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Labeling Monoclonal Antibodies with Metal Complexes: A Challenge for Coordination Chemists

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Abstract: Three examples are used to show how the coordination chemist can develop macrocyclic ligands for labeling monoclonal antibodies used in nuclear medicine for tumor diagnosis and therapy.

Keywords: Coordination chemistry · COST · Macrocyclic ligands · Monoclonal antibodies

Introduction

The covalent attachment of open-chain or macrocyclic chelators to monoclonal antibodies or small peptides (vectors) allows such compounds to be labeled with β- or γ-emitting radionuclides so that they can be used in nuclear medicine for therapeutic or diagnostic purposes (Fig. 1) [1].

The role of the coordination chemist is to design new ligands which specifically bind the radionuclide with high thermodynamic and kinetic stability [2]. This is of paramount importance in order to prevent transmetallation under physiological conditions. In addition, the ligands must be functionalized so that they can be covalently attached to the vector molecule through the linker. There are several isotopes with ideal properties for a medical application. ^{99m}Tc, which can be obtained from a generator in the hospital, has been used in many instances [3]. We therefore have focussed our studies on $^{111}In^{3+}$, $^{90}Y^{3+}$, $^{64}Cu^{2+}$, and $^{111}Ag^{+}$, which have interesting radiophysical properties and have not yet been investigated in detail.

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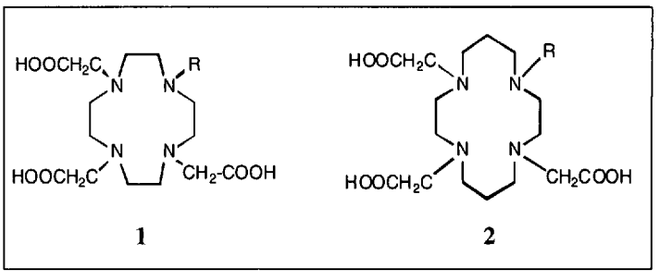
Ligands for $^{111}In^{3+}$

It is well known that macrocyclic amino carboxylates such as **1** and **2** (R = H or CH_2COOH) are very good ligands for trivalent metal ions [4]. Therefore we have studied the structure of In^{3+} complexes with **1** and **2** (R = H and *p*- CH_2–C_6H_4–NO_2) which can be coupled to a vector molecule. Both ligands with R = H form very similar heptacoordinate In^{3+} species in which the four nitrogens and the three carboxylates are coordinated to give a capped trigonal prismatic geometry [5].

Bond lengths are somewhat shorter for the complex with **1** (R = H) compared with those of the complex with **2** (R = H). However, the serum stability of the complexes is completely different. The In^{3+} complex of **1** (R = H) very slowly exchanges the metal ion in blood serum, whereas that of **2** (R = H or CH_2–C_2H_4–NO_2)



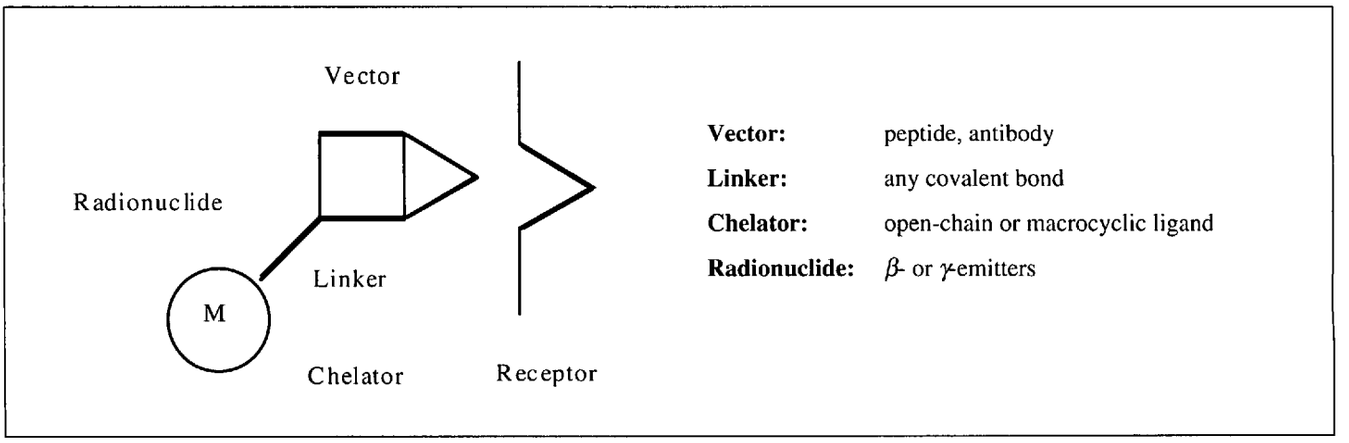


Fig. 1. Schematic representation of a vector molecule labeled with a covalently attached radionuclide

