Synthesis and Spectroscopic / DFT Structural Characterization of Coordination Compounds of Nb(V) and Ti(IV) with Bioactive Carboxylic Acids

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Abstract

The reactions are reported of NbX₅ (X= Cl, Br), TiCl₄ and Ti(O’Pr)₄ with a selection of carboxylic acids exhibiting a known biological role, in a chlorinated solvent. The reactions of NbX₅ with acetylsalicylic acid (aspirin) proceeded with selective deacetylation of the organic reactant and formation of the salicylate complexes NbX₄(C₇H₅O₃) (1a, X = Cl; 1b, X = Br) in 60-65% yields. NbCl₅ reacted with diclofenac and ethacrynic acid (EA…CO₂H) to give NbCl₅[κ³O,O,N…O₂CCH₂(C₆H₄)NC₆H₃Cl₂], 2 (80% yield), and NbCl₄(O₂C-EA), 3 (72% yield), respectively. Ti(O’Pr)₄ reacted with ethacrynic acid giving Ti(O’Pr)₂(O₂C-EA)₂, 4, in 74% yield, as a mixture of two isomers. All the products were characterized by means of analytical and spectroscopic methods, moreover DFT studies were carried out to give insight into structural features.

Keywords: niobium pentahalides, titanium tetrachloride, titanium isopropoxide, coordination chemistry, bioactive carboxylic acids

1. Introduction

Amongst the three important classes of transition metal derivatives containing a M–O–C bond (i.e. metal alkoxides, β-diketonates and carboxylates), metal carboxylates have been known for the longest time [1]. The reactions of transition metal chlorides with acetic acid and related halo-α-substituted compounds usually take place via the release of hydrogen chloride and may represent an entry into the rich chemistry of carboxylato complexes [1, 2]. This reactivity has been ascertained, inter alia, for oxophilic halides of metals belonging to the groups 4 [3] and 5 [4]. More precisely, the reactions of several carboxylic acids or the corresponding alkali salts with titanium(IV) halides are known to yield derivatives of general formula TiX₄−ₙ(O₂CR)ₙ (n = 1-4, X = Cl, Br) [3]. The latter have been used as catalytic precursors for olefin polymerization [5] and for the synthesis of TiO₂-based nano-crystalline materials [6], compounds with antiwear properties [7] or exhibiting
solvent absorption and desorption properties [8]. Moreover, recently, titanium carboxylates have aroused interest for their possible biological activity [9] and, thus, for biomedical purposes [10]. Niobium and tantalum pentahalides remained for a long time in the shadow of metal complexes of group 4, probably in the light of the extraordinary applications of the latter in alkene chemistry [11]. However, in the last fifteen years, a significant progress has been traced concerning the chemistry of niobium and tantalum pentahalides [11, 12], encouraged by their easy availability, the relative nontoxicity of the metal elements [13], and the unusual reactivity patterns [12e,h, 14]. As far as metal carboxylates are concerned, adducts of the type MCl$_4$(OOCR) (M = Nb, Ta, R = alkyl or haloalkyl substituents) [4c, 4d, 15], beside a variety of oxo-chloride species of general formula MOCl(OOCR)$_2$ [15a,15b,15c], MOCl$_2$(OOCR) [15a] and MO$_2$(OOCR) [15c], were obtained from the reactions of MCl$_5$ with RCOOH or (RCO)$_2$O. On the other hand, the reactions of aryl carboxylic acids (ArCO$_2$H) with MCl$_5$ generally result in the formation of dinuclear carboxylato-bridged species, M$_2$Cl$_8$(OOCAr)$_2$ (M = Nb, Ta, Ar = aryl) [16].

In this context, the exploration of the chemistry of early transition, high valent metal compounds with carboxylic acids containing additional functional groups still remains in its infancy. This is presumably a consequence of the variety of complicated reaction pathways that may be working when such oxophilic metal species are allowed to contact with oxygen functions [12h, 17].

