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Review

Group 4 metallocenes in bioorganometallic chemistry

Gerhard Erker *

Organisch-Chemisches Institut der Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

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Dedicated to Professor Stefano Maiorana.

Abstract

Group 4 metallocene complexes can form adducts or condensation products with a variety of typical biogenic molecules. In this account, examples are presented and discussed for the reactions of zirconocene or titanocene complexes with suitably protected/deprotected carbohydrate derivatives. Some methodological developments are shown for the attachment of aminoacid or peptide derived functional groups at the Cp-rings of the Group 4 bent metallocenes. Eventually, the reactions of methylzirconocene- and methyltitanocene cations with a series of short oligopeptides are discussed that lead to the formation of primary κO-adducts followed by O,N,O-chelate complex formation with methane evolution. The dynamic features of some such systems are discussed.

Keywords: Titanocene; Zirconocene; Carbohydrate complexes; Functionalized cyclopentadienides; Peptide complexes

Contents

1. Introduction

Titanocene dichloride and some of its derivatives have been found to have cancerostatic properties [1–3]. Potentially some such organometallic systems may have a potential to be developed into potent drugs for the treatment of cancer and other diseases [4]. In contrast to other metal containing compounds that are established in chemotherapy, such as, e.g. cisplatin [5], the mechanisms of biological action as well as the physiological targets of Cp_2TiCl_2 bioactivity have not been determined securely. Titanocene dichloride interactions with proteins (e.g. transporter proteins) have been found and studied [6] but their actual role (e.g. target or transporter) in the overall metallocene bioactivity needs to be established.

So we felt that there was a specific need to study and elucidate the structural nature of the titanocene peptide interaction – but beyond that there might be a desire to gain

* Fax: +49 251 83 36503.
E-mail address: erker@uni-muenster.de.

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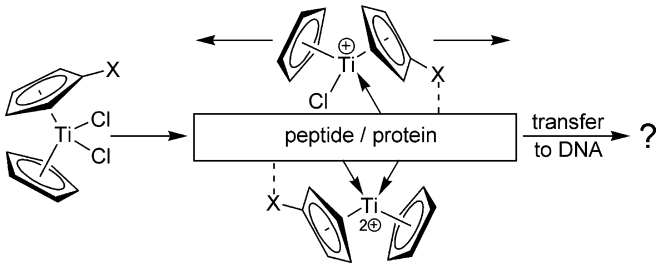
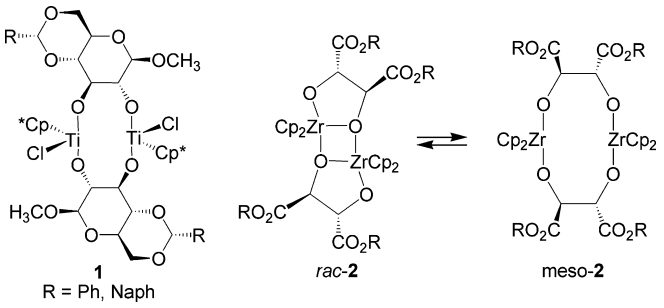


Scheme 1.



Scheme 2.

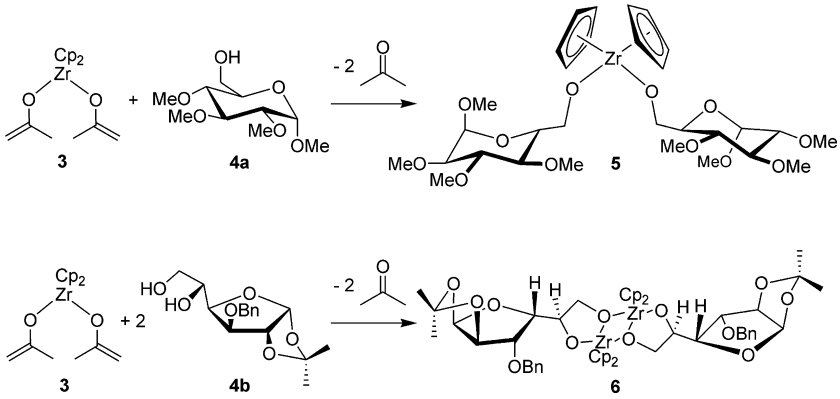
some advanced knowledge about the chemistry of the Group 4 bent metallocenes with biogenic molecules in general. Therefore, we set out to find ways to synthesize new metallocene complexes with compounds (or models thereof) that the rather sensitive $Cp_2M(IV)X_2$ species might encounter in biological systems and study their structural and chemical properties. In this account, we will describe some reactions of the Group 4 bent metallocenes with sugar derivatives. We will learn about methods to attach aminoacids and small peptides at the Cp-ligand framework of the bent metallocenes and eventually see how reactive zirconocene and titanocene derivaties might react with and chemically behave at the framework of model oligopeptide chains (see Scheme 1).

2. Carbohydrate metallocene complexes

A variety of carbohydrate metal complexes have been described in the literature especially of the middle to late transition metals of the periodic table [7]. Much less is known about such complexes of the Group 4 transition metals. Early work by Hafner, Togni et al. [8] has centered on the use of, e.g. $CpTi(X)(carbohydrate)_2$ complexes as stoichiometric chiral auxiliaries for e.g. asymmetric allylation processes. Recently, Heck et al. [9] have prepared a remotely related mono-Cp^*Ti carbohydrate complex (**1**) by treatment of a selectively protected glucose derivative and determined its dimetallic ten-membered ring core structure by X-ray diffraction (Scheme 2).

We had previously shown that structurally related zirconocene tartrate complexes (**2**) could easily be prepared. They exhibit a dynamic equilibrium situation between a monocyclic 10-membered dimetallacyclic structure (meso-**2**, closely related to **1**) and a doubly oxygen-bridged dimetalla-tricyclic isomeric situation (**2**/ent–**2**). Examples of both these general framework types were characterized by X-ray diffraction [10]. Therefore, it was tempting to search for related anellated structures in Group 4 metallocene carbohydrate chemistry.

