Reactivity and Function of Macrocyclic Metal Complexes

Thomas A. Kaden*

Abstract: The introduction of side chains into tetraazamacrocycles allows the preparation of metal complexes with functional properties. On the one hand donor groups at the end of the side chain can be used to control the coordination geometry of the metal ion. On the other hand reactive groups can be incorporated into the side chain and their reactivity can be enhanced by the fact that the group comes close to the metal ion (metal ion induced reaction). Finally the side chain can be used to covalently attach macrocyclic metal complexes to antibodies for diagnostic and therapeutic applications in nuclear medicine.

Keywords: Coordination geometry · Macrocycles · Medical applications · Reactivity · Supramolecular chemistry

1. Introduction

Macrocycles, cryptands, and cavitands are well-known examples of molecules which can form host–guest complexes, and because of the different sizes of their cavities, have interesting molecular recognition properties [1]. In order to further develop these properties we have been involved in the study of metal complexes of macrocyclic ligands carrying pendant group with three main aims:

Control of the coordination geometry. The introduction of side chains containing coordinating groups allows the preparation of multidentate ligands and the control of the geometry of their metal complexes.

Enhancement of the reactivity of side chain group. Through the side chain a reactive group can be brought close to the metal center so that metal-induced reactions can be studied.

Applications in nuclear medicine. Functional side chains can also be used to covalently attach macrocyclic ligands la-

beled with radioisotopes to monoclonal antibodies so that diagnostic and therapeutic applications in tumor treatment can be achieved.

2. Coordination Geometry Control

In general macrocycles, being more rigid than open chain ligands, enforce a coordination geometry onto the metal ion. So 1,4,8,11-tetraazacyclotetradecane (cyclam, **1**) mostly forms square planar or *trans*-octahedral species, the macrocycle assuming the *trans-III* configuration which is ideal to bring all four nitrogen donors in a plane [2].

Of course the size of the macrocyclic ring also plays an important role. Whereas the 14-membered cyclam is able to encompass 3d-transition metal ions, the 12-membered ring or the 9-membered 1,4,7-triazacyclononane are too small so that the metal ion cannot be bound in the center of the cavity. Facial (Fig. 1) or folded structures leading to *cis*-octahedral geometry thus result.

The introduction of side chains with additional donor groups into tetra-azamacrocycles is an additional way to modulate and control the coordination geometry of the metal ion [3].

The mono-N-functionalization of the 14-membered ring gives ligands with potentially five donors. In the case of deriv-
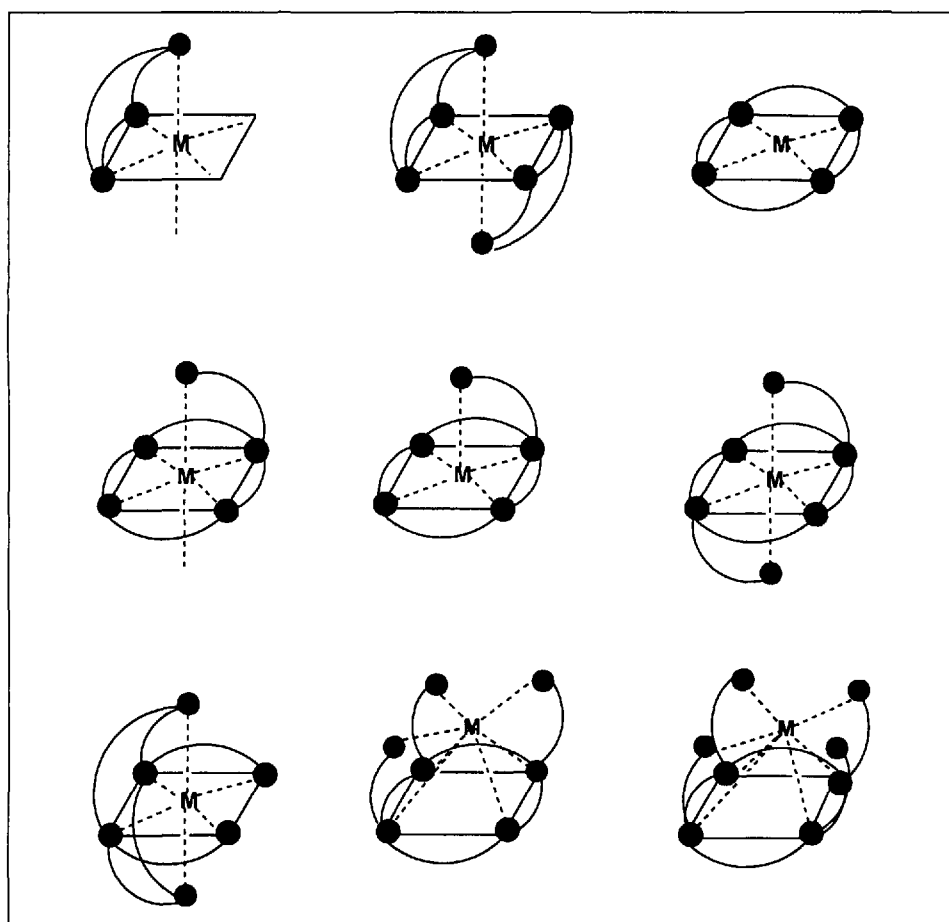
atives such as **2**, which have secondary and tertiary nitrogens, *trans*-octahedral species were observed, the solvent occupying the sixth coordination position [4]. However, with derivatives of the trimethyl macrocycle **3** the resulting complexes exhibit practically all pentacoordination, whereby square pyramidal, trigonal bipyramidal and intermediate geometries were found depending on the nature of the donor group [3][5]. It is also interesting that in all these species the 14-membered macrocycle adopts the *trans-I* configuration in which all substituents are on the same side of the N_4-plane.

