and examples of HYNIC complexes with tricine and various hydrophilic ternary ligands.



Scheme 6.

given by future clinical application. These aspects have recently led to the development of different approaches based on nitridotechnetium complexes or organometallic compounds. To the latter group belong tricarbonylrhenium(I) and -technetium(I) complexes, which have been extensively studied by structural chemical methods and a synthesis for the $[^{99m}Tc(CO)_3]^+$ core has been established.[30] It can be performed in a kit-like fashion starting from $^{99m}TcO_4^-$ (Scheme 6) by use of boranocarbonate, $Na_2[H_3BCOO]$, as a source of carbon monoxide. The three water ligands in the resulting *fac*-$[Tc(CO)_3(OH_2)_3]^+$ cation are readily replaced by incoming ligands. According to their d^6 electronic configurations, the resulting complexes are kinetically inert. A large number of substitution products have been isolated and structurally characterized.[31] It is remarkable that essentially all kind of donor atoms can be used since the stability of the complexes is purely kinetic.[32] Mono-, bi- and -tridentate ligands are only cleaved under drastic conditions such as high temperatures or strongly acidic solutions. The $[^{99m}Tc(CO)_3]^+$ moiety shows in particular a high affinity for aromatic amines such as imidazoles or pyridine. Several complexes have been prepared following this approach and this concept has proven useful for the direct labeling of his-tagged recombinant antibodies.[33] Figure 9 summarizes some of the recently prepared and structurally characterized tricarbonylrhenium(I) and –technetium(I) complexes including histidine (A), thioether (B), half-sandwich (C) and aminocarboxylato complexes (D) with this core. Additionally some derivatives are shown, which use this complex type for the labeling of bioactive molecules such as steroids or peptides (E-G). More examples are contained in an excellent review, which covers the current use and future potential of organometallic radiopharmaceuticals.[34]

Slight modifications of the tricarbonyl core by the exchange of one of the carbonyl ligands by a nitrosyl results in the formation of the $[M(CO)_2(NO)]^{2+}$ core, which is isoelectronic to $[M(CO)_3]^+$ (M = Re, Tc).[35] Such a modification may not change the stability of the resulting complexes, but due to its higher charge it is assumed to possess more enhanced binding affinities to the anionic chelators that are frequently used for couplings to biomolecules.

Preparative access to suitable precursor molecules has been found by simple nitrosylations starting from the well-known $[M(CO)_3X_3]^{2-}$ anions (M = Re, Tc; X =

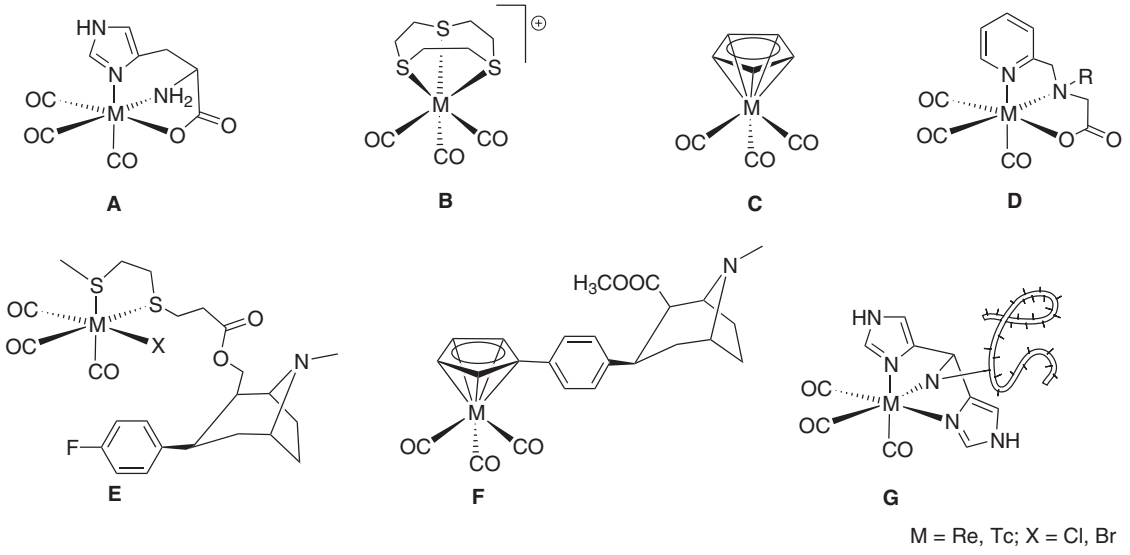
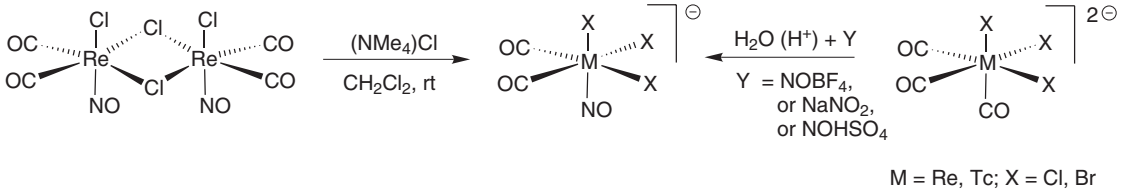