In view of this, and of the great interest aroused by the interaction of metal ions with bioactive molecules, finding extensive application for pharmacological issues [18], herein we describe a work on the reactivity of NbX$_5$ (X = Cl, Br), TiCl$_4$ and Ti(O'Pr)$_4$ with some carboxylic acids with a known biological role (Figure 1) [19]. The formation of coordination compounds, their structural characterization by means of spectroscopic and computational studies, and the NbCl$_5$-induced deacetylation of aspirin will be discussed.
2. Results and Discussion

The reactions of NbX₅ (X = Cl, Br) with acetylsalicylic acid led to the isolation of dark red solid compounds of formula NbX₄(C₇H₅O₃) (1a, X = Cl; 1b, X = Br), according to elemental analysis. Both the reactions proceeded with the release of the corresponding acetyl halide, as evidenced by NMR (see Experimental). After hydrolysis of the reaction mixtures [20, 21], salicylic acid was cleanly recovered as unique organic species, and detected by IR and NMR spectroscopy.

Scheme 1. Reaction of NbX₅ (X = Cl, Br) with acetylsalicylic acid.

The deacetylation of aryl acetates to phenols is a well known reaction [22], and actually the most important way of action of acetylsalicylic acid (aspirin) is to irreversibly acetylate amino-acids in the human body [23]. Nevertheless, the outcome of the reaction described in Scheme 1 is surprising since it proceeds with selective chlorination of the ester function, while NbCl₅ usually coordinates (and not activate) esters at ambient temperature [24]. On the other hand, other high valent transition metal chlorides easily convert carboxylic acids into the corresponding acyl chlorides [17a, 25]. The analogous reaction between PCl₅, selected as a representative main group pentachloride, and acetylsalicylic acid led to chlorination of the carboxylic acid group, preserving the acetato moiety (Scheme 2) [26].
The niobium derivatives 1a-b were characterized by IR and NMR spectroscopy. The IR spectra do not show any absorption around 1750 cm\(^{-1}\), diagnostic for the acetyloxy group belonging to acetylsalicylic acid, thus confirming the loss of this fragment. On the other hand, two strong absorptions have been observed around 1500 and 1380 cm\(^{-1}\). These have been attributed, respectively, to the asymmetric (\(\nu_{as}\)) and the symmetric (\(\nu_{s}\)) stretching vibration of the metal-coordinated carboxylate. In general, the wavenumber difference (\(\Delta \nu_{as-s} = \nu_{as} - \nu_{s}\)) is considered as a useful parameter to discriminate between monodentate, chelating, and bridging bidentate carboxylato ligands. \(\Delta \nu_{as-s}\) values within the range 100 to 150 cm\(^{-1}\) are typical of either chelating or bridging bidentate carboxylates [27]. The IR data available for 1a-b, \(i.e.\) \(\Delta \nu_{as-s}\) is 112 (1a) and 126 (1b) cm\(^{-1}\), are consistent with a bidentate coordination fashion, thus two possible structures can be envisaged in principle (Figure 2).

![Scheme 2](image)

**Scheme 2.** Reaction of PCl\(_5\) with acetylsalicylic acid.

Many attempts were done to collect X-ray quality crystals of 1a-b, but unsuccessfully. Therefore, we decided to perform a DFT investigation on 1a to elucidate its structure. The dimeric structure with two bridging carboxylato ligands (Figures 2-II and 3) resulted more stable than the mononuclear \(\kappa^2\)-carboxylate complex (Figures 2-I and S1) by about 6.2 kcal mol\(^{-1}\) (Gibbs free energy change).
energy, referred to the mononuclear stoichiometry). In both cases, the hydroxyl group is expected to participate to intramolecular hydrogen bonding. According to the computational result, it is reasonable that 1a and the homolog compound 1b adopt the dimeric structure, that is reminiscent of what previously described for other MX₄(OOCAr) compounds (M = Nb, Ta; Ar = aryl group) [16].

\[ \text{Figure 3. DFT-optimized structure of the most stable isomer of 1a (C-PCM/oB97X calculations).} \]

A control of the literature data has shown that 1a,b constitute the first examples of niobium(V) halides containing salicylate as a ligand, other similar cases being referred to alkoxide derivatives [28].

