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Review

The particular role of radiopharmacy within bioorganometallic chemistry

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Abstract

This article will emphasize the particular role of organometallic radiopharmaceutical chemistry, namely the need for syntheses from water and the emerging implications for other (bio)organometallic fields. After some basic insights into the different directions of bioorganometallic chemistry, some facets of the $[M(CO)_3]^+$ (M = Tc, Re) moiety are reviewed and discussed in the respective context. The mechanism for the synthesis of $[M(OH_2)_3(CO)_3]^+$ which is still little understood, will be touched. The formation of additional M–C bonds is exemplified with cyclopentadienyl chemistry, the potential impact on targeted molecular imaging with the labelling of amino acids and the reactivity towards essential biomolecules such as guanine is shown. Future perspectives and implications for organometallic radiopharmaceutical chemistry will close this article.
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Keywords: Bioorganometallic; Technetium; Radiopharmacy; Carbonyl; Targeting

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1. Introduction

Bioorganometallic chemistry refers to the application of metal complexes comprising M–C bonds for biological or medicinal purposes [1]. The application of metal complexes for biological or medicinal applications has a long tradition dating back to the origin of life [2]. Nature immediately recognized that metal cations have characteristics which can hardly be taken over by organic compounds. In particular, catalytic reactivity and redox properties are almost unique features of metal cations. Whereas nature extensively exploits metal-based reactivity, it scarcely uses small metal containing compounds, for e.g. receptor binding through structural recognition. On the other hand, structural changes imposed on proteins or nucleic acids

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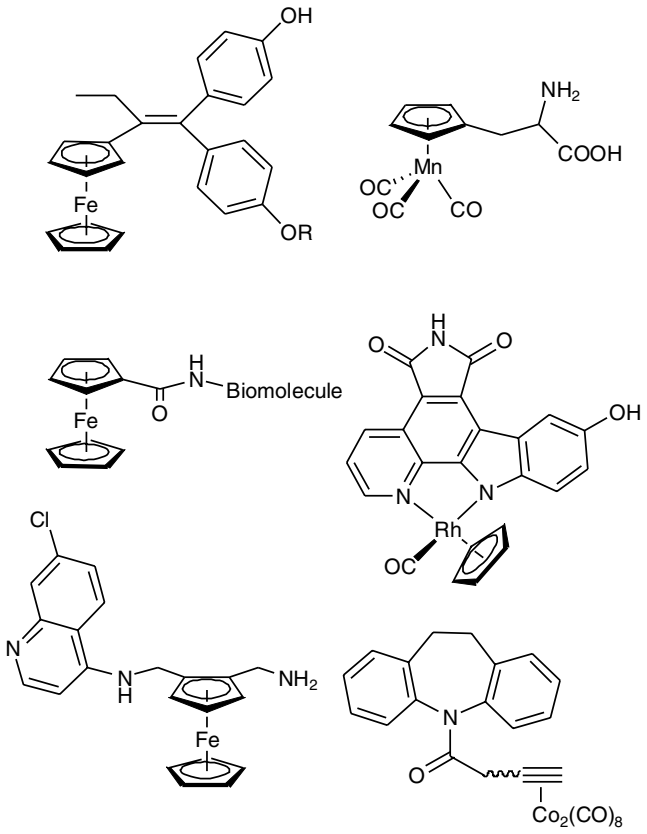
by metal cations such as Ca^{2+} or Zn^{2+} are essential for the initiation of catalytic processes [3]. Receptor binding with all its biological consequences is in nature the area of organic substrates. Consequently, the vast majority of pharmaceuticals consists of organic molecules acting structurally as e.g. inhibitors for receptors or, rarely, chemically as e.g. alkylating agents. Structurally active coordination compounds are still rare, despite the fact that the topological realm they can provide is much larger than what is possible for organic compounds. Admittedly, coordination compounds tend to exchange ligands relatively easy but organometallic compounds often do not, especially if they have a closed shell d^6 electronic configuration. This fact led to the advent of the medicinal branch of bioorganometallic chemistry, the way to which was paved by Beck et al. and practically explored for the first time with the ferrocifens by Jaouen et al. [4–7]. Ferrocene, a widely used building block in bioorganometallic chemistry, mimics and replaces a benzene ring in tamoxifen enabling the treatment of breast cancer [8–11]. Similarly, ferroquine is at an advanced stage in the development of anti-malarial agents [12–16] and ferrocene, attached to biological molecules can also be used as a redox probe [17,18]. Ferrocene, despite having the inherent property of redox chemistry acts, as far as is known, mainly through its structure [19]. Metal-based reactivity such as Fenton chemistry is occasionally suspected but usually not directly observed. Other substitution inert organometallic complexes such as $[CpRe(CO)_3]$ can sometimes substitute ferrocene while keeping the biological activity of the lead compound intact [20,21]. Similarly, carbonyl complexes can be used as probes due to the high sensitivity of the CO stretching frequency in infrared spectroscopy. This has been used, for instance, in metalloimmunoassays developed by Salmain et al. [22]. Strong fluorescence is often a characteristic of organometallic compounds. Metzler-Nolte et al. combined a Mo(0) complex with a tridentate pyridine based amine ligand, the complex of which was bound to proteins, peptides and PNA's as luminescent probes [23–25]. There are more examples in which the metal complexes are solely structurally active or by their physico-chemical properties [26,27]. For all is in common that the metal centre in the complex does not show chemical activity (making and breaking of bonds) but defines a structure which is the key for understanding its function. A selection of these complexes is given in Scheme 1.