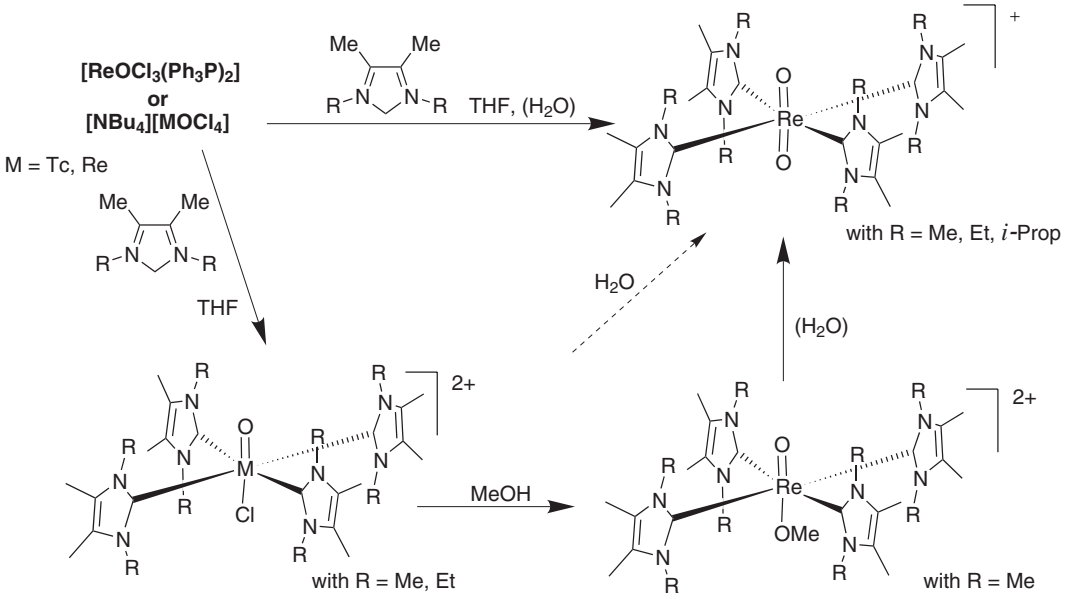
Figure 9. Tricarbonylrhenium(I) and -technetium(I) complexes with potential for radiopharmaceutical applications.

Cl, Br) or by splitting reactions of the chloro-bridged dimer $[ReCl_2(CO)_2(NO)]_2$ (Scheme 7). The course of the nitrosylation reactions is slightly different for technetium and rhenium. It is remarkable that dimeric dicarbonylnitrosyltechnetium compounds are formed during such procedures, while corresponding reactions with rhenium give the monomeric compound in excellent yields. For both metals, substitution of more than one CO ligand was not observed. The resulting $[M(CO)_2(NO)X_3]^-$ complexes are stable in water and show the expected ligand exchange behavior. Several compounds with organic ligands, including cyclic thioethers, diimines or aminocarboxylic acids, have been isolated and structurally characterized. Further studies with biologically relevant ligand systems and chelators, which are promising for the bifunctional approach, are currently underway in several groups and it is to be expected that this new class of technetium and rhenium compounds will play a role in future radiopharmaceutical research.

Another class of stable organometallic rhenium and technetium complexes, which has been developed in recent years, is the class of complexes with N-heterocyclic carbenes. Such ligands have been used in the coordination chemistry of many transition metals for quite a long time, but the first well-characterized rhenium and technetium compounds were not published until 2003.[36] This is surprising, particularly in the light that some of the compounds possess remarkable stability, which is mainly determined by the high sterical demand of the ligands systems, which protect the metal centers and prevent further ligand exchange and/or hydrolysis. The influence of ligand substituents has been carefully studied for oxorhenium(V) complexes with a series of 1,3-dialkyl-4,5-dimethylimidazol-2-ylidenes.[37] These studies confirm that reactions at the metal core are only possible when the alkyl substituents are methyl or ethyl, as with the corresponding iso-propyl-substituted ligands the dioxo complex, which is stable against further hydrolysis, is directly formed (Scheme 8). An analogous behavior was also observed for corresponding technetium(V) compounds and recommends this class of complexes as candidates for future nuclear-medical labeling procedures. One clear disadvantage for such



Scheme 7.