When two side chains are incorporated into the tetraazamacrocycle, two possibilities have been observed (Fig. 1). Either the donor groups of the side chains are coordinated in a *trans*-octahedral geometry, the four nitrogens of the macrocycle forming a plane [6], or in a *cis*-octahedral arrangement, when the macrocycle folds as in the case of 1,4,7,10-tetraazacyclododecane, which is too small to encompass the metal ion [7]. When more than two side chains are incorporated and the number of donors exceeds six, then 3d-transition metal ions only use six of them to reach the octahedral coordination and leave one or two unused [8], whereas larger ions such as In^{3+} [9] or lanthanides [10] coordinate all of them forming seven, eight or in some cases nine coordinated structures.

*Correspondence: Prof. Dr. T.A. Kaden
Department of Chemistry
University of Basel
Spitalstrasse 51
CH–4056 Basel
Tel. +41 61 267 10 06
Fax +41 61 267 10 20
E-Mail: th.kaden@unibas.ch
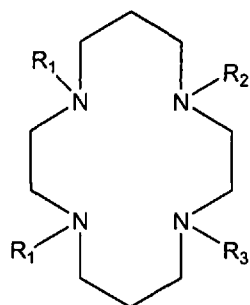
1   $R_1 = R_2 = R_3 = H$

2   $R_1 = R_2 = H$, $R_3 = (CH_2)_nCOOH$

3   $R_1 = R_2 = CH_3$, $R_3 = CH_2COOH$

4   $R_1 = R_2 = CH_3$, $R_3 = CH_2COOEt$

5   $R_1 = R_2 = CH_3$, $R_3 = CH_2PO(OEt)_2$

6   $R_1 = R_2 = CH_3$, $R_3 = (CH_2)_nCN$

7   $R_1 = R_2 = CH_3$, $R_3 = CH_2CN$

8   $R_1 = CH_3$, $R_2 = R_3 = o\text{-}CH_2C_6H_4SMe$

9   $R_1 = R_2 = CH_3$, $R_3 = p\text{-}CH_2C_6H_4SMe$

10 $R_1 = R_2 = CH_3$, $R_3 = CH_2CH_2SCH_3$

11 $R_1 = R_2 = CH_3$, $R_3 = CH_2CH_2OCH_3$

Fig. 1. Different coordination geometries for metal complexes with macrocyclic ligands having pendant side chains.

In summary, the introduction of side chains with additional donor groups allows the coordination geometry to be controlled in the different complexes and when the fit between the requirements of the metal ion and the coordination potential of the macrocyclic ligand is optimal, very high complex stabilities result.