Scheme 1. Some structurally active bioorganometallic complexes mentioned in the text.

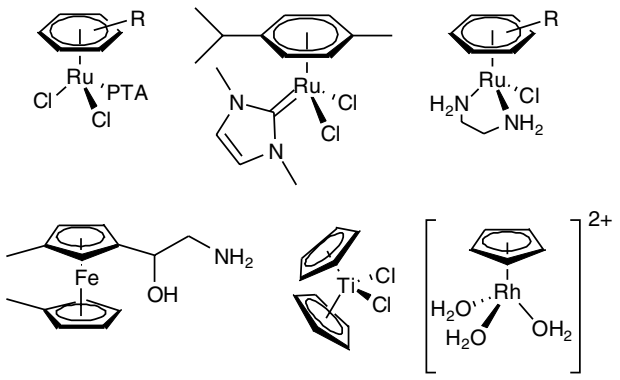
Let us turn our attention to complexes *with* metal-based reactivity. Cisplatin is certainly the prototype for this class of compounds. In the intracellular space, one chloride in *cis*-$[Pt(NH_3)_2Cl_2]$ is substituted by H_2O thereby activating the complex. The activated species then penetrates the cell nucleus and performs its well known action of alkylating DNA [28]. Square planar d^8 systems are generally robust, therefore the reactions are comparably slow and the amines are not touched. In fact, we can consider the *cis*-$[Pt(NH_3)_2]^{2+}$ moiety as a new sort of platinum with two available coordination sites left, a point of view that is often found in bioinorganic textbooks where haemoglobin is referred to as a new kind of iron. To transform metal-based reactivity from square planar to octahedral complexes is challenging since two more coordination sites have to be taken into account. That is why and where organometallic compounds come into play. How to irreversibly shield coordination sites from substitution with a ligand while keeping the option of tuning the metal centre's electronic properties (reactivity) intact? The shielding of three sites can be achieved with Werner-type ligands such as scorpionates, macrocycles or other polydentate systems. However, the resulting moieties are relatively bulky and further functionalization of the ligands not routine. Furthermore, they are prone to base or acid catalysed substitution and cleavage. A logical but not immediately obvious alternative are organometallic ligands such as cyclopentadienyl (Cp) or arene based systems [29–31]. Archetypical, these are complex fragments such as $[Ru(arene)L]^{2+}$, $[Cp^*Rh]^{2+}$ and a few others. Following the bioinorganic view, we can consider these cores as a new kind of ruthenium or rhodium, respectively. Out of the six-coordination sites, metal-based reactivity is restricted to two or three positions, similar to cisplatin. The option of varying the organometallic ligand or introducing additional coligands such as ethylenediamine or PTA in e.g. Ru enables fine tuning of the biological behaviour and the reactivity [32]. Tuning of the arene in $[Ru(arene)(en)Cl]^+$ is convenient and has