The \(^1\)H and \(^{13}\)C NMR spectra of 1a, b display several resonances in the aromatic region. This fact may be due to the presence of isomeric forms, or to intermolecular interactions promoted by the OH groups. The \(^{93}\)Nb NMR spectrum of 1a clearly consists of a unique, broad resonance at \(-271 \text{ (}\Delta\nu\text{)} = 4 \times 10^3 \text{ Hz}) \text{ ppm [29].} \)

\text{NbCl}_5 \text{ quickly reacted with diclofenac in dichloromethane affording a red solution which, on standing at RT for 48 h, gave a yellow precipitate. This solid was identified as NbCl}_5[\text{κ}^3\text{O,O,N-} \text{O}_2\text{CCH}_2(\text{C}_6\text{H}_4)\text{NCOH}_2\text{Cl}_2], 2, \text{i.e. a niobium(V) complex containing a tridentate, dianionic, OON- coordinated ligand (Scheme 3). The characterization was based on analytical, IR (two strong}
absorptions have been observed around 1599 and 1458 cm\(^{-1}\) due to asymmetric and symmetric (\(v_s\)) stretching vibrations of the carboxylato group) and NMR data. The \(^1\)H NMR spectrum displayed a single set of resonances, and N-bound hydrogens were not recognized. The \(^{93}\)Nb NMR spectrum (broad resonance centered at \(-564\) ppm) ruled out the possible existence of an ionic pair including [NbCl\(_6\)]\(^-\) [25b,c, 29, 30, 31], and suggested 2 to be a symmetric compound.

![Scheme 3](image)

Scheme 3. The reaction of NbCl\(_5\) with diclofenac.

According to DFT calculations, the lowest energy form of 2 is a dinuclear structure where the organic ligand coordinates the metal centers in a bridging fashion via the carboxylate group, similarly to what discussed for 1a. The enthalpy variation associated to the dimerization of pentacoordinate NbCl\(_5\)[O\(_2\)CCH\(_2\)(C\(_6\)H\(_4\))NC\(_6\)H\(_3\)Cl\(_2\)] (Figure S2) is around \(-17.1\) kcal mol\(^{-1}\).

![Figure 4](image)

Figure 4. DFT-optimized structure of the most stable isomer of 2 (C-PCM/\(\omega\)B97X calculations). After geometry optimization, the molecule has approximately \(C_i\) symmetry. Selected bond lengths (Å, average values): Nb-O 2.065, 2.108 2.144; Nb-Cl (\(trans\) N) 2.412; Nb-Cl (\(cis\) N) 2.341, 2.342; C-O 1.256, 1.263. Selected angles (deg, average values): O-Nb-O 82.3; N-Nb-Cl 93.5, 114.0, 157.6. C-O-Nb 132.8, 142.7. Colour map: Nb, light blue; Cl, green; O, red; C, grey; H, light gray.
The reaction of niobium pentachloride with ethacrynic acid (EA-COOH) resulted in the formation of a moisture-sensitive orange precipitate, which was characterized as the Nb(V) ethacrylate NbCl$_4$(O$_2$C-EA), 3. The low solubility in common organic solvents precluded the growth of single crystals. The IR spectrum of 3 (in the solid state) shows a strong absorption at 1674 cm$^{-1}$, assigned to the combination of the asymmetric stretching absorption of the carboxylate and the non-coordinated ketone (the C=O stretching vibration of the ketonic group of EA-CO$_2$H falls at 1670 cm$^{-1}$), and a medium to strong absorption at 1462 cm$^{-1}$, assigned to the symmetric stretching vibration of the carboxylate.

The presence of the intact EACOO unit within complex 3 is witnessed by the fact that, upon hydrolysis [20], EACOOH was cleanly recovered and identified by NMR spectroscopy.

