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 NbX_5 (X= Cl, Br), $TiCl_4$ and $Ti(O^iPr)_4$ with a selection of carboxylic acids exhibiting a known biological role, in a chlorinated solvent. The reactions of NbX_5 with acetylsalicylic acid (aspirin) proceeded with selective deacetylation of the organic reactant and formation of the salicylate complexes $NbX_4(C_7H_5O_3)$ (**1a**, X = Cl; **1b**, X = Br) in 60-65% yields. $NbCl_5$ reacted with diclofenac and ethacrynic acid (EA-CO_2H) to give $NbCl_3[\kappa^3_{O,O,N}$-$O_2CCH_2(C_6H_4)NC_6H_3Cl_2]$, **2** (80% yield), and $NbCl_4(O_2C$-EA), **3** (72% yield), respectively. $Ti(O^iPr)_4$ reacted with ethacrynic acid giving $Ti(O^iPr)_2(O_2C$-$EA)_2$, **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

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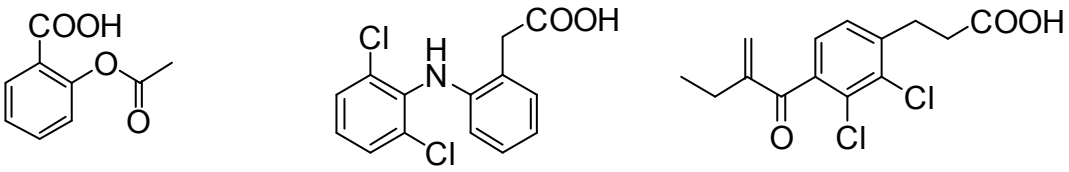
1. Introduction

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 $TiX_{4-n}(O_2CR)_n$ (n = 1-4, X = Cl, Br) [3]. The latter have been used as catalytic precursors for olefin polymerization [5] and for the synthesis of TiO_2-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 $(RCO)_2O$. On the other hand, the reactions of aryl carboxylic acids ($ArCO_2H$) with MCl_5 generally result in the formation of dinuclear carboxylato-bridged species, $M_2Cl_8(OOCAr)_2$ (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 $Ti(O^iPr)_4$ 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.

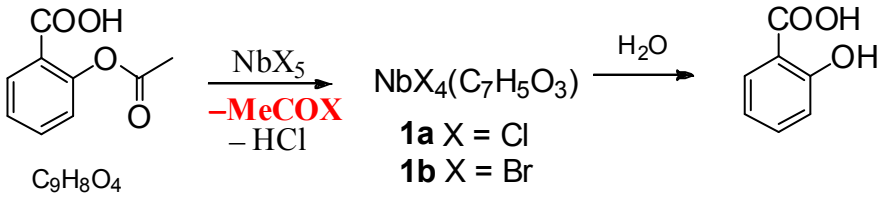


acetylsalicylic acid | diclofenac (DF-COOH) | ethacrynic acid EA-COOH

Figure 1. Bioactive carboxylic acids treated in this work.

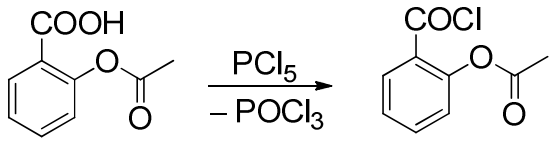
2. Results and Discussion

The reactions of NbX_5 (X = Cl, Br) with acetylsalicylic acid led to the isolation of dark red solid compounds of formula $NbX_4(C_7H_5O_3)$ (**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 NbX_5 (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 $NbCl_5$ 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 PCl_5, 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].



Scheme 2. Reaction of PCl_5 with acetylsalicylic acid.

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 (ν_{as}) and the symmetric (ν_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.* $\Delta\nu_{a-s}$ 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).