revealed extremely interesting structure–activity relationships [33]. Some of these complexes have or will enter clinical trials.

A number of multinuclear complexes based on one of the above-mentioned cores, especially $[Cp^*Rh]^{2+}$, are receptors for small biomolecules. Fish et al. pioneered this sort of cyclic trimers for molecular recognition in host–guest chemistry for small biological molecules in general and amino acids in particular [34]. Severin recently extended this principle to the detection of anions [35–37]. A last and exciting example for metal-based reactivity is enantioselective catalysis based on the avidin-biotin technology discovered by Ward et al. [38]. Some representative examples for complexes with metal-based reactivity are given in Scheme 2.

Resuming this very brief overview about bioorganometallic principles, it is noted that the making or breaking of M–C bonds rarely shows up as an essential step in these reactions or reactivities. It is, in contrast, the essential step in B12 chemistry which is frequently referred to as the archetype compound of bioorganometallic chemistry. The authentic feature is that the carbon bound ligands tune the electronics of the metal centre, thus, generating complex fragments with unique properties. Their behaviour is not only gradually but also principally different from structurally related complexes with Werner-type ligands. Possible for some of the mentioned precursors, there is still no need to synthesize them from water, the essential prerequisite being stability of the complex fragments in water.

The situation is now different in radiopharmaceutical chemistry [39]. Since radioisotopes such as ^{99m}Tc are exclusively available in aqueous solution at high dilution, any complex or complex fragment must be prepared from this solvent. Due to their inherent instability or non-existence in water, some ligand types are therefore excluded in advance. The need for aqueous syntheses opens, on the other hand, the exploration of synthetic approaches along uncommon pathways. This is later shown with the preparation of carbonyl or Cp-complexes. Ultimately, such procedures can be adopted to further transition elements, thereby fertilizing synthetic strategies and gaining access to new and otherwise unavailable complexes.



Scheme 2. Some selected organometallic complexes with metal-based activity.

2. Organometallic radiopharmaceutical chemistry

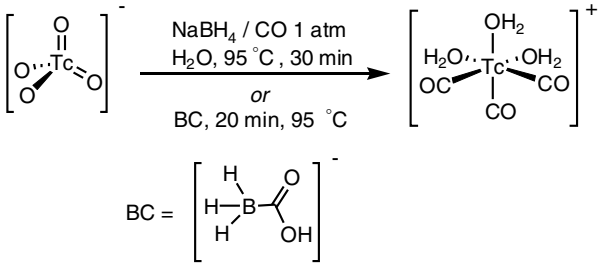
The radionuclide ^{99m}Tc is extensively applied in diagnostic imaging in nuclear medicine and is only available as $[^{99m}TcO_4]^-$ in saline (0.9% NaCl in water). Any chemistry aiming at application has ultimately to be performed in this media. Therefore, if ^{99m}Tc based organometallic compounds are synthesized, the formation of M–C bonds must occur in water. Following the principles of stable but reactive complex precursors, three positions must irreversibly be occupied and the other three must remain exchangeable. Then, binding to a ligand conjugated to a targeting molecule or direct coordination to a potential binding site in a biomolecule leads to labelling [40]. At that stage, a robust complex should be formed which has neither structural nor metal-based reactivity but is, chemically spoken, an innocent entity. In practice of course, this is never realized since any complex represents an additional structural motif that contributes to recognition and interactions.