DFT calculations suggested a coordination mode of the ethacrylate moiety comparable to that proposed for the carboxylato ligands in 1a and 2, i.e. the carboxylic group acting as a bridging ligand between two niobium centers (see Figure 5). This feature is in alignment with previous findings in the literature [16]. Alternative, mononuclear structures with a $\kappa^2$-ethacrylate ligand or dinuclear structures with Cl-bridges resulted to be computationally less stable isomers (Figure S3).

**Figure 5.** DFT-optimized structure of the most stable isomer of 3 (C-PCM/ωB97X calculations). After geometry optimization, the molecule has approximately $C_2$ symmetry. Selected bond lengths (Å, average values): Nb-O 2.023, 2.132; Nb-Cl 2.279, 2.291, 2.325, 2.330; C-O 1.250, 1.260. Selected angles (°, average values): O-Nb-O 84.9; C-O-Nb 139.9, 171.5. Colour map: Nb, light blue; Cl, green; O, red; C, grey; H, light gray.
The reactions of TiCl₄ with diclofenac and acetylsalicylic acid were studied too, but they afforded insoluble solid materials which could not be identified.

We decided then to extend the present research to the reactivity of titanium alkoxide with ethacrynic acid. In general, Ti(O\text{Pr})₄ reacts with carboxylic acids giving replacement of one or more alkoxide ligands by an equal number of carboxylate units [32]. This kind of titanium alkoxide derivatives have been proposed as possible antitumoral agents [33].

The reaction of Ti(O\text{Pr})₄ with two equivalents of ethacrynic acid in refluxing CHCl₃ afforded good yields of Ti(O\text{Pr})₂(O₂C-EA)₂, 4, as an ivory solid stable in air for short periods of time (Scheme 4).

\[
\text{Ti(O\text{Pr})₄} \xrightarrow{\text{EA-CO\text{OH}}} \text{Ti(O\text{Pr})₂(OOC-EA)₂}
\]

**Scheme 4.** Reaction of Ti(O\text{Pr})₄ with ethacrynic acid

It is interesting to note that the use of EA-COOH / Ti molar ratio = 3 or 4 did not change the nature of the prevalently isolated product.

Compound 4 was characterized by analytical and spectroscopic data. The IR spectrum shows two strong absorptions at 1614 and 1467 cm\(^{-1}\), assigned to the asymmetric (\(v_{as}\)) and the symmetric (\(v_s\)) stretching vibrations of the carboxylato group. The value \(\Delta v_{as-s} = v_{as} - v_s\) of 147 cm\(^{-1}\) is indicative of either a chelating or a bridging bidentate carboxylate [27]. On account of the IR spectrum and the DFT results (vide infra), we propose a bidentate coordination of the ethacrynate ligand to the titanium fragment.

The \(^1\)H relative integration of the signals of the iso-propoxy and the ethacrynate moieties suggests that these are present in 1:1 molar ratio, reflecting the Ti(O\text{Pr})₂(O₂C-EA)₂ stoichiometry. The \(^1\)H- and \(^{13}\)C-NMR spectra of 4 consist of two set of resonances of comparable intensity, presumably due to the co-existence of isomeric forms. Based on the analytical data, we presume that 4 is in fact a mixture of two linkage isomers, namely 4a and 4b.

DFT calculations with implicit solvation ruled out the possibility of *cis/trans* isomerism; indeed all
the geometry optimizations afforded stationary points wherein the two iso-propoxy ligands are mutually cis. Equilibrium geometries with comparable Gibbs free energy values (ΔG = 2.3 kcal mol⁻¹) are instead differentiated in the coordination mode of one of the two ethacrynate ligands. The favorable coordination mode resulted to be κ¹ in the most stable species and κ² in the secondary one, despite the fact that one Ti–O bond appeared relatively weak (calculated bond length = 2.309 Å). The second O₂C-EA ligand should be bidentate in both the isomers. Figure 6 shows the DFT-optimized structures of 4a and 4b.