Scheme 8.

applications is doubtlessly the fact that four identical ligands form the equatorial coordination sphere of the metal atom and, thus, the introduction of one defined coupling position to a biomolecule is complicated. Possible solutions for this kind of problem are the use of chelating N-heterocyclic carbenes or the modification of the central $[TcO_2]^+$ core. A synthetic variation of the latter approach is the introduction of a central phenylimido ligand instead of an oxo one.

Phenylimido complexes with 1,3-dialkyl-4,5-dimethylimidazol-2-ylidenes can readily be prepared from $[Re(NPh)Cl_3(PPh_3)_2]$ (Scheme 9).[38] The compounds contain highly shielded metal centers and the axial halide or hydroxo ligands are not subject to substitution. Thus, the $[Re(NPh)(L)_4]^{2+}$ complexes are stable in solution and resist hydrolysis, even when they are heated in aqueous solutions. This is remarkable with respect to previous studies with phenylimido rhenium(V) complexes, for which hydrolysis of the metal-nitrogen bond and the final formation of oxo complexes was observed.[39] On the other hand, the higher stability of the carbene complexes is not unexpected with regard to the sterical bulk of the ligands used. This makes this class of compounds interesting for coupling reactions with biomolecules. Figure 10 depicts a space-filling model of the molecular structure of the phenylimidorhenium(V) complex with four equatorial 1,3-diethyl-4,5-dimethylimidazol-2-ylidene ligands. It

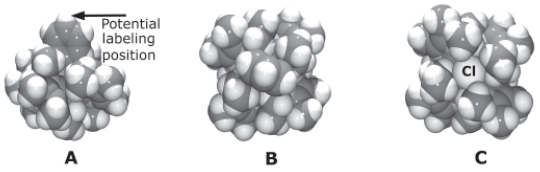
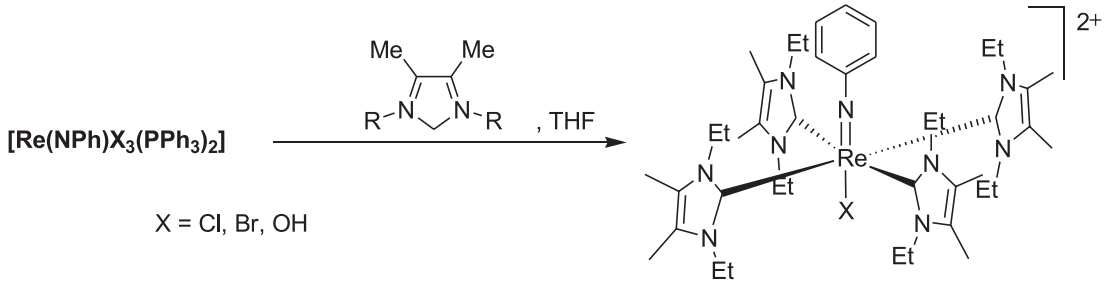


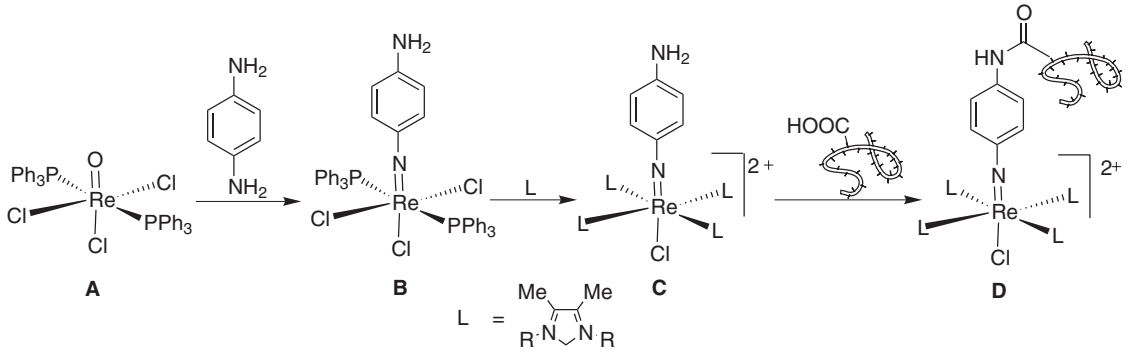
Figure 10. Space-filling model of the molecular structure of the $[Re(NPh)Cl(1,3\text{-ethyl-}4,5\text{-dimethylimidazol-}2\text{-ylidene})_4]^{2+}$ cation (A: side view; B: top view of the NPh^{2-} ligand; C: top view to the Cl^- ligand).