As will be seen later, the dual option for a precursor of forming robust complexes (labelling) or directly interacting with coordinating sites in biomolecules leads to the unparalleled possibility of combining radiotoxicity with chemotoxicity.

2.1. The $[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor

The formation of M–C bonds in water was preceded by the synthesis of binary Tc(I) isocyanide complexes by Davison et al. [41]. Complexes $[^{99m}Tc(CN–R)_6]^+$ have become the most important myocardial imaging agents on the market. Important synthetic inspiration can be received for the preparation of carbonyl complexes since CO and CN–R are isoelectronic ligands. Furthermore, Wester et al. reported the synthesis of bis-arene complexes $[Tc(arene)_2]^+$, not from water but they showed these compounds to be stable in water. This result was not obvious at all without being familiar with bioorganometallic chemistry [42]. Baldas reported about the synthesis of the Tc(III) complex $[Tc(dtc)_3(CO)]$ comprising CO which did form and coordinate in situ [43].

CO is a versatile ligand due to its small size and tight bond to metal centres. It is, however, a gas with particular low solubility in water. Our unprecedented approach with $Na[BH_4]$ and gaseous CO lead to the quantitative preparation of $[^{99m}Tc(OH_2)_3(CO)_3]^+$. This compound turned out to be a very useful starting material for bioorganometallic radiopharmaceutical chemistry [44]. It follows bioorganometallic principles and has the desired properties as outlined in the beginning of this section. We called it a "semi-aquo-ion". The request from industry for in situ preparation of CO (also in water) directed us toward the boranocarbonates [45], a class of compounds that had been introduced by a pioneer in boron chemistry, Malone and Parry but boranocarbonates have scarcely been used for syntheses [46]. The approaches to the preparation of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ are summarized in Scheme 3.



Scheme 3. The two reaction pathways to $[^{99m}Tc(OH_2)_3(CO)_3]^+$. Six electrons and 3 CO's are transferred, how does it happen?

Kits for the preparation of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ (Isolink®, Mallinckrodt Med. B.V.) are distributed for research purposes. Despite the apparently facile synthesis, many scientific questions remain to be elucidated. The mechanism of the reaction is unknown. A total of 6 e^- are transferred during the reduction without any intermediate being observed. Three CO's must coordinate at an extremely low ^{99m}Tc and very low CO concentration. So far, we found only complexes with 3 CO's, not with two and not with one CO. According to theoretical calculations, at least the former one should exist. Complexes with more CO's are unlikely since the trans effect induces immediate cleavage at the temperature of synthesis.

It is an incentive to have a closer look into the reaction mechanism. The implication from our discovery is the question of adopting the principles to further transition elements receiving new mixed water–CO complexes. These are sometimes hardly accessible along other pathways and only a very few are known at all. In single experiments, we qualitatively found the formation of carbonyl complexes with Cr, Mo and Ni complexes but do not know yet their authenticity.

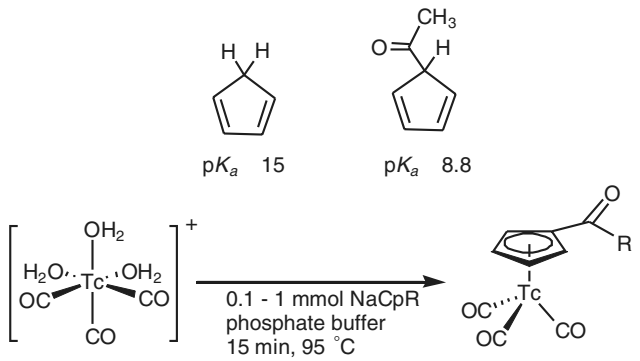
The precursor complexes $[^{99m}Tc(OH_2)_3(CO)_3]^+$, $[^{99}Tc(OH_2)_3(CO)_3]^+$ and $[Re(OH_2)_3(CO)_3]^+$ found widespread application in research and many groups contributed to the understanding with very good chemistry for fundamental but also for application purposes [47,48]. To quote them all would exceed the range of this article. The picture on the cover page sketches these different possibilities. Put into the vial pertechnetate, boranocarbonate and a ligand of choice, one will receive very different complexes often in near quantitative yields. Shown is a carborane, a piano-stool cyclopentadienyl complex and two coordination compounds. Since it leads over to the next section, the preparation of carborane complexes reported by Valliant et al. is of particular interest [49–51]. Using carboranes as Cp analogues requires the formation of M–C bonds in water. A highly innovative approach has been developed by this group realizing the practicability of this unique class of bioorganometallic compounds. A realm of pure coordination chemistry has been performed, among them the formation of agostic hydride complexes from water and with stability in water deserves special attention since not been observed before [52]. Most of the chemistry published is coordination chemistry with an organometallic fragment but it remains to emphasize that the three CO ligands change the properties of the Tc centre in a very particular way.