A further interesting aspect of the combination of a rigid macrocyclic unit and a more flexible side chain donor was observed when the pH dependence of the spectra of several complexes was studied [5][11]. In acidic solution the donor group of the side chain is protonated and thus cannot bind to the metal ion, whereas at higher pH, when deprotonation occurs, the donor group coordinates in the axial position of the metal ion (Fig. 2). Thus by fixing the pH, the geometry of the metal ion can be controlled, since in acidic solution only the four nitrogens of the macrocycle coordinate in a square planar geometry (Ni^{2+} or Cu^{2+}), but at more alkaline pH the side chain additionally binds to give five coordinate or *trans*-octahedral species, depending on whether a solvent molecule is participating to the coordination polyhedron or not. These complexes can be looked at as molecular devices, in which by controlling the pH, a color change and a movement of the side chain takes place.

3. Enhancement of the Reactivity of Side Chain Groups

Another way to use macrocyclic metal complexes in a functional way is to attach side chains carrying reactive groups, so that the group can come close to the metal center. With this the enzyme substrate interaction in a metallo-enzyme
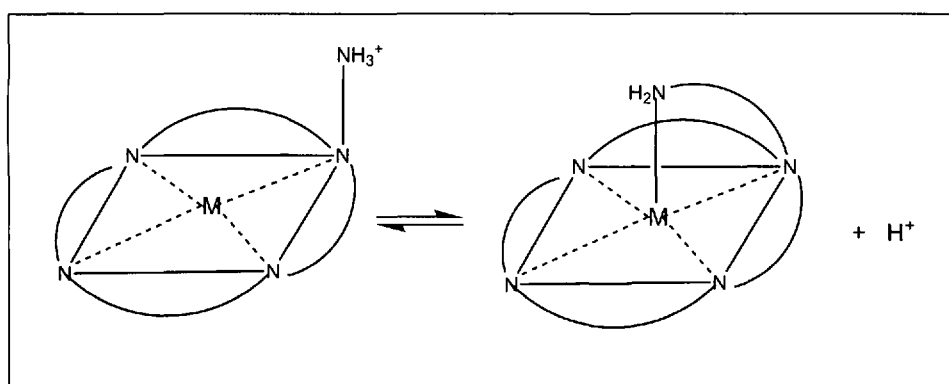

Fig. 2. pH-Dependence of the coordination geometry in macrocyclic complexes with a donor group in the side chain.
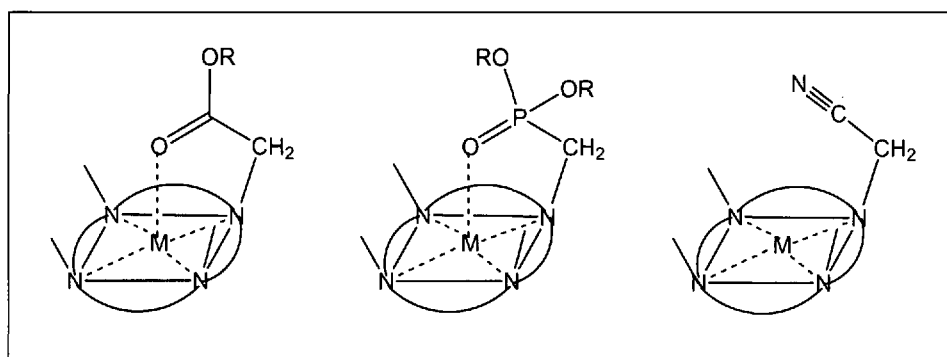
Fig. 3. Examples of macrocyclic complexes with reactive groups in their side chain.
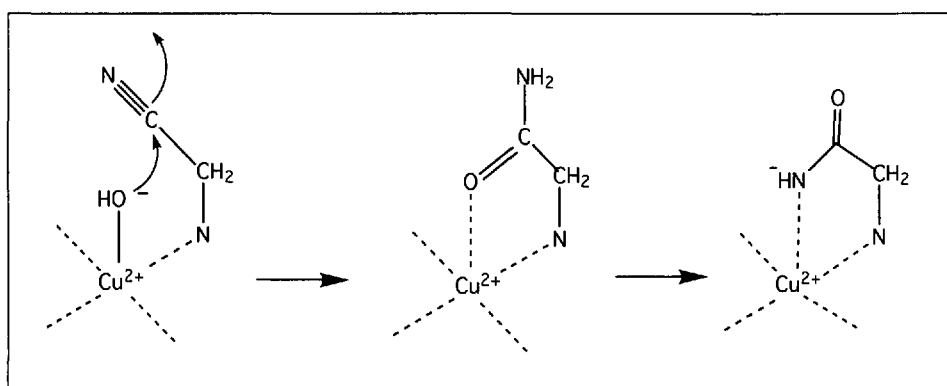