Previous synthetic work in metallocene enolate chemistry had revealed that the use of zirconium enolate reagents for κO-ligand attachment was favourable [11]. Therefore, we have treated bis(propenolato)zirconocene (**3**) [12] with the singly deprotected glucose derivative **4a**. In a clean reaction, two equivalents of acetone were liberated and the zirconocene glucose derivative **5** was formed (Scheme 3). Complex **5** was characterized by X-ray diffraction (see Fig. 1) [13]. In a similar reaction, the doubly deprotected glucose derivative **4b** was treated with the enolato zirconium reagent **3** in a 1:1 molar ratio. Again, two molar equivalents of acetone were formed. We assume that a five-membered metallacyclic product was formed initially that rapidly dimerized to yield the observed and isolated dimetallic product **6**. The X-ray crystal structure analysis of **6** has revealed its dimetallatricyclic core structure (see Fig. 2) that was formed by a



Scheme 3.

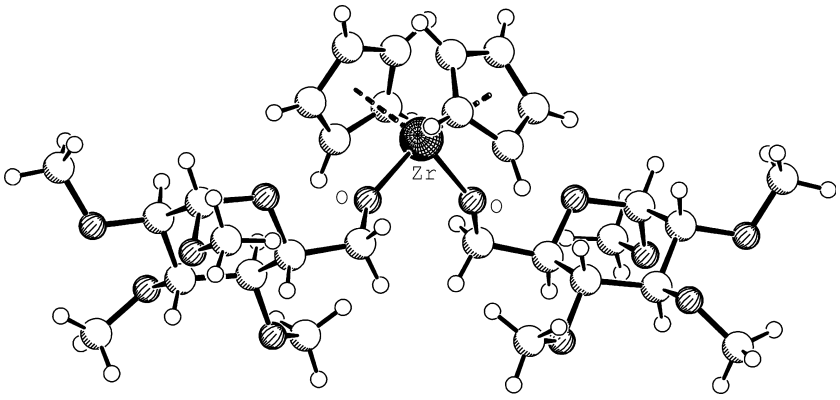


Fig. 1. A view of the molecular structure of complex **5**.

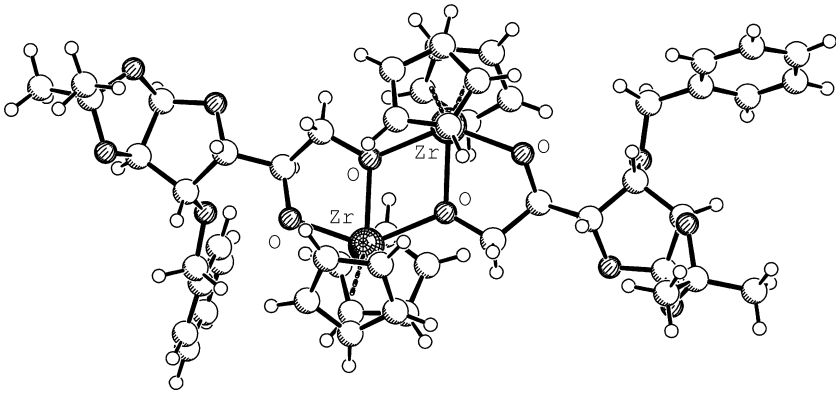
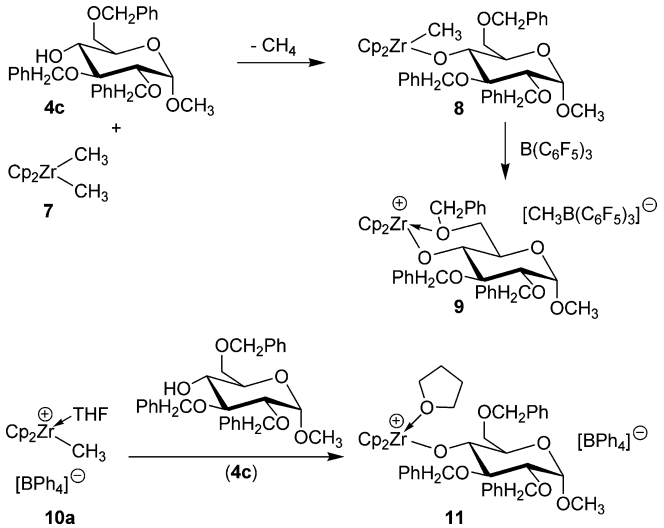
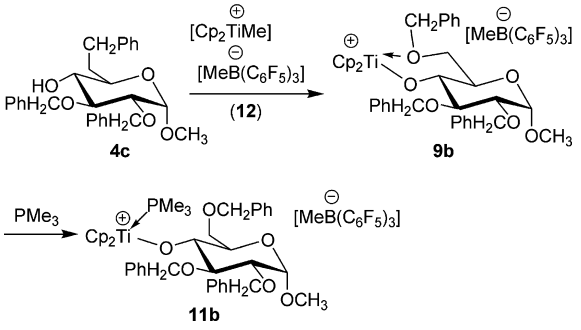


Fig. 2. A projection of the molecular structure of complex **6**.



Scheme 4.



Scheme 5.

lateral dimerization of the incipient five-membered metallacyclic building blocks [13].

Zirconocene dimethyl (**7**) can also react selectively with suitably deprotected carbohydrate derivatives, although the resulting complexes are rather sensitive. The singly deprotected "4-OH" glucopyranoside (**4c**) reacts with **7** with evolution of methane and formation of the sensitive product **8**. The remaining Zr-bound methyl substituent is readily removed by treatment with $B(C_6F_5)_3$. The resulting salt **9** was characterized by a detailed NMR analysis. It revealed that the respective cation probably features a six-membered chelate structure at zirconium which involved internal coordination of the C6-OCH_2Ph group. Consequently, complex **9** features diastereotypic Cp ligands at zirconium. The analogous reaction of **4c** with the THF stabilized methylzirconocene cation reagent (**10a**) leads to the formation of the related THF stabilized carbohydrate zirconocene cation complex **11** (with BPh_4^- anion) [14] (see Scheme 4).