2.2. The Cp problem – formation of further M–C bonds in water

Cyclopentadienyl is a very versatile ligand, having a low molecular weight, blocking three coordination sites and including the possibility of conjugating targeting vectors. Cyclopentadien is, on the other hand, insoluble and unstable in water, tends to di- and polymerise and can hardly be deprotonated ($pK_a \approx 15$). Some successful approaches to $[Cp^{99m}Tc(CO)_3]$ have been reported but they suffer from harsh conditions and the need for organic solvents [53,54]. We assumed that lowering the pK_a value would lead to more facile deprotonation with the negatively charged cyclopentadienyl ligand be more prone for coordination, a hypothesis that turned out to be correct [55]. Introducing an acetyl group in cyclopentadien lowered the pK_a value to around 8.7 as determined by simple potentiometric pH titration and provided increased water solubility and stability to the ligand. Reaction of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ with e.g. acetyl-cyclopentadien with a keto group in α-position and with or without an attached targeting molecule lead to quantitative formation of piano stool Cp complexes as shown in Scheme 4 [56].

Originally we assumed that deprotonation only is crucial for this surprisingly easy formation of Cp complexes but later we also suspected that the enol–keton tautomerism plays a role. The enolate offers an initial anchoring group for the metal complex with a subsequent "haptotropic" shift to η^5-Cp coordination. Very recent results with $[C_5H_6$–COOH] supported this assumption since this ligand also forms the corresponding piano stool complexes with $[^{99m}Tc(OH_2)_3(CO)_3]^+$. This is unexpected since the C-acidity of the ligand is much lower than in free Cp.

The implications of our findings are similar to those from Section 2.1. The need for preparing complexes directly from water revealed that Cp derivatives can, in principle, be regarded as Werner-type ligands. Therefore, new mixed Cp–H_2O or other mixed ligand complexes with



Scheme 4. Aqueous preparation of $[CpTc(CO)_3]$ complexes with or without conjugated targeting molecule R.

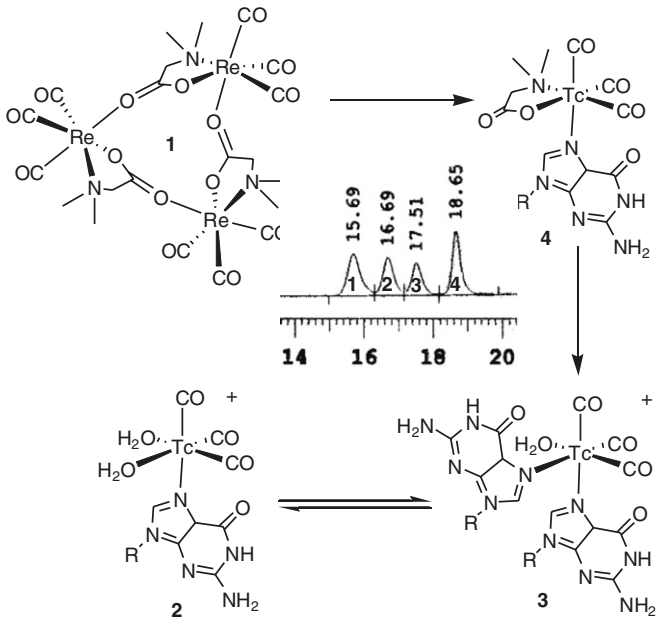
Cp might be available with versatile physico-chemical or biological properties.