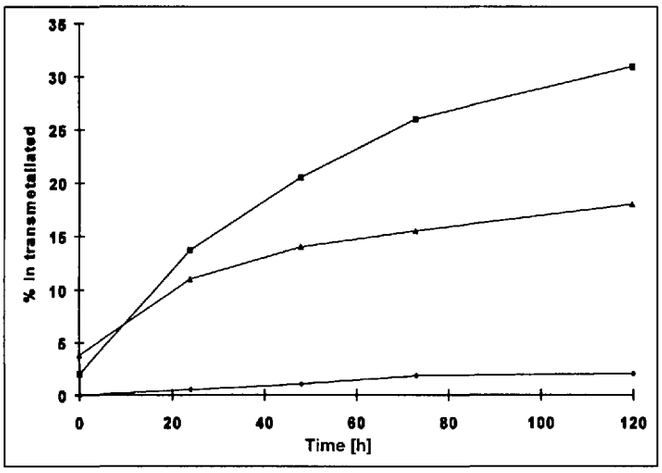
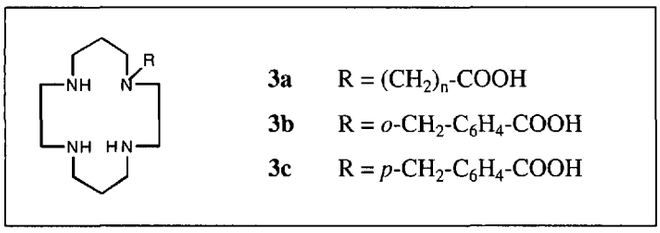


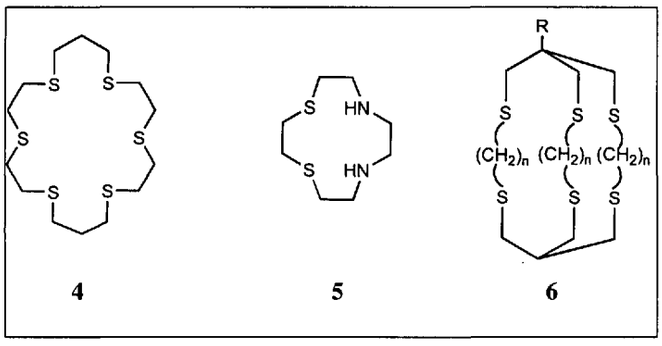
Fig. 2. Time dependence of the transmetallation of the $^{111}In^{3+}$ complexes of **1** (R = H) ♦, **2** (R = H) ■, and **2** (R = *p*-CH_2–C_6H_4–NO_2) ▲ in blood serum



3a R = $(CH_2)_n$-COOH

3b R = *o*-CH_2-C_6H_4-COOH

3c R = *p*-CH_2-C_6H_4-COOH



4 **5** **6**

releases the In^{3+} at a much higher rate and therefore cannot be used in nuclear medicine (Fig. 2).

Cu^{2+}-Specific Ligands

A second example is the development of a Cu^{2+}-specific ligand which can be covalently attached to an antibody. During our studies on functionalized tetraazamacrocycles with carboxylic side chains (**3a**) [6] we have found that in the *o*-toluic acid derivative **3b** the carboxylate axially binds to the Cu^{2+}, whereas in the *p*-toluilic derivative **3c** the carboxylic acid is not involved in coordination. It can be reacted using standard methods of peptide chemistry with an amino group of the substrate to give an amide bond as linker.

Thus we have used **3c** to label the monoclonal antibody b12 with the macrocycle in which $^{64}Cu^{2+}$ was coordinated [7]. Animal experiments showed that the conjugated antibody selectively binds to the receptors with a very good blood/tumor ratio and thus allows the detection of the size and position of the tumor with high precision.

Search for $^{111}Ag^{+}$-Specific Ligands

$^{111}Ag^{+}$ is an especially interesting isotope, since it has γ- and β-radiation, both of which are ideal for nuclear medicine. Being a very labile metal ion, ligands must be developed which form thermodynamically stable and possibly also kinetically inert complexes. Studies to bind Ag^{+} with S_6-(**4**) and N_2S_2-(**5**) macrocycles have shown that these ligands, although they form rather stable complexes, are not able to prevent transmetallation in physiological fluids.

We have therefore prepared a series of S_6-cages (**6**) with different bridging lengths between the thioether groups and different size of the capping unit. Studies on the complexation of these ligands with Ag^{+} gave complexes in which the Ag^{+} ion is not incorporated into the cage, but sits outside [8]. These complexes proved to be too weak for a medical application.

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