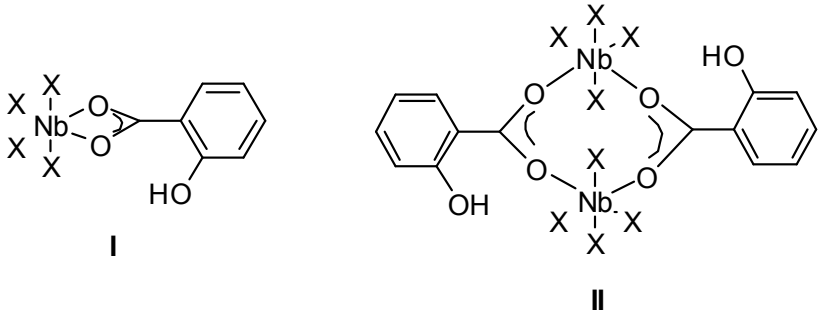


Figure 2. Possible structures of niobium(V) tetrahalide salicylate complexes (X = Cl, Br).

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 κ^2-carboxylate complex (Figures 2-I and S1) by about 6.2 kcal mol^{-1} (Gibbs free

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 $MX_4(OOCAr)$ compounds (M = Nb, Ta; Ar = aryl group) [16].

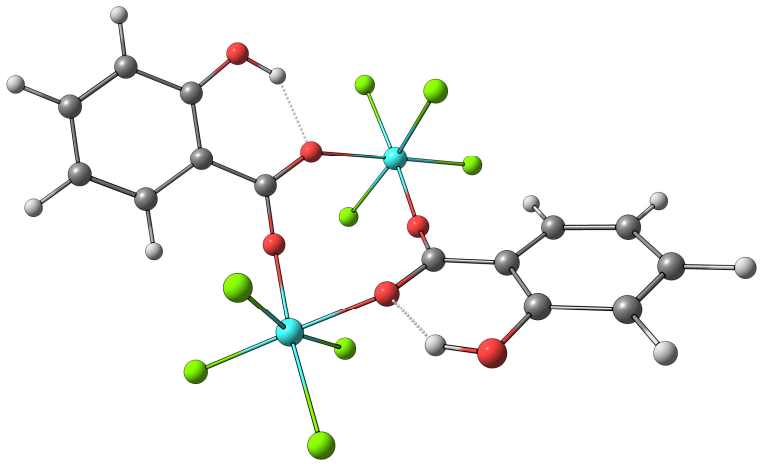


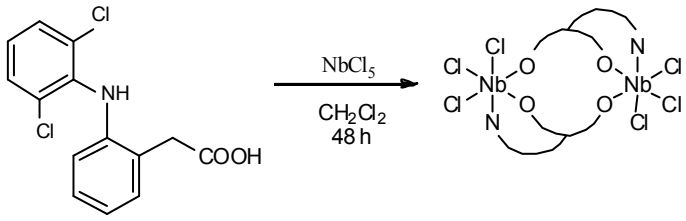
Figure 3. DFT-optimized structure of the most stable isomer of **1a** (C-PCM/ωB97X calculations). After geometry optimization, the molecule has C_2 symmetry. Selected bond lengths (Å): Nb-O 1.992, 2.144; Nb-Cl 2.284, 2.308, 2.316, 2.353; C-O 1.267, 1.284; O-H 0.972; H---O 1.817. Selected angles (deg): O-Nb-O 87.3; C-O-Nb 140.7, 156.0. Colour map: Nb, light blue; Cl, green; O, red; C, grey; H, light gray.

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 ($\Delta\nu_{1/2} = 4 \cdot 10^3$ Hz) ppm [29].

$NbCl_5$ 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 $NbCl_3[\kappa^3_{O,O,N}\text{-}O_2CCH_2(C_6H_4)NC_6H_3Cl_2]$, **2**, 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 (ν_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. 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 $NbCl_3[O_2CCH_2(C_6H_4)NC_6H_3Cl_2]$ (Figure S2) is around −17.1 kcal mol^{-1}.

