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Oxa-Michael reaction of metallocarbonyl complexes bearing the maleimidato ligand. Reactivity studies with selected hydroxy compounds

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ABSTRACT

Metallocarbonyl complexes display specific and intense absorption bands in the mid-IR spectral range due to the stretching vibrations of carbonyl ligands, which makes them useful labels for biocompounds. In the course of searching for new labelling methods for biomolecules, we attempted *O*-alkylation of various hydroxyl compounds. Methanol, selected glycols and carbohydrates as well as model nucleoside were subjected to a reaction with metallocarbonyl complexes bearing the maleimidato ligand. In all cases, and using spectroscopic methods, we confirmed the formation of products with the addition of the hydroxyl group to the ethylenic bond of the maleimidato ligand. The ruthenium complex obtained in the reaction with methanol was also characterized by X-ray diffraction.

1. Introduction

Hetero-Michael addition reactions such as aza-Michael, sulfa-Michael, phospha-Michael and oxa-Michael are effective for the formation of carbon-hetero-atom bonds and have widely been used in inter- and intra-molecular reactions in order to obtain various products [1]. Among these, the oxa-Michael addition attracted less attention due to the poor nucleophilicity of the Michael donors that were employed. Although this process still remains a challenge, recent developments have shown that efficient catalysts and suitable acceptors could greatly expand application of the oxa-Michael reaction in natural products synthesis [2]. Reported methods for Michael addition of alcohols to activated olefins and alkynes mostly use bases such as amines (DBU, DIPEA, TEA, etc.) [3–5], K_2CO_3 [6], and transition metal complexes as catalysts.

Maleimide derivatives are useful Michael acceptors which react with different heteronucleophiles, but the reaction goes easily only with thiols and without any catalyst in mild conditions. Therefore, *N*-substituted maleimides are mostly known as reagents for selective alkylation of thiols and are widely applied for biomolecular modification [7]. Although reactions of maleimide derivatives with hydroxyl groups have seldom been reported [6], we find this process useful for carbohydrate and nucleoside modifications by metallocarbonyl complexes that bear the maleimidato ligand.

Functionalization of sugars by metal complexes leads to hybrid molecules with combined properties of saccharides and metal complexes. The carbohydrate substituents influence biocompatibility of the organometallic complexes as well as their activity and targeting properties. Sugar-substituted metal complexes offer great possibilities for the discovery of better targeted drugs and new molecules with suitable spectroscopic or electrochemical markers that may be useful in biomedical diagnostics [8]. Metallocarbonyl complexes linked to saccharides may also be applied as IR labels, which could offer better insight into the processing of sugars and their derivatives in biological systems. The labelling of carbohydrates should enable highly sensitive detection in order to reduce the amounts of samples that are required for the investigations. Different labelling approaches are being developed to meet these expectations.

Considerable attention has recently been focused on the binding of metal ions and metal complexes to purines, pyrimodines, nucleosides, nucleotides and nucleic acids. The reasons for these investigations are manifold. Nucleosides, nucleotides and oligonucleotides

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that are site-specifically modified with metal complexes are of interest for analytical applications (hybridization complex) [9], therapeutic uses (anticancer agents, radiopharmaceuticals) [10,11], as novel materials for the assembly of nanostructures [12], and as new biomaterials [13]. Metal-containing nucleosides have predominantly been produced by the synthesis of nucleoside-chelator conjugates followed by metal complexation [14], or by coupling the nucleoside moiety with metal complexes [13].

Metallocarbonyl complex (η^5-C_5H_5)Fe(CO)$_2$(η^1-*N*-Maleimidato) **1** (Fig. 1) can easily be attached to other molecules thanks to the presence of maleimide ligands which undergo the Michael addition with heteroatomic nucleophiles containing sulfur, nitrogen and phosphorus. We have already reported that the ethylenic bond of the maleimidato ligand in complexes (η^5-C_5H_5)M(CO)$_n$ (η^1-*N*-Maleimidato) (M = Fe, W, Mo; n = 2, 3) **1**–**4** easily reacts with thiols in neutral conditions [15–17], and complex **1** reacts with amino groups [18] and phosphites [19] at pH 9–10. All of these reactions enable the introduction of metallocarbonyl labels to the biomolecules. The obtained bioconjugates are easy to detect with the use of IR spectroscopy due to the presence of strong absorption bands in the 1800–2150 cm^{-1} (ν CO) spectral range, which is free of any biomolecule absorption [20,21].

Recently, we have observed that metallocarbonyl maleimide complexes may undergo the oxa-Michael reaction with compounds bearing hydroxyl groups. Here, we report the oxa-Michael addition of methanol to the maleimide double bond of (η^5-C_5H_5)M(CO)$_n$(η^1-*N*-maleimidato) (M = Fe, Ru, W, Mo; n = 2,3) complexes **1**–**4** (Fig. 1) and we discuss the kinetic studies of this reaction. The X-ray structural study of the oxa-Michael addition product of the ruthenium complex is presented and discussed. We also report the oxa-Michael reaction of iron complex **1** with selected glycols and we present the preliminary studies of the reaction of iron complex **1** and ruthenium complex **2** with selected carbohydrates and of complex **1** with nucleoside. The formation of oxa-Michael products was confirmed by liquid chromatography coupled to high resolution mass spectrometry (LC/HRMS).