Fig. 4. Transition state in the hydrolysis of the side chain nitrile group in a macrocyclic complex.

can be mimicked and mechanism for metal induced reactions can be studied.

For this purpose we have prepared a series of compounds bearing functionality capable of hydrolysis (Fig. 3) [12]. Whereas with the ester 4 and phosphonate ester 5 hydrolysis was not very efficient, the hydrolysis of the nitrile derivative 6 (n = 1) is very fast [13]. The mechanism of this reaction indicates that the active species is a hydroxo complex and that an intramolecular nucleophilic attack of the coordinated hydroxo group onto the nitrile function of the side chain takes place in a cyclic five-center transition state. The reaction is very fast with a half life of about 50 ms at pH 12, which is probably due to the very favorable transition state (Fig. 4). In fact, by making the chain longer by one CH_2 unit (6, n= 2), the rate decreases by a factor of about 1000.

Also interesting is the observation that in the Cu^{2+} complex of the dinitrile derivative 7 only one of the two nitrile groups is hydrolyzed at a rate similar to that of compound 6 (n = 1). This can be explained if one assumes that the hydrolysis of the first nitrile group produces an amide, which deprotonated at high pH, binds to the axial position of the metal ion and thus prevents the formation of a

new hydroxo species, which could hydrolyze the second nitrile group. In the language of enzyme kinetics this would be called product inhibition, in the context of this reaction it is a nice example how one can obtain a unsymmetrical substituted macrocycle starting from one with two identical side chains.

Another metal-induced reaction we have studied is the reductive cleavage of methyl thioethers to give methane as models for methyl-coenzyme M-reductase, which requires as a cofactor F430, a Ni^{2+} complex of a hydrocorphine ligand [14]. A series of thioether functionalized macrocycles 8–10 were prepared and studied under reductive conditions [15]. In the presence of Na-amalgame, the Ni^{2+} complexes were rapidly reduced to Ni^+, as confirmed by EPR and VIS spectroscopy. In the case of the *ortho*-derivative 8 and of the aliphatic thioether 10 small amounts (about 5%) of methane were detected by gas chromatography as reaction product, whereas the corresponding *para*-derivatives 9 or the methoxy compound 11 did not produce any methane under similar conditions. Here again we think that the close proximity of the Ni^+ and the thioether group is of paramount importance for the formation of methane (Fig. 5).

4. Labeling Monoclonal Antibodies and Medical Applications

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 diagnostic or therapeutic purposes (Fig. 6) [16].

The design of new ligands which specifically bind the radionuclide with high thermodynamic and kinetic stability is of paramount importance in order to prevent
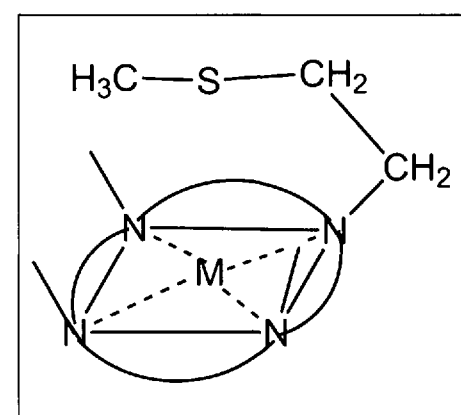