**Figure 6.** DFT-optimized isomers of compound 4 (C-PCM/ωB97X calculations, hydrogen atoms omitted for clarity). Selected bond lengths (Å) for 4a: Ti-O(PrO) 1.724, 1.725; Ti-O(κ²-COO) 2.074, 2.187; Ti-O(κ¹-COO) 1.911; C-O(κ²-COO) 1.249, 1.272; C-O(κ¹-COO) 1.214, 1.308. Selected angles (°) for 4a: O(PrO)-Ti-O(PrO) 106.5; O(κ¹-COO)-Ti-O(PrO) 99.5, 106.3; O(κ¹-COO)-Ti-O(κ²-COO) 84.5, 138.9; O(κ²-COO)-Nb-O(κ²-COO) 61.0. Selected bond lengths (Å) for 4b: Ti-O(PrO) 1.738, 1.740; Ti-O(κ²-COO⁵⁻) 2.064, 2.145; Ti-O(κ²-COO⁵⁺) 2.012, 2.309; C-O(κ²-COO⁵⁺) 1.257, 1.266; C-O(κ²-COO⁵⁻) 1.243, 1.281. Selected angles (°) for 4b: O(PrO)-Ti-O(PrO) 102.4; O(κ²-COO⁵⁺)-Nb-O(κ²-COO⁵⁻) 61.9; O(κ²-COO⁵⁻)-Nb-O(k²-COO⁵⁺) 60.1. Colour map: Ti, blue; Cl, green; O, red; C, grey; H, light gray.

3. Conclusions

Despite the chemistry of middle to late transition metal halides with carboxylic acids has been largely investigated, relatively little is known about the analogous reactions of high valent, early transition metal species. Herein, we have described the study of the reactivity of NbX₅ (X = Cl, Br) and Ti(O²Pr)₄ with a selection of carboxylic acids exhibiting a known biological role. The reactions proceed to afford metal compounds containing bidentate carboxylates, whose structures have been
elucidated by means of spectroscopic and computational analyses. One or more HX units (X = Cl, Br, OiPr) are generally lost during the reactions, moreover selective deacetylation of the organic moiety occurs during the interaction NbX₅/aspirin. This latter case traces a clear distinction with the parallel reactivity displayed by the main group homologue PCl₅.

![Scheme 5. Overview of the reactivity of NbCl₅ with bioactive carboxylic acids.](image)

4. Experimental

All manipulations of air and/or moisture-sensitive compounds were performed under an atmosphere of pre-purified nitrogen using standard Schlenk techniques. The reaction vessels were oven dried at 150 °C prior to use, evacuated (10⁻² mmHg) and then filled with argon.

TiCl₄ (99%, Strem), NbCl₅ (99+% Strem), Ti(OiPr₄) (98%, Strem), PCl₅ (>98%, Sigma Aldrich), Ag₂O (99+% Sigma Aldrich) and organic reactants (highest purity available, from TCI Europe or Sigma Aldrich) were commercial products stored under nitrogen atmosphere as received. NbBr₅ was prepared according to the literature procedure and stored under nitrogen atmosphere [34]. Once isolated, the metal products were conserved in sealed glass tubes under nitrogen. Solvents (Sigma-Aldrich) were distilled from appropriate drying agents. Reflectance infrared
spectra of solid materials were recorded at 298 K on a FT IR-Perkin Elmer Spectrometer, equipped with a UATR sampling accessory. NMR spectra were recorded at 293 K on a Bruker Avance II DRX400 instrument equipped with a BBFO broadband probe. The chemical shifts for \(^1H\) and \(^{13}C\) were referenced to the non-deuterated aliquot of the solvent, while the chemical shifts for \(^{93}Nb\) were referenced to [NEt\(_4\)][NbCl\(_6\)] as an external reference. Carbon, hydrogen and nitrogen analyses were performed on a Carlo Erba mod. 1106 instrument. The halide content was determined by the Mohr method [35] on solutions prepared by dissolution of the solid samples in aqueous KOH and heated at boiling temperature for 72 hours, followed by cooling to room temperature and addition of HNO\(_3\) up to neutralization.