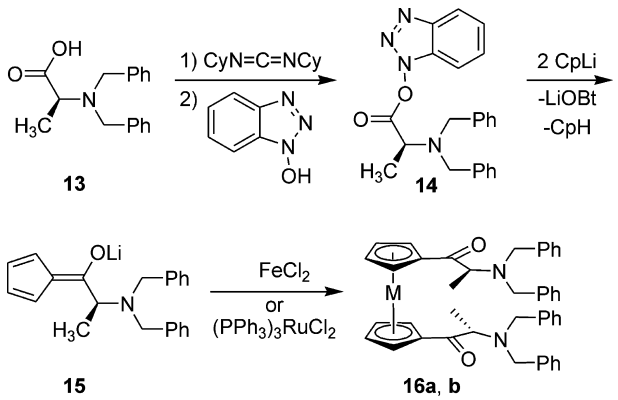
The corresponding cationic titanocene complexes are more stable. Several such systems could be isolated analytically pure. However, the titanocene reagents used for their preparation are less reactive. Thus, titanocene dimethyl did not react with **4c** under our typical reaction conditions. It had to be activated, e.g. by treatment with $B(C_6F_5)_3$ to yield $[(Cp_2TiCH_3)^+ (CH_3B(C_6F_5)_3)^-]$ (**12**), which then reacted with **4c** to yield the chelate system **4b**. Subsequent treatment with PMe_3 resulted in the formation of the corresponding adduct **11b** (Scheme 5) [14].

3. Aminoacid and peptide functionalized Cp-ligands

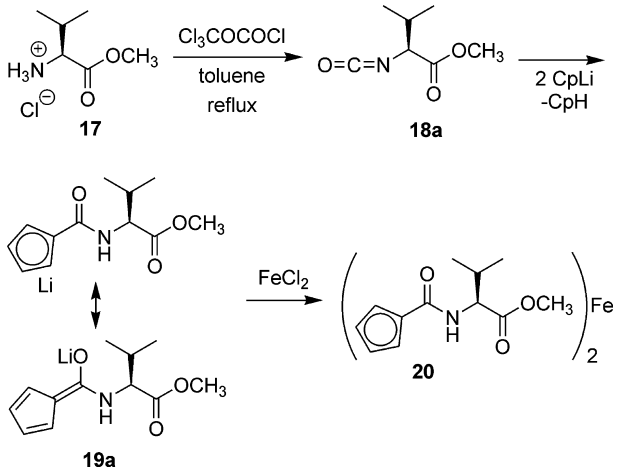
Carrying out organic functional group chemistry at the frameworks of the sensitive Group 4 bent metallocenes is difficult. Quite different from e.g. ferrocene chemistry [15] attachment and conversion of functional groups at e.g. the intact zirconocene unit has only recently been achieved for selected examples [16]. This general problem in the organometallic chemistry of the early metal bent metallocenes was earlier mostly solved by the attachment of the respective functional groups at the ligand stage prior to the final transmetallation step. We have developed a variety of such methods for the introduction of aminoacid, peptide and related functional groups at the bent metallocene frameworks.

One such development has used and adapted standard methodology from peptide synthesis [17]. Bisbenzyl protected L-alanin **13** was activated by subsequent treatment first with dicyclohexylcarbodiimide followed by hydroxybenztriazole. The activated alanine derivative (**14**) was then nucleophilically attacked by lithium cyclopentadienide. Excess LiCp is necessary because of the rapid subsequent deprotonation to yield the acyl-functionalized cyclopentadienyl anion reagent **15** (which in Scheme 6 is drawn in a preferred fulvenoid resonance form according to the X-ray crystal structure analysis) [18]. The reagent **15** was transmetallated to iron and ruthenium to yield aminoacid functionalized metallocenes.

Another route utilized the strongly electrophilic character of the isocyanate function [19–21]. As a typical example,



Scheme 6.



Scheme 7.

L-valin methylester (**17**) was converted to the isocyanate **18a** by treatment with the (very toxic) "phosgene dimer". Subsequent treatment with LiCp resulted in addition followed by deprotonation to yield the valinester substituted cyclopentadienide reagent **19a** (see Scheme 7). This was employed in transmetallation to iron to eventually yield the valin-functionalized ferrocene derivate **20** (see Scheme 7 and Fig. 3) [22].

The isocyanate method was also used for the preparation of carboxamide substituted titanocene complexes. The reaction of sodium cyclopentadienide with adamantylisocyanate (**18b**) is a typical example. The resulting product (**19b**) of the addition/deprotonation sequence was reacted with $CpTiCl_3$ to yield the corresponding functionalized titanocene complex **21** (Scheme 8). Complex **21** was characterized by X-ray diffraction (Fig. 4) [22].

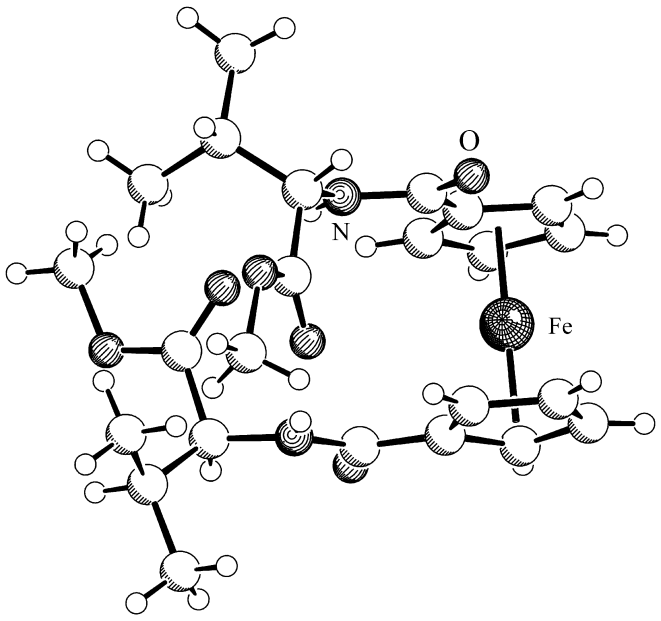
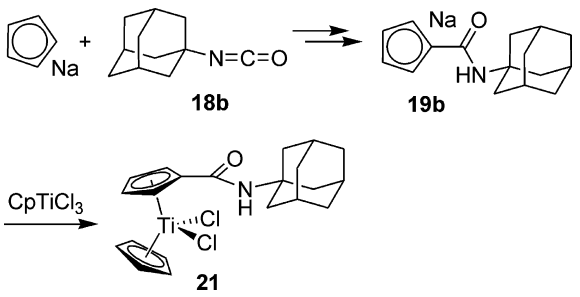


Fig. 3. A view of the molecular structure of the valin-functionalized ferrocene derivative **20**.



Scheme 8.