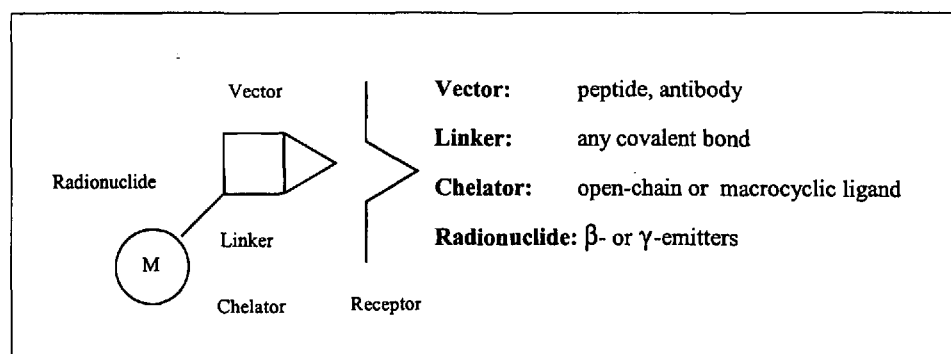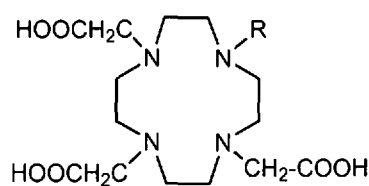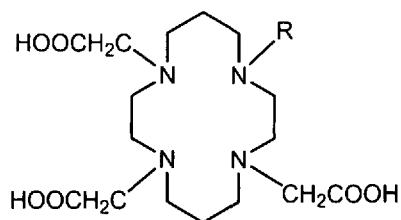Fig. 5. Example of a methyl thioether functionalized macrocyclic metal complex.

Fig. 6. Schematic representation of a vector molecule labeled with a covalently attached radionuclide.
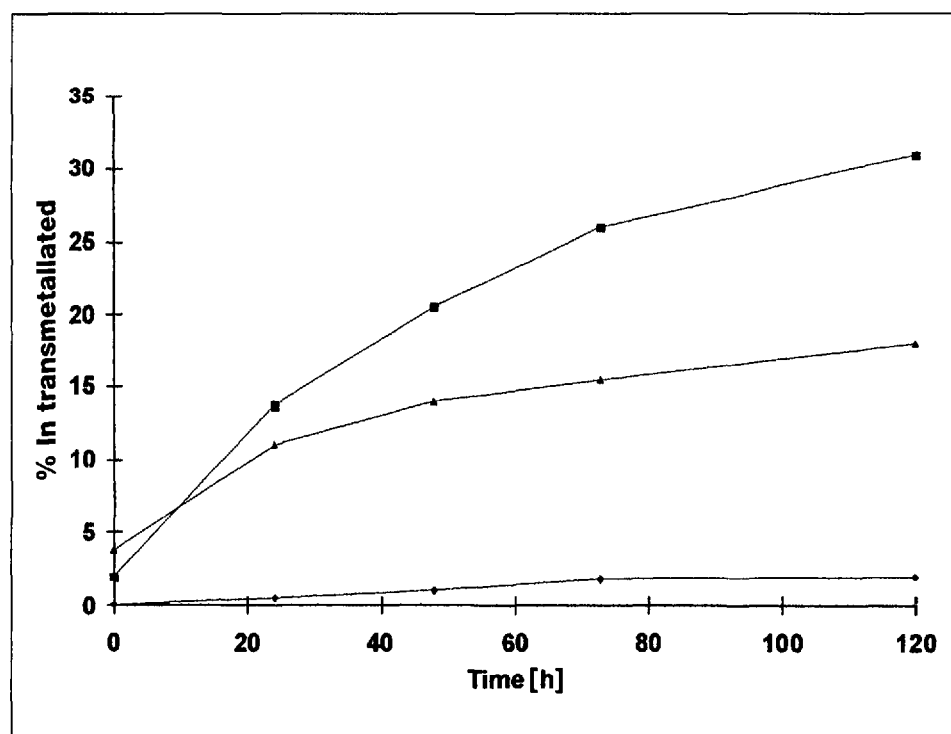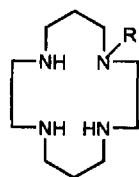

12

13

Fig. 7. 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$_6$H$_4$-NO$_2$) ▲ in blood serum.

|	
14a	R = (CH$_2$)$_n$-COOH
14b	R = o-CH$_2$-C$_6$H$_4$-COOH
14c	R = p-CH$_2$-C$_6$H$_4$-COOH

transmetallation under physiological conditions [17]. Of the different isotopes with ideal properties for a medical application we have focused our studies on $^{111}In^{3+}$, $^{90}Y^{3+}$, $^{64}Cu^{2+}$, and $^{111}Ag^+$.