2.3. Combining radiotoxicity with chemotoxicity?

It has been pointed out in the literature that randomized trials have demonstrated the superiority of chemotherapy plus radiotherapy to radiotherapy alone [57,58]. These trials have been performed with chemotoxic agents being different from the radiotoxic agents. It would be intriguing to have the identical compound for both modes of action. The metal-based reactivity of $[Re(OH_2)_3(CO)_3]^+$ as used for labelling could in principle also be applied to direct interaction in a cisplatin like way with coordinating sites in biomolecules such as N7 in guanine of DNA. The availability of the therapeutic radionuclides $^{186/188}$Re allows to complement chemotoxicity with radiotoxicity from identical compounds, provided that the agents can be guided into specific cell nuclei. Beside the hard β-emitters $^{186/188}$Re the Auger and conversion electrons from ^{99m}Tc induce also radiotoxicity [59].

We have studied the basic behaviour of $[Re(OH_2)_3(CO)_3]^+$ with 7Me-G and with 9Me-G. We found the coordination of a maximum of two bases coordinated to the Re centre in a head to tail and a head to head conformation [60,61]. Some crystal structures are depicted in Fig. 1.

Unlike cisplatin, however, $[Re(OH_2)_3(CO)_3]^+$ reacts in serum rapidly and irreversibly with serum proteins and is therefore not available anymore for penetrating cells. We reasoned that a sort of prodrug is required with at least two sites on rhenium reversibly protected by a bidentate ligand. Amino acids are a choice but they bind in general too strongly. Only hindered amino acids such as *N*,*N*-dimethyl-glycine (Hdmg) turned out to be labile enough to be substituted by e.g. 9Me-G. The complexes with Hdmg formed the cyclic trimer $[Re(dmg)(CO)_3]_3$, a structural feature that has frequently been found in bioorganometallic chemistry [37]. Exposing $[Re(dmg)(CO)_3]_3$ to 9Me-G showed a nice and stepwise substitution of dmg by 9Me-G. Reaction with pDNA induced structural scrambling as observed with cisplatin or $[Re(OH_2)_3(CO)_3]^+$ albeit in a 10 times higher concentration only (Scheme 5) [62].



Scheme 5. Stepwise substitution of *N*,*N*-dimethyl-glycin with 9Me-G. Assignments are from HPLC–MS.