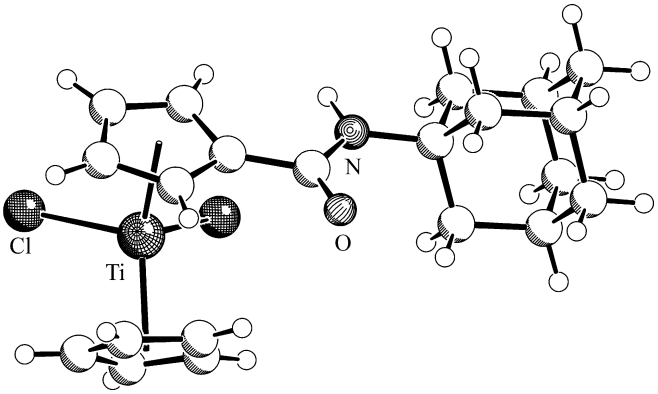


Fig. 4. Molecular structure of **21**.

In order to learn about the possible interaction of a carboxamido group (similar as it is found in a peptide), we have connected a $-CONR_2$ functionality to a Cp ring by a saturated hydrocarbon spacer. The synthesis was carried out by the fulvene route [23]. The ketone **22** was selectively converted to the fulvene **23** by treatment with cyclopentadiene and pyrrolidine by means of the "Stone/Little procedure" [24]. The functionalized fulvene (**23**) was then treated with a soft nucleophilic methylating agent. This leads to formal CH_3 anion addition at the electrophilic fulvene C6 carbon atom. Hydrolytic workup followed by deprotonation (LDA) yielded the functionalized cyclopentadienide reagents **24** ($-NMe_2$, $-NEt_2$ or $-N(CH_2)_4$ was used). Transmetallation to zirconium or titanium was effected by the reaction with $CpMCl_3$ (M = Ti, Zr) to yield **25**. In the products **25**, we have not found any evidence for

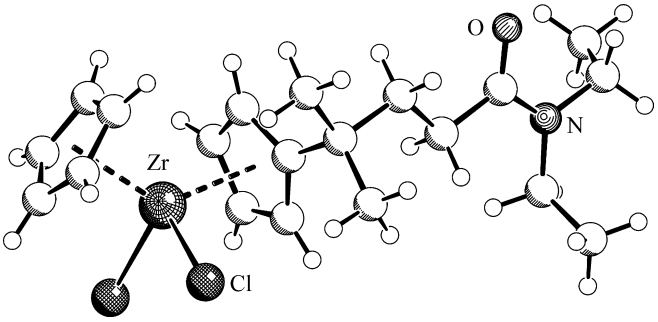


Fig. 5. A view of the molecular geometry of complex **25a**.

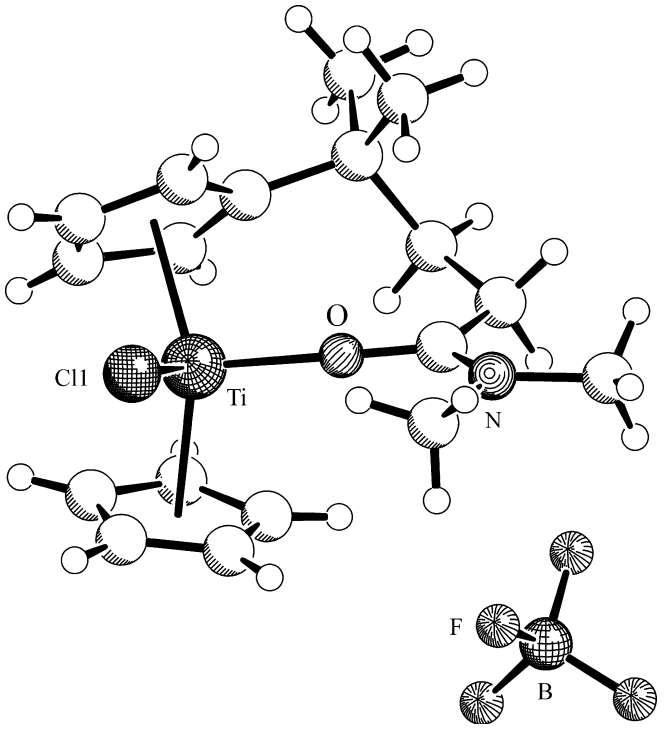
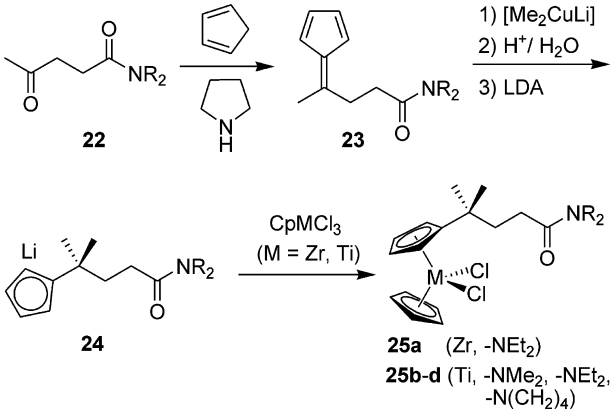


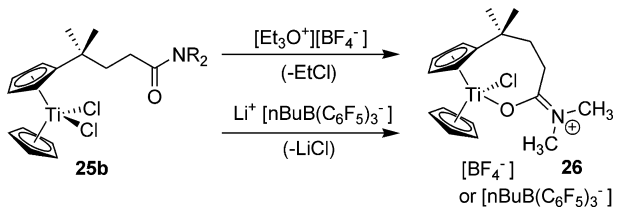
Fig. 6. A view of the molecular geometry of **26** (with BF_4^- anion).

a direct interaction of the weakly electrophilic metal centers with the pendant $-CONR_2$ functionalities. This is illustrated in Fig. 5 by the results of the X-ray crystal structure analysis of the complex **25a** (M = Zr, $-NEt_2$) [25].

The situation is changed when the metal center becomes more electrophilic. This was demonstrated by the reaction of the titanium derivate **25b** with $Li^+[n\text{BuB}(C_6F_5)_3^-]$ or with Meerwein's reagent [25]. Both resulted in the abstraction of chloride ion from titanium. The resulting titanocene cation complex (**26**) features a strong interaction between the metal center and the carbonyl oxygen atom of the pendant carboxamide functional group (see Fig. 6), similar as it has been found in titanocene cation peptide complexes (see below) (Schemes 9 and 10).



Scheme 9.