4.1. Reactions of Nb(V) halides with acetylsalicylic acid: synthesis of NbX\(_4\)[\(\kappa^2\)-C\(_6\)H\(_4\)(O)(CO\(_2\)H)] (X = Cl, \(1a\); X = Br, \(1b\)). The synthesis of \(1a\) is described in detail, \(1b\) being prepared by a similar procedure. NbCl\(_5\) (240 mg, 0.888 mmol), acetylsalicylic acid (160 mg, 0.888 mmol) and CH\(_2\)Cl\(_2\) (15 mL) were introduced into a Schlenk tube in the order given. The mixture was allowed to stir at room temperature for 48 h. The resulting red solution was concentrated up to 5 mL, layered with pentane and stored at \(-30^\circ\)C for one week. The product, \(1a\), was recovered as a dark red microcrystalline solid. Yield 215 mg, 65%. Anal. Calc. for C\(_7\)H\(_5\)Cl\(_4\)NbO\(_3\): C, 22.61; H, 1.36; Cl, 38.14. Found: C, 22.50; H, 1.63; Cl, 38.05. IR (solid state, cm\(^{-1}\)): 2898vw, 2129w, 1597s, 1577vs, 1506s, 1434m, 1393vs, 1375vs, 1312m, 1265m, 1230s, 1165m, 1104m, 1099m, 1031w, 902s, 857w, 799w-m, 753vs, 691w, 673s cm\(^{-1}\). \(^1H\) NMR (CDCl\(_3\)): \(\delta = 11.5\) (br, 1 H, OH); 8.28, 7.93, 7.43, 7.15 (m-br, 4 H, arom CH) ppm. \(^{13}C\) NMR (CDCl\(_3\)): \(\delta = 173.1\) (COO); 162.4 (arom C-O); 139.5, 133.2, 127.2, 118.4 (arom CH); 119.0 (arom C-C) ppm. \(^{93}Nb\) NMR (CDCl\(_3\)): \(\delta = -271\) (\(\Delta\nu/2 = 4\times10^3\) Hz) ppm.

\(1b\). Dark red solid, from NbBr\(_5\) (300 mg, 0.609 mmol) and acetylsalicylic acid (110 mg, 0.611 mmol). Yield 201 mg, 60%. Anal. Calc. for C\(_7\)H\(_5\)Br\(_4\)NbO\(_3\): C, 15.30; H, 0.92; Br, 58.15. Found: C, 15.22; H, 1.05; Br, 57.93. IR (solid state, cm\(^{-1}\)): 3070w-br, 2922w, 2853w, 1603s, 1589s, 1556m,
The reactions of NbX₅ with acetylsalicylic acid were also performed in CD₂Cl₂ under conditions analogous to those described above. NMR analysis of the reaction solutions after 30 hours clearly indicated the formation of acetyl chloride.

4.2. Reaction of NbCl₅ with diclofenac: synthesis of NbCl₅[κ³-O,O,N-O₂CCH₂(C₆H₄)N C₆H₃Cl₂], 2.

The reaction of NbCl₅ (464 mg, 1.71 mmol) with diclofenac (506 mg, 1.71 mmol) was carried out by a procedure analogous to that described for NbCl₅/acetylsalicylic acid. The progressive formation of an abundant, yellow precipitate occurred. Compound 2 was finally isolated as a yellow solid. Yield 675 mg, 80%. Anal. Calc. for C₁₄H₉Cl₅NNbO₂: C, 34.08; H, 1.84; N, 2.84; Cl (inorganic), 21.56. Found: C, 34.21; H, 1.70; N, 2.76; Cl (inorganic), 22.15. IR (solid state, cm⁻¹): 2941w, 2909w, 1633m, 1599vs (νasCOO), 1570m, 1496w, 1458m (νsCOO), 1440m, 1398w, 1362m, 1300w, 1262w, 1200m, 1097w, 997w, 943w, 779vs, 750s, 737m-s, 709m, 686s cm⁻¹. ¹H NMR (CD₃CN): δ = 7.68, 7.57, 7.47, 7.28, 7.19, 6.52 (m, 7 H, arom CH); 3.86 (s, 2 H, CH₂) ppm. ⁹³Nb NMR (CD₃CN): δ = −564 (Δν½ = 2·10³ Hz) ppm.