2. Results and discussion

It is well known that the oxygen atom of hydroxyl group has weak nucleophilicity due to the high electronegativity of oxygen and its low polarizability. The Michael addition of various hydroxyl compounds to activated alkenes seems to be a difficult task to achieve. In all cases, the use of catalysts such as trialkylphosphine or tertiary amine is necessary in order to obtain hydroalkoxylation products [22]. The reaction of *N*-substituted maleimide derivatives with alcohols was previously studied. In 2003, Mhaske and Agrade reported that *N*-aryl maleimides react with alcohols in the presence of K_2CO_3 [6]. However, alkoxysuccinimides were formed in this reaction which underwent alcoholysis, thus producing alkoxy succinanilates. In 2010, we applied the oxa-Michael reaction to synthesize the alkyne metallocarbonyl succinimide derivative for a 'click chemistry' reaction [23]. Here we present extended studies on the oxa-Michael reaction of metallocarbonyl complexes **1**–**4** with various compounds containing hydroxyl groups.

2.1. Synthesis of complexes 1–4

Half-sandwich complexes (η^5-cyclopentadienyl)M(CO)$_n$(η^1-*N*-maleimidato) (M = Fe, Ru, Mo; n = 2,3) **1**, **2** and **4** bearing the maleimide moiety were obtained by photochemical reaction of (η^5-cyclopentadienyl)M(CO)$_n$I (M = Fe, Ru, Mo; n = 2,3) with maleimide [15–17]. Metallocarbonyl tungsten complex **3** was obtained in the reaction of (η^5-cyclopentadienyl)W(CO)$_3$I with the thallium salt of maleimide [16].

2.2. Reactions of complexes 1–4 with methanol

The reaction of metallocarbonyl complexes **1**–**4** was carried out under mild conditions using methanol both as a substrate and solvent. We found that complexes **1**–**4** react at room temperature with methanol in the presence of K_2CO_3, forming oxa-Michael products **5a–d** (Scheme 1) with good yields (64–74%). The obtained compounds **5a–c** were characterized by spectroscopic methods. The ^{1}H NMR spectra of these compounds did not show ethylenic proton signals that are characteristic of **1**–**4**, but instead complex patterns assigned to the CH–CH$_2$ of the succinimide part as well as the methyl group signal in the 2.9–4.2 ppm range. The obtained products **5a–c** were also characterized by elemental analysis, and for **5d** by LC/HRMS. The formation of a succinimide product was confirmed for ruthenium compound **5b** by X-ray crystallography.

In order to compare the resulting compounds of the Oxa-Michael addition **5a–c** with the metallocarbonyl maleimide substrates **1**–**3** we gathered the IR and ^{1}H NMR spectral data in Table 1. The IR spectra of products **5a–c** exhibited two strong ν(C≡O) bands characteristic of the CpM(CO)$_n$ moiety, which were only slightly shifted toward higher wavenumbers in comparison to those of the maleimide precursors **1**–**3**. The ^{1}H NMR spectra of products **5a–c** show singlet at ca. 5–5.5 ppm assigned to the Cp ring, which are slightly moved upfield in comparison to peaks of substrates **1**–**3**.

Comparing the crystal structure of ruthenium compounds **2** and **5b** we also do not observe any significant changes concerning molecular three dimensional structure around the metal atoms. The detailed comparison of molecular geometrical parameters is presented in the Table 2. One can see there is a slight change of Ru-N distance upon addition to double C=C bond (about 0.02 Å). However, the observed differences are not meaningful within statistical 3σ criterion. The simple structural comparison of ruthenium complexes **2** and **5b** is presented in Fig. 2.

All these results show that upon the discussed reaction of oxa-Michael addition to metallocarbonyl maleimide complexes there can be obtained compounds of almost similar structure around metal atom.

2.3. Kinetic measurements

In order to gain further insight into the reaction mechanism between metallocarbonyl complexes **1**–**3** and methanol (Scheme 1), a kinetic study of the reactions was undertaken using the ^{1}H NMR technique. The reactions were carried out directly in

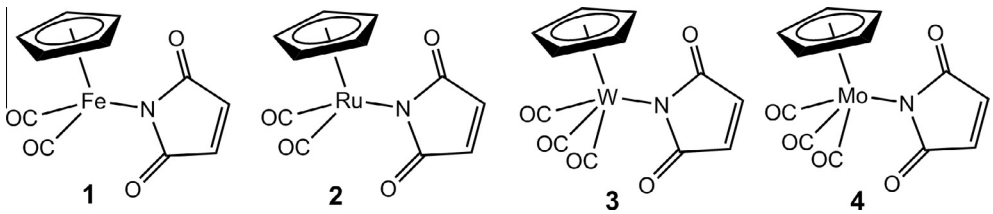

Fig. 1. Metallocarbonyl complexes **1**–**4**.