It is well known that macrocyclic amino carboxylates such as **12** and **13** (R = H, or CH$_2$COOH) are ideal ligands for trivalent metal ions [18]. Both ligands **12** and **13** with R = H form very similar heptacoordinate In^{3+} species in which the four nitrogens and the three carboxylates are coordinated giving a capped trigonal prismatic geometry [9]. Bond lengths are somewhat shorter for the complex with **12** (R = H) compared with those of the complex with **13** (R = H) suggesting a somewhat better fit between ligand and In^{3+}. However, the blood serum stability of the complexes is completely different. The In^{3+} complex of **12** (R = H) very slowly exchanges the metal ion in blood serum, whereas those of **13** (R = H or CH$_2$-C$_6$H$_4$-NO$_2$) release the In^{3+} at a much higher rate and therefore cannot be used in nuclear medicine (Fig. 7).

A second example for medical applications is the development of a Cu^{2+}-specific ligand which can be covalently attached to an antibody. During our studies on tetraazamacrocycles functionalized with carboxylic side chains (**14a**) [19] we have observed that in the *ortho*-derivative **14b** the carboxylate axially binds to the Cu^{2+}, whereas in the *para*-derivative **14c** the carboxylic acid is not involved in coordination. Thus it can be reacted using standard coupling methods of peptide chemistry with an amino group of a substrate to give an amide bond as linker.

We have used **14c** to modify the monoclonal antibody b12 and then labeled it with $^{64}Cu^{2+}$ [20]. Animal experiments showed that the conjugated antibody selectively binds to the receptors of tumor cells with a very good blood/tumor ratio and thus allows the detection of the size and position of the tumor in the body with high precision.

$^{111}Ag^+$ is an especially interesting isotope, since it has γ- and β-radiation, both of which are ideal for nuclear medicine. Little has been done yet since Ag$^+$ being a very labile metal ion, ligands must be developed which form thermodynamically very stable and possibly also kinetically inert complexes. Studies on the encapsulation of Ag$^+$ with S$_6$-(**15**) [21] and N$_2$S$_2$-(**16**) [22] macrocycles have shown that these ligands, although forming rather stable complexes, are not able to prevent transmetallation in physiological fluids.
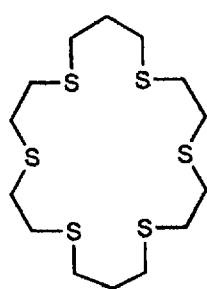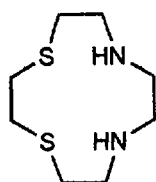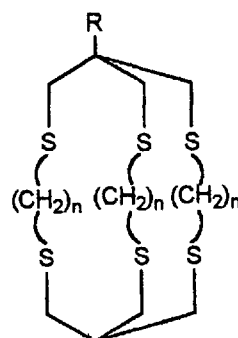
15 **16** **17**

We therefore have prepared a series of S_6-cages (**17**) with different bridging lengths between the thioether groups. The complexation of these ligands with Ag^+ gave complexes in which the Ag^+ ion is not incorporated into the cage, but sits outside [23]. These complexes proved also to be too weak for a medical application.

[1] See for example F. Vögtle, in 'Supramolekulare Chemie', Teubner Studienbücher, Stuttgart **1989**; B. Dietrich, P. Viout, J.-M. Lehn, in 'Macrocyclic Chemistry', VCH, Weinheim, **1993**.

[2] J.C.A. Boyens, S.M. Dobson, in 'Stereochemical and Stereophysical Behaviour of Macrocycles', Ed.: I. Bernal, Elsevier, Amsterdam, **1987**, p. 1.

[3] T.A. Kaden, *Topics Curr. Chemistry* **1984**, *121*, 157; T.A. Kaden, *Comments Inorg. Chem.* **1990**, *10*, 25.

[4] A. Schiegg, T.A. Kaden, *Helv. Chim. Acta* **1990**, *73*, 716; M. Studer, A. Riesen, T.A. Kaden, *Acta Cryst.* **1990**, *C46*, 741.

[5] D. Tschudin, A. Basak, T.A. Kaden, *Helv. Chim. Acta* **1988**, *71*, 100.