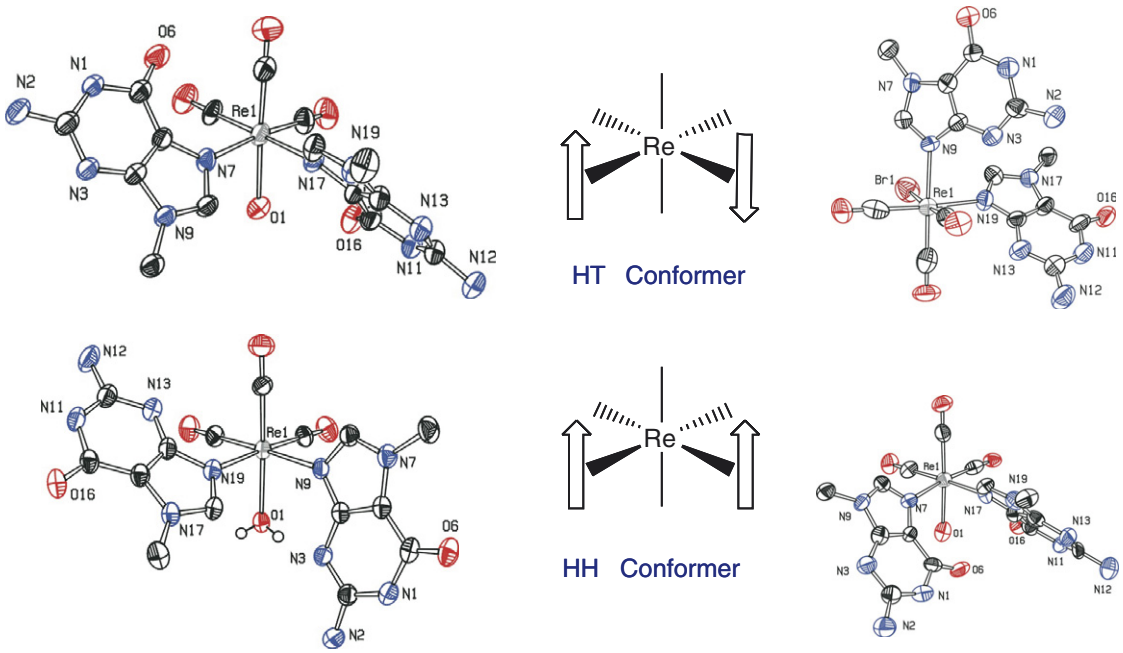


Fig. 1. The reaction of $[ReBr_3(CO)_3]^{2-}$ with [9Me-G] (top) and [7Me-G] (bottom) gives four complexes with different relative guanine orientation.

We showed in some preliminary studies that Auger electrons from ^{99m}Tc do double strand break DNA. In combination with the observed DNA interaction it seems possible that the combination of chemotoxicity and radiotoxicity is feasible but more detailed studies are required to confirm the superiority of such a combination.

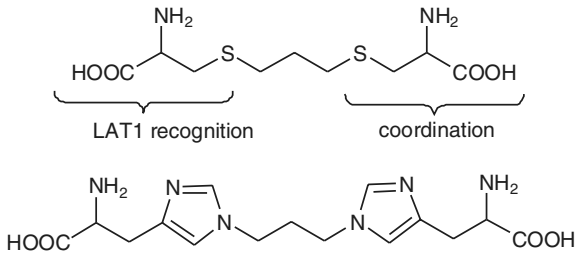
2.4. Classical labelling: amino acids

Radiolabelling describes the conjugation of stable, chemically innocent metal complexes to e.g. targeting molecules. The metal complex should not interfere with the receptor binding and ensure a reasonable clearance from the body without accumulation in undesired organs. A variety of labelled biomolecules, mainly peptides, with carbonyl complexes and, preferentially, with the traditional Tc(V) $[Tc{=}O]^{3+}$ core have been described [63]. Whereas the ligand types for the latter core are of relatively little flexibility, ligands and donor atoms can be altered for the $[^{99m}Tc(CO)_3]^+$ core over a wide range, enabling tuning of the physico-chemical properties of the labelled targeting agent. Since peptides are relatively large molecules, the metal complex can be conjugated to a functionality with small interference to the "lock".

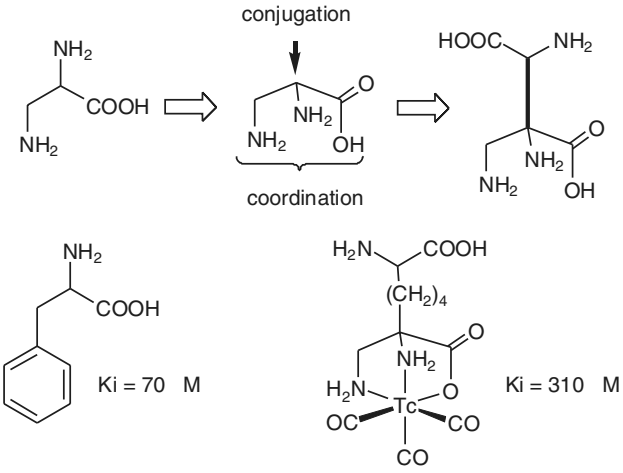
The labelling of small molecules which are actively transported through the e.g. cell membrane is much more challenging and has not yet been successfully achieved. It would be highly desirable to complement PET radiopharmaceuticals such as ^{18}FDG with ^{99m}Tc compounds. Labelled glucose especially would be an incentive but, despite many research efforts, there is no success so far [64–66]. Obviously, the metal complex is simply too large for a small substrate like glucose to remain still recognized *and* transported after labelling.