clearly illustrates that the metal center is highly shielded by the organic ligands and the metal core is almost completely wrapped by a non-polar organic envelope. Nevertheless, a substitution of the 4-position of the phenylimido ligand should be possible and, thus, some current research is directed towards the synthesis of 4-phenylsubstituted phenylimido complexes according to Scheme 10. First steps, such as the synthesis and structural characterization of the 4-amino-phenylimido complex $[Re(NPh\text{-}4\text{-}NH_2)Cl_3(PPh_3)_2]$ (B),[40] were successful. The synthesis of more derivatives, e.g. with alkylamino or alkylcarboxylate substituents on the aromatic ring are currently underway. They will allow a flexible coupling to biomolecules either by means of the carboxylic or amine terminus of peptides.

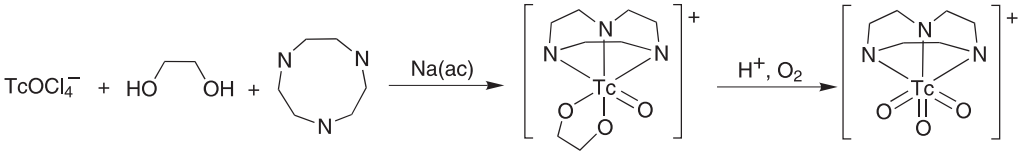
A completely different approach to new technetium complexes, which are interesting as potential radiopharmaceuticals, is currently under investigation in a



Scheme 9.



Scheme 10.



Scheme 11.

number of laboratories: the quest for stable and reproducibly available technetium(VII) complexes. A key species of this chemistry is the trioxotechnetate cation, $[TcO_3]^+$, which provides a most promising core for new, very flexible complexes. A number of complexes with this core having tridentate ligands are known.[1] However, the synthesis of most of them is not suitable for pharmaceutical preparations, since they use strong acids to convert $[TcO_4]^-$ into the pertechnetic acid, which then undergoes ligand exchange, or start from the volatile Tc_2O_7 or highly instable compounds such as $O_3TcOSiMe_3$.

A relatively easy excess to $[TcO_3]^+$ complexes is given by a redox procedure *via* technetium(V) intermediates that contain ethylene glycolato ligands. Such technetium complexes readily undergo oxidative decomposition under formation of the trioxo-technetium(VII) core. This approach was originally developed for analogous rhenium complexes[41] but has recently also been applied for technetium, using tripodal ligands such as 1,3,7-triazacyclononane (see Scheme 11) or scorpionato ligands such as bis(pyrazol-1-yl)acetic acid.[42]

7. Conclusions

It is obvious from the previous sections that coordination chemistry plays an important role in the development of novel rhenium and technetium radio-pharmaceuticals. Although kit preparations for the imaging of almost all main organs and organ systems exist and there is some experience in the labeling of biomolecules, there is still a need for new approaches and new labeling procedures. Many of the routine methods apply the same or related chelator systems and oxidation states of the transition metals. This strongly restricts the opportunities to influence specific properties of the metal-biomolecule conjugates.

It will remain a challenge for synthetic chemists to supply novel methods and compound for the radiopharmaceutical community. Promising contributions are expected from the coordination chemistry as well as from the organometallic chemistry of these two group VII elements.

Roger Alberto *accomplished the degree of "dipl. chem ETH" in 1982 and received his PhD from the same University in 1988. 1989 he moved to the Technical University of Munich as an "Alexander von Humboldt fellow" in Prof. W.A. Herrmanns group. After several scientific missions to the Los Alamos National Laboratory, he left Munich in 1993 and moved to Paul Scherrer Institute Würenlingen. Since 1999 he is working as Professor of Inorganic Chemistry at the University of Zurich. His research interests focus on the role of metals in life science such as Inorganic medicinal chemistry, bioinorganic chemistry and aqueous organometallic chemistry.*

Ulrich Abram *received his PhD in Chemistry from the University of Leipzig (Germany) in 1986. After several positions as researcher at the Research Centre of Rossendorf and the University of Tübingen, he joined the Institute of Chemistry of the Freie University Berlin in 2000, where he is now Professor of Inorganic and Radiochemistry. His main research interests are the coordination chemistry of metals with biological and medical importance and particularly the structural chemistry of rhenium and technetium complexes. He is author of several book chapters and reviews and has published more than 250 original contributions on this topic.*

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