[6] I.M. Helps, D. Parker, J.R. Morphy, J. Chapman, *Tetrahedron* **1989**, 45, 219; A. Comparone, T.A. Kaden, *Helv. Chim. Acta* **1998**, *79*, 1765.

[7] P.L. Anelli, M. Murru, F. Uggeri, M. Virtuani, *J. Chem. Soc., Chem. Commun.* **1991**, 1317.

[8] A. Riesen, M. Zehnder, T.A. Kaden, *Helv. Chim. Acta* **1986**, *69*, 2067; A. Riesen, M. Zehnder, T.A. Kaden, *Acta Cryst.* **1988**, *C44*, 1740.

[9] A. Riesen, T.A. Kaden, W. Ritter, H.R. Mäcke, *J. Chem. Soc., Chem. Commun.* **1989**, 462.

[10] J.P. Dubost, J.M. Leger, M.H. Langlois, D. Meyer, M. Schaefer, *C. R. Acad. Sci. Paris*, **1991**, *312*, 349; S. Aime, A. Benetollo, F. Bombieri, G. Botta, F. Uggeri, *Inorg. Chem.* **1997**, *36*, 4287; A. Benetollo, F. Bombieri, S. Aime, G. Botta, *Acta Cryst.* **1999**, *C55*, 353.

[11] T. Lotz, T.A. Kaden, *J. Chem. Soc., Chem. Commun.* **1977**, 15; T. Lotz, T.A. Kaden, *Helv. Chim. Acta* **1978**, *61*, 1376.

[12] T.A. Kaden, *Pure Appl. Chem.* **1988**, *60*, 1117; D. Tschudin, T.A. Kaden, *Pure Appl. Chem.* **1988**, *60*, 489; D. Tschudin, A. Riesen, T.A. Kaden, *Helv. Chim. Acta* **1989**, *72*, 131.

[13] W. Schibler, T.A. Kaden, *J. Chem. Soc., Chem. Commun.* **1981**, 603; L. Siegfied, R. Kowallick, T.A. Kaden, *Supramolecular Chemistry*, in press.

[14] R.S. Wolfe, *Trends Biochem. Sci.* **1985**, *10*, 396.

[15] C. Schmid, C. Kempf, A. Taubert, M. Neuburger, M. Zehnder, T.A. Kaden, K. Bujno, R. Bilewicz, *Helv. Chim. Acta* **1996**, *79*, 1011; C. Schmid, M. Neuburger, M. Zehnder, T.A. Kaden, K. Bujno, R. Bilewicz, *Helv. Chim. Acta* **1997**, *80*, 241.

[16] A.J. Fischman, J.W. Babich, W. Strauss, *J. Nucl. Med.* **1993**, *34*, 2253.

[17] H. Maumela, R.D. Hancock, L. Carlton, J.H. Reibenspies, K.P. Wainwright, *J. Am. Chem. Soc.* **1995**, *117*, 6698; G. Ruser, W. Ritter, H.R. Mäcke, *Bioconj. Chem.* **1990**, 2, 345.

[18] V. Alexander, *Chem. Rev.* **1995**, *95*, 273; R.M. Izatt, K. Pawlak, J.S. Bradshaw, R.L. Bruening, *Chem. Rev.* **1995**, *95*, 2529; A.E. Martell, R.D. Hancock, R.J. Medicates, *Coord. Chem. Rev.* **1994**, *133*, 39.

[19] M. Studer, T.A. Kaden, *Helv. Chim. Acta*, **1986**, *69*, 2081.

[20] P.M. Smith-Jones, R. Fridrich, T.A. Kaden, I. Novak-Hofer, K. Siebold, D. Tschudin, H.R. Mäcke, *Bioconj. Chem.* **1991**, 2, 415.

[21] R. Alberto, W. Nef, A. Smith. T.A. Kaden, M. Neuburger, M. Zehnder, A. Frey, U. Abram, P.A. Schubiger, *Inorg. Chem.* **1996**, *35*, 3420.

[22] P.C. Riesen, T.A. Kaden, Helv. *Chim. Acta* **1995**, *78*, 1325.

[23] R. Alberto, D. Angst, U. Abram, K. Ortner, A.P. Schubiger, *Chem. Commun.* **1999**, 1513.