Due to the possibility of receiving small complexes with the *fac*-$[^{99m}Tc(CO)_3]^+$ moiety, we turned our attention to the labelling of α-amino acids. LAT1 is the antiport transporter for neutral amino acids and is overexpressed on some tumour cell lines [67]. LAT1 accepts a range of amino acids, its selectivity is therefore not as strong as the one of GLUT1 for instance. Admittedly, the amino acid functionality is very small but it is hypothesized that recognition of the side chain is mainly based on its neutral character and lipophilic interaction with a pocket inside the transporter. For simplicity, we chose in the first attempts the twining of amino acids such as cysteine or histidine. Twining of these natural amino acids yielded on one end the amino acid part and on the other the label. Still, we never observed any affinity to or transport by LAT1. This came not as a surprise but rather as a confirmation of the paradigm that small transported molecules cannot be labelled with metal complexes (Scheme 6).

We switched then to 2,3-diaminopropionic acid, a nice tripod which is hardly used as a ligand. Derivatization at the α-C with a spacer and a terminal amino acid functionality would yield a "slim" label of low molecular weight.



Scheme 6. "Twining" of cysteine and histidine. Labelled with $[Re(CO)_3]^+$ on one end abolishes any affinity to LAT1.



Scheme 7. 2,3-Diamino-propionic acid based amino acid derivatives with tripod ligand.

Lengthy and tedious chemistry was required to prepare this seemingly simple molecule (Scheme 7).

Selective and quantitative labelling occurs at the tripod and the corresponding cold rhenium complexes could be prepared. In vitro studies showed that the Re-labelled amino acid with a C4 spacer had a reasonable affinity for LAT1 of 300 μM in comparison to phenyl-alanine (70 μM). Since LAT1 is an antiport system, the uptake of cold compound can be quantified if efflux of a previously taken up radioactively labelled amino acid such as [^{3}H]-L-Phe is observed. This was the case, proving that the labelled amino acids are taken up into the intracellular space. These complexes represent the first examples of metal-labelled small molecules that are recognized and transported by *trans*-membrane proteins such as LAT1.

3. Conclusion

To be awarded after W. Beck and G. Jaouen with the "Prize for Outstanding Research in Bioorganometallic Chemistry" during the 3rd International Symposium on Bioorganometallic Chemistry in Milano 2006, means a strong motivation for further exploring the potential of the very simple *fac*-$[Tc(CO)_3]^+$ core. I have chosen these examples since they not only demonstrate the particular role and requirements of radiopharmaceutical chemistry

within bioorganometallic chemistry, but also since they imply perspectives and further directions as well into, generally spoken, aqueous organometallic chemistry.

Acknowledgements

Honoured by the price, I express my gratitude to past and present co-workers and collaborators who contributed with their enthusiasm and experimental efforts to the realization of this chemistry: Ulrich Abram, Nikos Agorastos, Patrizia Allegro, Paul Benny, Jonathan Bernard, Alice Bizzozero, André Egli, Pascal Häfliger, Gérard Jaouen, Thomas Kaden, Lukas Kromer, Susanne Kunze, Philipp Kurz, Yu Liu, André Merbach, Stefan Mundwiler, Kirstin Ortner, JaeKyong Pak, Benjamin Probst, Dirk Rattat, Pilar Sanchez, Isabel Santos, Maung Maung Saw, Roger Schibli, Paul Schmutz, August Schubiger, Bernhard Spingler, Yuji Tooyama, Karlijn van der Schilden, Dave van Staveren, Joachim Wald, Wenwu Wang, and Fabio Zobi.

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