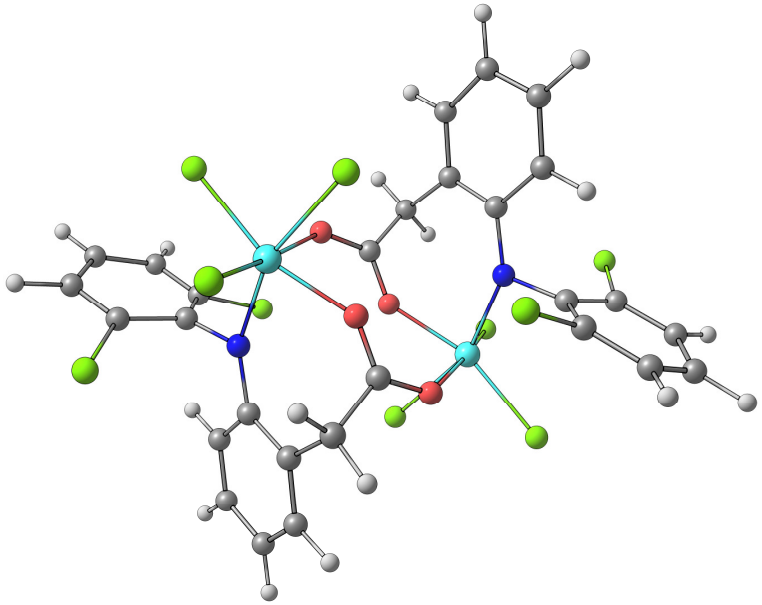


Figure 4. DFT-optimized structure of the most stable isomer of **2** (C-PCM/ωB97X calculations). After geometry optimization, the molecule has approximately C_i symmetry. Selected bond lengths (Å, average values): Nb-O 2.065, 2.108 2.144; Nb-Cl (*trans* N) 2.412; Nb-Cl (*cis* N) 2.341, 2.342; C-O 1.256, 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) ethacrynate $NbCl_4(O_2C\text{-}EA)$, **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_2H 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 ethacrynate 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 κ^2-ethacrynate ligand or dinuclear structures with Cl-bridges resulted to be computationally less stable isomers (Figure S3).

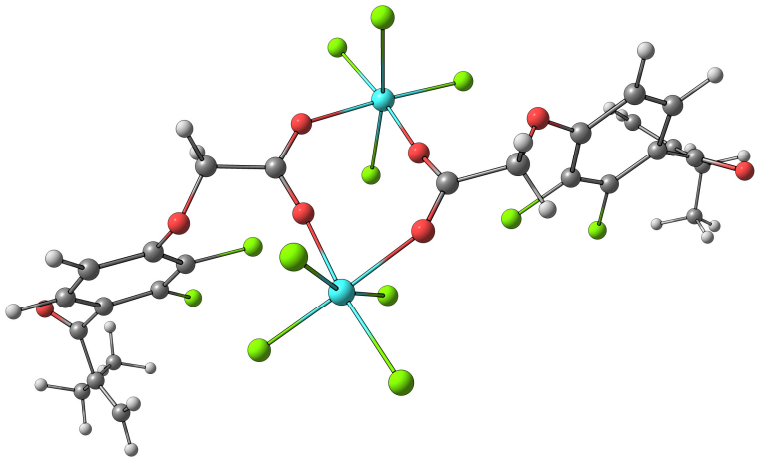
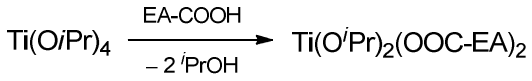


Figure 5. DFT-optimized structure of the most stable isomer of **3** (C-PCM/ωB97X calculations). After geometry optimization, the molecule has approximately C_2 symmetry. Selected bond lengths (Å, average values): Nb-O 2.023, 2.132; Nb-Cl 2.279, 2.291, 2.325, 2.330; C-O 1.250, 1.260. Selected angles (°, 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 $TiCl_4$ 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, $Ti(O^iPr)_4$ 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 $Ti(O^iPr)_4$ with two equivalents of ethacrynic acid in refluxing $CHCl_3$ afforded good yields of $Ti(O^iPr)_2(O_2C\text{-}EA)_2$, **4**, as an ivory solid stable in air for short periods of time (Scheme 4).



Scheme 4. Reaction of $Ti(O^iPr)_4$ 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 (ν_{as}) and the symmetric (ν_s) stretching vibrations of the carboxylato group. The value $\Delta\nu_{as-s} = \nu_{as} - \nu_s$ 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 ^1H 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 $Ti(O^iPr)_2(O_2C\text{-}EA)_2$ stoichiometry. The ^1H- 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 κ^1 in the most stable species and κ^2 in the secondary one, despite the fact that one Ti–O bond appeared relatively weak (calculated bond length = 2.309 Å). The second O_2C-EA ligand should be bidentate in both the isomers. Figure 6 shows the DFT-optimized structures of **4a** and **4b**.