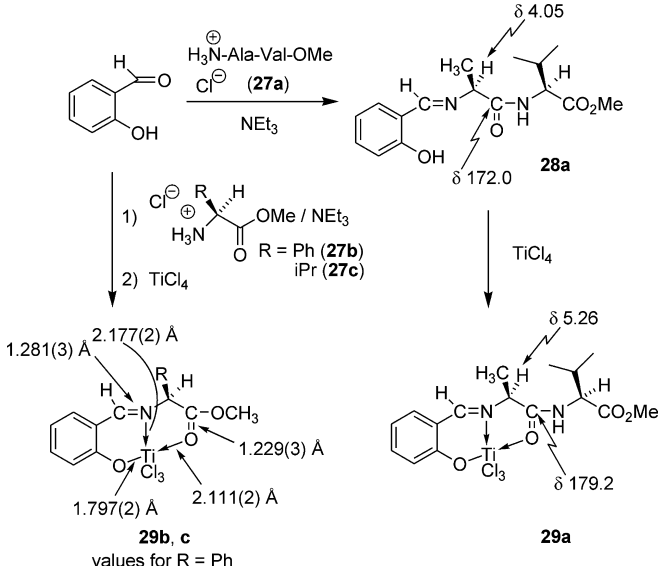


Scheme 10.

4. Peptide metallocene complexes

As we will see below, peptide derivatives have a pronounced tendency to form formally monoanionic ligands in tridentate *O*,*N*,*O*-chelate Group 4 metal complex systems. We shall first describe a closely related system and discuss its typical structural features, namely the (Ala-Val-OMe-salicylaldiminato)$TiCl_3$ complex **29a** [26]. The corresponding ligand system (**28a**) was prepared by a condensation reaction between salicylaldehyde and alanylvalinethylester hydrochloride (**27a**). Its reaction with $TiCl_4$ gave the *O*,*N*,*O*-chelate complex **29a**. Complex formation resulted in a very characteristic shifting of the Ala-carboxamide C═O ^{13}C NMR resonance by ca. $\Delta\delta = 7$ ppm to a larger δ-value (see Scheme 11). This typical feature is observed for a large variety of related complexes (see below). The closely related phenylglycinester derived chelate complex **29b** was characterized by X-ray diffraction (see Fig. 7). It features a short (phenolate)O–Ti bond and a much longer Ti—O═C (carboxamide) interaction.

We have used the reactivity of aminoacid and peptide derived isocyanates toward nucleophilic organometallic reagents again in this project. This time the valinester iso-



Scheme 11.

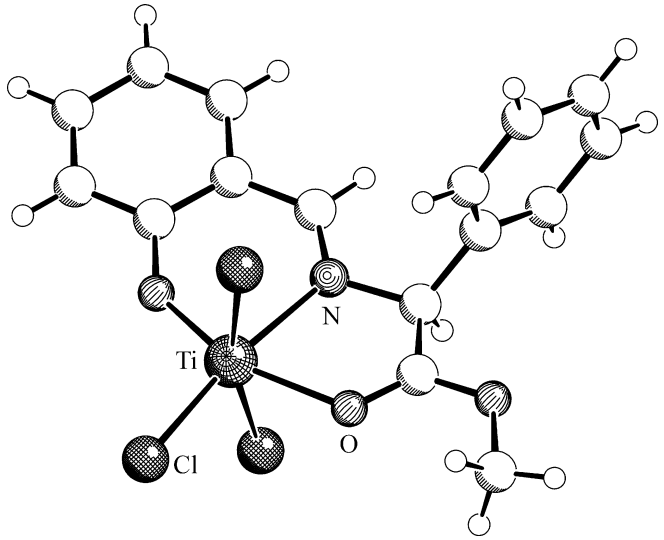


Fig. 7. Molecular structure of the *O*,*N*,*O*-chelate complex **29b**.

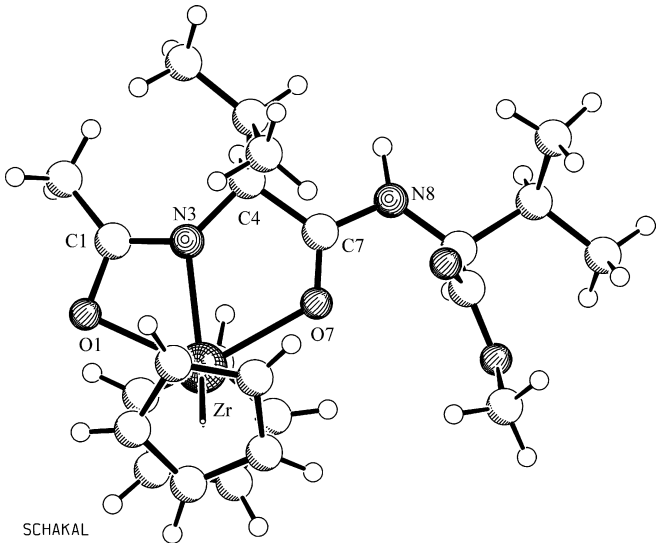
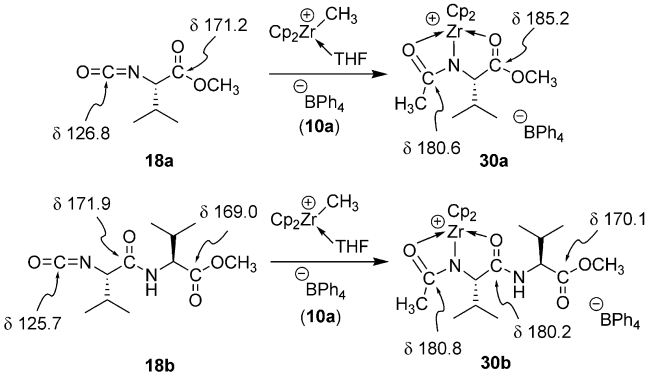
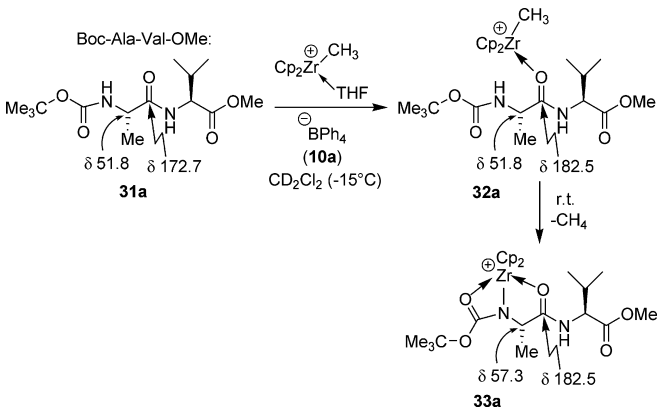


Fig. 8. A view of the molecular geometry of complex **30b**. Selected bond lengths (Å) and angles (°): Zr–O1 2.185(12), Zr–N3 2.167(12), Zr–O7 2.251(11), C1–O1 1.35(2), C1–N3 1.32(2), N3–C4 1.48(2), C4–C7 1.53(2), C7–O7 1.22(2), C7–N8 1.33(2), Zr–O1–C1 94.4(10), Zr–N3–C1 96.3(10), Zr–O7–C7 122.2(11), O1–Zr–O7 125.9(5).