4.3. Reaction of NbCl₅ with ethacrynic acid: synthesis of NbCl₄(O₂C-EA), 3.

NbCl₅ (141 mg, 0.522 mmol), ethacrynic acid (158 mg, 0.521 mmol) and CH₂Cl₂ (8 mL) were introduced into a Schlenk tube in the order given. A red solution was immediately obtained and the precipitation of an orange compound began shortly afterwards. The suspension was stirred at room temperature for 4 h. Compound 3 was obtained as a moisture-sensitive orange solid upon removal of the solvent under reduced pressure. Yield 203 mg, 72%. The product is insoluble in toluene and chlorinated solvents, and is not stable in acetonitrile or diethyl ether. Anal. Calc. for
C$_{26}$H$_{22}$Cl$_2$Nb$_2$O$_8$: C, 29.08; H, 2.06; Cl (inorganic), 26.42. Found: C, 28.80; H, 2.17; Cl, 28.90. IR (solid state): $\nu = 2973w$, 2939w, 2878 w, 1675s-br ($\nu_{as,CO2} + \nu_{C=O, keto}$), 1642w-sh, 1583s ($\nu_{C=CH2}$), 1464s ($\nu_{s,CO2}$), 1431m, 1387m, 1338w, 1286m, 1261m, 1240m, 1217m, 1166w, 1128m, 1100s, 1087s, 1070s, 972w, 943w, 898s, 849w, 830m, 822m, 733m, 718m-sh, 687m. Rapid increase of absorption intensities at 3400-3000 ($\nu_{OH}$) 1735 ($\nu_{C=O,acid,EACO2H}$) and 1642 cm$^{-1}$ ($\delta_{OH}$) was observed upon brief air exposition of the solid sample.

4.4. Reactions of TiCl$_4$ with diclofenac and acetylsalicylic acid.

A solution of diclofenac (296 mg, 1.00 mmol) in CH$_2$Cl$_2$ (10 mL) was added of TiCl$_4$ (1.89 mL, 1.00 mmol). After 24 h, the liquors were removed and the abundant precipitate was washed with pentane and dried under vacuo, thus affording a yellow solid (yield 200 mg). IR (solid state, cm$^{-1}$): 3079w-br, 1645w, 1604w, 1542m, 1510s, 1500sh, 1454m, 1440m-s, 1404s, 1349w, 1276w, 1199w, 1153w, 1098w-m, 947w, 902w-m, 781m-s, 756s, 724s, 708m, 690s, 654vs cm$^{-1}$. $^1$H NMR (CD$_3$CN): $\delta = 7.67$-6.97 (m, arom CH); 6.54, 6.48 (br); 4.00, 3.80 (br, CH$_2$) ppm.

The reaction of TiCl$_4$ (1.00 mmol) with acetylsalicylic acid (1.00 mmol) was carried out by a procedure analogous to that described for TiCl$_4$/diclofenac, and a red solid was finally isolated (yield ca. 150 mg). IR (solid state, cm$^{-1}$): 1599s, 1575s, 1557m-s, 1489s, 1474s, 1442s, 1377vs, 1313m-s, 1265m, 1251m-s, 1223vs, 1163m, 1152m, 1096m, 1031w-m, 961w, 891vs, 870m, 858m, 819w-m, 789m, 760vs, 694m, 666vs cm$^{-1}$.