Scheme 12.



Scheme 13.

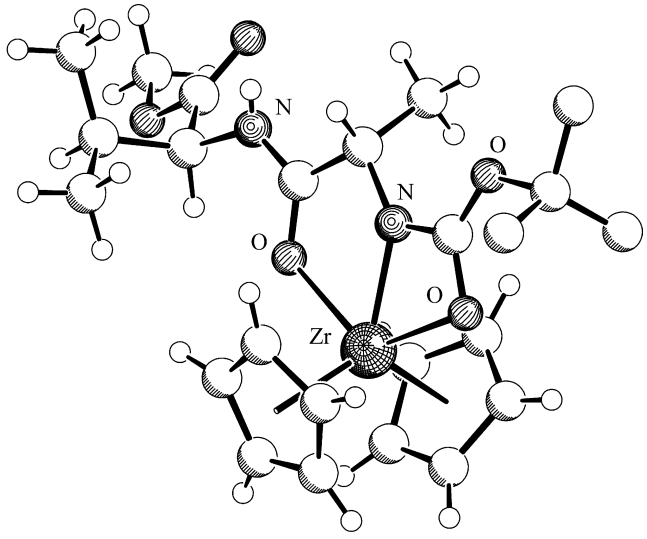
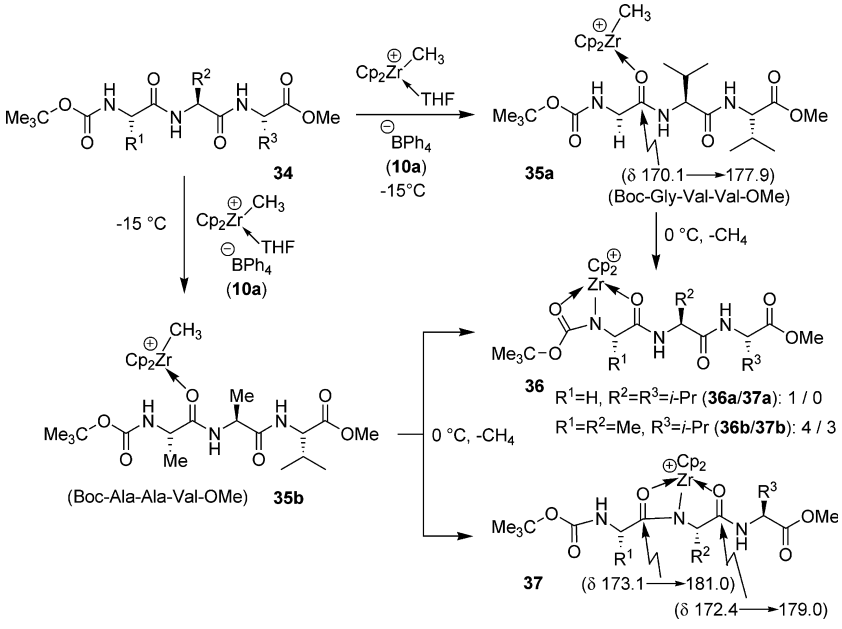


Fig. 9. A view of the molecular structure of complex **33a** (only the cation is depicted).

cyanate (**18a**) was reacted with the THF-stabilized methylzirconocene cation (**10a**) [27]. In this reaction, formally a methyl anion moiety is transferred from the metal center to the isocyanate sp-carbon. This results in the formation of a metallated *N*-acyl valinester derivative (**30a**). The detailed NMR analysis [28] indicated the formation of a typical *O*,*N*,*O*-chelate product. The analogous reaction took place upon treatment of valinylvalinester isocyanate (**18b**) with "Jordan's cation" (**10a**) [27]. The NMR analysis of the isolated organometallic product indicated the formation of the typical *O*,*N*,*O*-peptide-metallocene cation chelate complex (**30b**) at the N-terminus of the peptide chain. In this case single crystals could be obtained; the X-ray crystal structure analysis confirmed the characteristic structural composition of the product **30b** (see Fig. 8 and Scheme 12) [27].

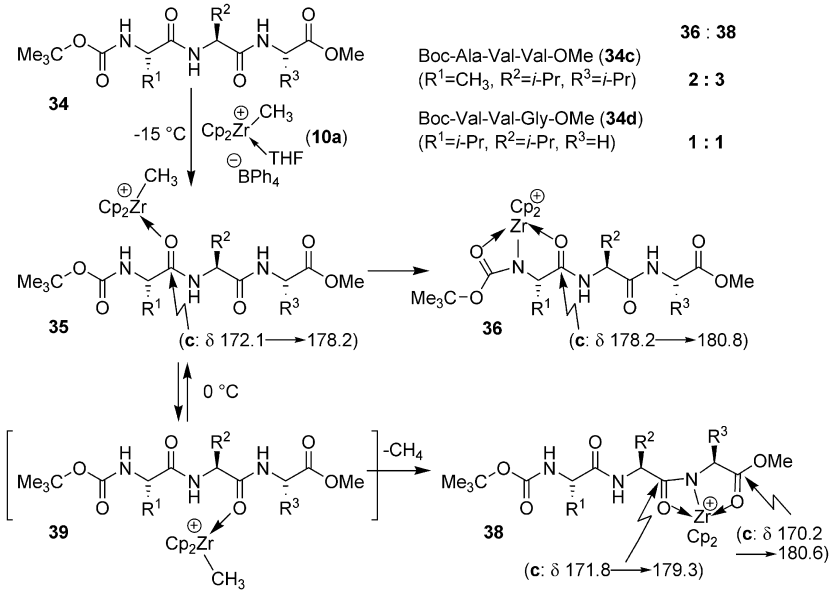
We have reacted a variety of di- and tripeptide derivatives with $[Cp_2ZrCH_3(THF)^+][BPh_4^-]$ (**10a**) [29]. As a typical example the reaction of **10a** with Boc-Ala-Val-OMe (**31a**) in d_2-dichloromethane at −15 °C gave the adduct (**32a**) that was characterized by a detailed NMR analysis. It revealed that the reactive $[Cp_2ZrCH_3^+]$ moiety was added to the central Ala-carbonyl oxygen atom. This had become evident by a pronounced "low field shift" of the corresponding ^{13}C NMR carbonyl carbon resonance from δ 172.7 in the free peptide **31a** to δ 182.5 in the $[Cp_2ZrCH_3^+]$-carbonyl adduct **32a** (see Scheme 13). The adduct **32a** is rather unstable and can only be observed at low temperature. Warming the sample to room temperature rapidly led to the evolution of methane with formation of the *O*,*N*,*O*-chelate complex **33a**. Complex **33a** was isolated and characterized by X-ray diffraction. The *O*,*N*,*O*-chelate was formed at the N-terminal site of the peptide chain with inclusion of the carbonyl group of the (Boc)-protecting group (see Fig. 9).



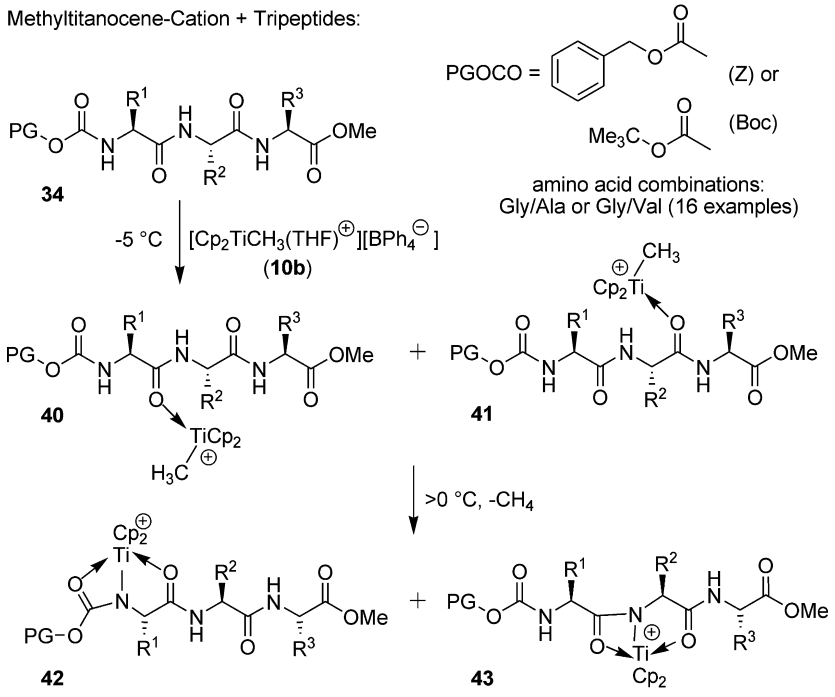
Scheme 14.

The reaction of $[Cp_2ZrCH_3^+]$ with tripeptide derivatives is more complicated but offers additional interesting information. In all the cases that we have studied so far the alkyl metallocene cation initially becomes coordinated to the internal carbonyl group of the N-terminal amino acid. Thus, treatment of the tripeptide Boc-Gly-Val-Val-OMe (**34a**) with $[Cp_2ZrCH_3(THF)^+][BPh_4^-]$ (**10a**) in CD_2Cl_2 at −15° led to the formation of the adduct **35a**. This transformation is accompanied by a very characteristic shifting of the corresponding Gly ^{13}C NMR carbonyl resonance from δ 170.1 (free peptide **34a**) to δ 177.9 κO-adduct (**35a**) [29]. At ca. 0 °C, methane evolution was observed and the formation of a single *O*,*N*,*O*-chelate complex **36a** took place. This product features the typical tridentate chelate structure at the N-terminus of the chain formed with inclusion of the Boc-carbonyl group (see Scheme 14).

The tripeptide derivative Boc-Ala-Ala-Val-OMe also forms the initial $[Cp_2ZrCH_3^+]$ adduct at the terminal



Scheme 15.



Scheme 16.

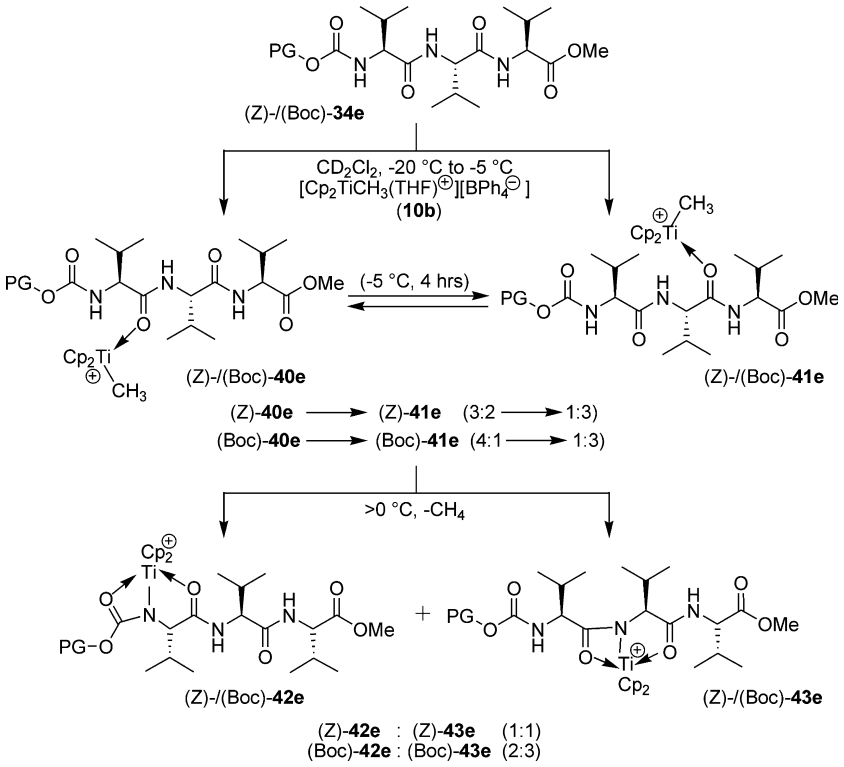
Table 1
Ratio of the primary κO-coordination products (**40/41**) and secondary *O*,*N*,*O*-chelate products (**42/43**) obtained in the reaction of $[Cp_2TiCH_3(THF)^+][BPh_4^-]$ (**10b**) with a series of (*Z*)- and (Boc)-protected tripeptide methyl esters (**34**)