4.5. Identification of the organic species.

Diethyl ether (ca. 5 mL) and then H$_2$O (ca. 2 mL) were added to the appropriate metal product (ca. 0.5 mmol). The mixture was stirred at room temperature for 48 h. Then the organic phase was separated and dried in vacuo. The following compounds were detected by NMR spectroscopy as the only organic species. From 1a-b: salicylic acid; from 1: diclofenac; from 2: ethacryn nic acid; from 3: 
ethacrynic acid; from TiCl₄/diclofenac: diclofenac; from TiCl₄/aspirin: aspirin. Salicylic acid was identified by IR in the solid state too [36].

4.6. Reaction of Ti(OiPr)₄ with ethacrynic acid: synthesis of Ti(O filme (O₂C-EA)₂, 4.

A solution of Ti(OiPr)₄ (0.1 ml, 0.33 mmol) in CHCl₃ (20 ml) was treated with ethacrynic acid (0.201 g, 0.663 mmol) After 24 h heating to the reflux temperature, the mixture was cooled at room temperature and the volatiles were removed in vacuo at room temperature. The solid was washed with hexane and dried in vacuo a room temperature affording 0.188 g (74%) of 4 as a colorless solid. Anal. Calc. for C₅₂H₅₂Cl₄O₁₀Ti: C, 53.16; H, 6.10; Ti, 5.57. Found: C, 52.98; H: 5.86; Ti, 5.08. IR (solid state, cm⁻¹): 2969w, 2934w, 2107w-br, 1756w, 1664s (C=O), 1614m (νas COO), 1583vs, 1574m-sh, 1467s (νs COO), 1455s, 1421s, 1383m, 1339m, 1286s, 1259vs, 1206m 1120m, 1076vs, 1001s, 938m, 894w, 800s, 755vs cm⁻¹. ¹H NMR (CDCl₃): δ = 7.13 (d, 1 H, 3JHH = 8.80 Hz, C10-H); 6.78 (m, 1 H, C11-H); 5.93, 5.59 (d, 2 H, J = 1 Hz, C4-H); 5.13, 4.28 (m, 2 H, OCH); 4.75, 4.71 (s, 2 H, C12-H); 2.46 (m, 2 H, C2-H); 1.26, 1.13, 0.87 (m, 9 H, C1-H + OCH₃) ppm. ¹³C NMR (CDCl₃): δ = 195.8 (C5); 167.8, 167.2 (C13); 155.6 (C9); 150.2 (C6); 133.8 (C7), 131.4 (C8); 128.5 (C4); 126.7 (C11); 123.4 (C3); 110.8 (C10); 69.7, 61.7 (OCH); 66.4, 66.3 (C12); 31.6, 22.6, 21.7, 14.1 (OCH₃) 23.4 (C2); 12.4 (C1) ppm.

5. Computational details

The computational geometry optimizations were carried out without symmetry constrains, using the range-separated DFT functional oB97X [37], in combination with the split-valence polarized basis set of Ahlrichs and Weigend, with ECP for the niobium centre [38]. The C-PCM implicit solvation model was added to oB97X calculations, considering chloroform as continuous
medium [39]. The “restricted” formalism was always applied. The stationary points were characterized by IR simulations (harmonic approximation), from which zero-point vibrational energies and thermal corrections (T = 298.15 K) were obtained [40]. The software used was Gaussian '09 [41]. Further computational details are provided as Supporting Information.

6. Acknowledgments

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7. Supporting Information

Figures S1-S3 show the DFT-optimized structures of isomers of compounds 1a, 2 and 3. Cartesian coordinates of the DFT-optimized structures are given in a separated .xyz file.

8. References


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[20] The treatment of the reaction mixtures with water facilitates the release of the organic compounds from the highly oxophilic metal products, and allows the spectroscopic identification of the former. This strategy has been successfully adopted by ourselves in previous works, having proved that H2O is generally inert towards ligand activation reactions [see ref. 21, and references therein].


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