Peptide	40/41	42/43
Alanine series		
Z-Gly-Ala-Ala-OMe	2:1	–:1
Boc-Gly-Ala-Ala-OMe	3:1	1:2
Z-Ala-Gly-Ala-OMe	–:1	1:2
Boc-Ala-Gly-Ala-OMe	–:1	1:2
Z-Ala-Ala-Gly-OMe	–:1	–:1
Boc-Ala-Ala-Gly-OMe	–:1	1:2
Z-Ala-Ala-Ala-OMe	–:1	–:1
Boc-Ala-Ala-Ala-OMe	–:1	3:2
Valine series		
Z-Gly-Val-Val-OMe	1:–	1:–
Boc-Gly-Val-Val-OMe	1:1	1:–
Z-Val-Gly-Val-OMe	–:1	–:1
Boc-Val-Gly-Val-OMe	–:1	–:1
Z-Val-Val-Gly-OMe	–:1	2:3
Boc-Val-Val-Gly-OMe	–:1	2:3
Z-Val-Val-Val-OMe	3:2	1:1
Boc-Val-Val-Val-OMe	4:1	2:3

Ala-carbonyl group upon treatment with **10a** under kinetic control at −15 °C. Warming to >0 °C in this case, however, resulted in the formation of a pair of isomeric *O*,*N*,*O*-chelate products (**36b**, **37b**) in a 4:3 ratio. In addition to the terminal *O*,*N*,*O*-chelate (**36b**) formation of a central *O*,*N*,*O*-chelate product (**37b**) is also observed [29] in this case.

An additional product type was observed upon treatment of **10a** with Boc-Ala-Val-Val-OMe (**34c**) or Boc-Val-Val-Gly-OMe (**34d**). In both cases, the initially formed product at −15 °C is the respective κO-adduct (**35c**, **35d**). Warming of the samples again resulted in methane formation by peptide NH deprotonation. In these cases mixtures of two *O*,*N*,*O*-chelate products were obtained, namely the N-terminal *O*,*N*,*O*-chelates **36c** and **36d**, respectively, that were accompanied by the products **38c** and **38d**, where the *O*,*N*,*O*-chelate was found at the O-terminus, here being formed with the inclusion of the ester carbonyl group (see Scheme 15) [29]. This observation may potentially indicate migration of the $[Cp_2Zr\text{-}CH_3^+]$ unit along the peptide chain (e.g. via the isomeric κO-adducts **39**) before it eventually reacts with a NH functionality to cleave off methane with formation of the respective *O*,*N*,*O*-chelate moiety.

We have extended this study to the tripeptide-methyltitanocene cation adduct chemistry. A series of both (*Z*)- and (Boc)-protected tripeptide methylesters derived from systematic variations of glycine, alanine and valine amino acid building blocks totaling 16 individual examples was treated with $[Cp_2TiCH_3(THF)^+][BPh_4^-]$ (**10b**). At − 5°C the reaction in d_2-dichloromethane in most cases gave mixtures of the κO-coordination compounds **40** (coordination at the carbonyl group of the N-terminal aminoacid residue) and **41** (κO-coordination at the carbonyl group of the central amino acid building block) [30] (see Scheme 16 and Table 1). Methane evolution was observed in all these cases upon warming to temperatures ⩾0 °C and the corresponding *O*,*N*,*O*-chelate complexes **42** (involving the N-terminal aminoacid plus the carbonyl function of the protecting



Scheme 17.

group) and **43** (using *N*,*O* of the central aminoacid plus the carbonyl oxygen of the adjacent N-terminal aminoacid) were formed. It is evident from Table 1 that the observed ratio of the primary κO-coordination products **40/41** and secondary *O*,*N*,*O*-chelate products **42/43** are quite different in many of the cases studied.

This behaviour indicates mobility of the methyltitanocene cation at the peptide chain. This interesting conclusion was further supported by some specific observation made when the *Z*- or Boc-Val-Val-Val-OMe peptides (*Z*)-**34c** and (Boc)-**34e** were treated with $[Cp_2TiCH_3(THF)^+]$-$[BPh_4^-]$ (**10b**). Upon warming the reaction mixture (in d_2-dichloromethane) from −20 °C to −5 °C the adduct formation set in and resulted in the observation of an initial ratio of the κO-coordination complexes (*Z*)-**40e**/(*Z*)-**41e** of 3:2. Keeping this mixture for 4h at −5 °C resulted in a gradual change of this ratio to eventually arrive at a 1:3 value. Similary, the (Boc)-protected system gave an initial ratio of κO-coordination products of (Boc)-**40e**/(Boc)-**41e** of 4:1 that after 4 h at −5 °C had changed to 1:3 (see Scheme 17). Warming to $\geqslant$0 °C then resulted in methane evolution and formation of the corresponding *O*,*N*,*O*-chelate products. Again, they were formed in ratios that were unrelated to the ratios of their respective κO-coordination product precursors (see Scheme 17) [31].

5. Conclusions

Our work has shown that the Group 4 bent metallocene complexes can sometimes be quite compatible with typical bioorganic molecules. Even some rather sensitive zirconocene or titanocene cations can be bonded to e.g. carbohydrate derivatives if some specific structural (i.e. protective groups) and technical situations (i.e. suitable reaction pathways and conditions) are met. The very sensitive $[Cp_2MCH_3^+]$ cations (M = Ti, Zr) even seem to be stable toward the backbone functionalities of some peptides under sufficiently mild conditions and even their secondary *O*,*N*,*O*-chelate products derived from the primary κO-adducts by methane formation may show some interesting dynamic features. We are, of course, aware that $Cp_2M(IV)$ complexes with simple biomolecules, such as the examples described in this account are still quite far away from related bioorganometallic systems found in in vivo situations with regard to chemical reactivities and kinetic behaviour – but such studies and examples might point out some of the major structural types that might be encountered under biological conditions. We will see whether a further development of such model approaches using more realistic functional bioorganic/organometallic combinations is feasable and useful to gain some increased understanding of the function of specific active organometallic compounds in biosystems.

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