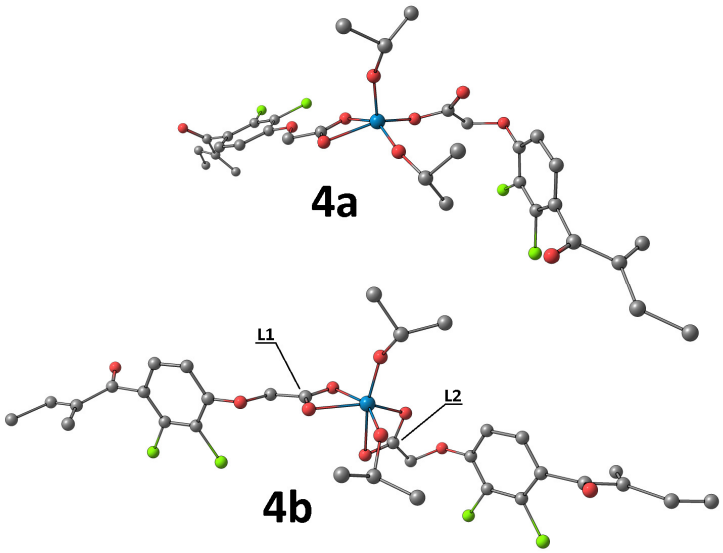
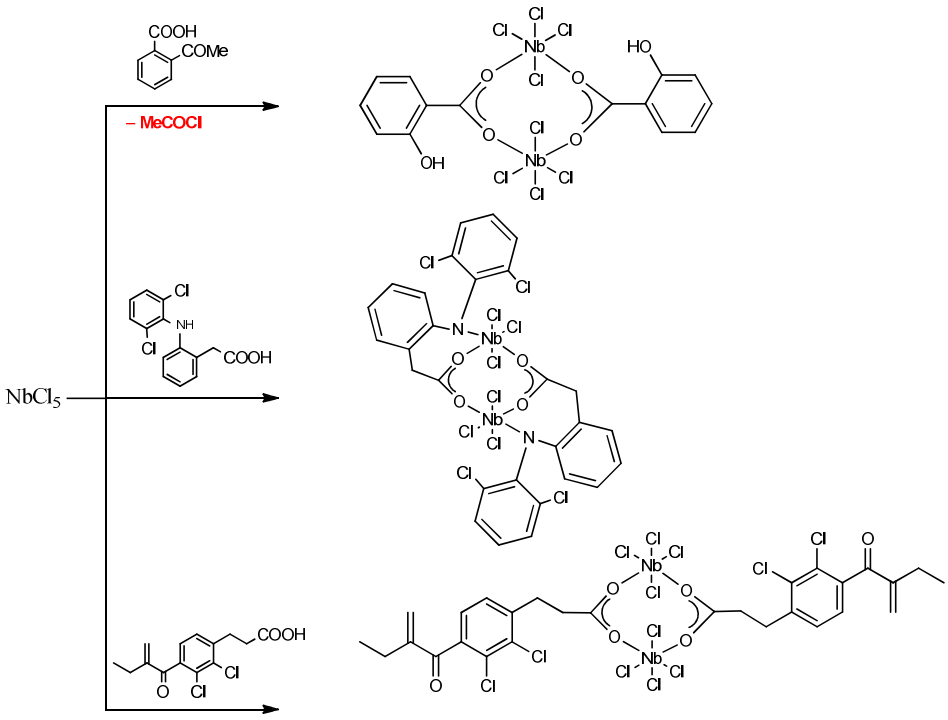


Figure 6. DFT-optimized isomers of compound **4** (C-PCM/ωB97X calculations, hydrogen atoms omitted for clarity). Selected bond lengths (Å) for **4a**: Ti-O(^{i}PrO) 1.724, 1.725; Ti-O(κ^2-COO) 2.074, 2.187; Ti-O(κ^1-COO) 1.911; C-O(κ^2-COO) 1.249, 1.272; C-O(κ^1-COO) 1.214, 1.308. Selected angles (°) for **4a**: O(^{i}PrO)-Ti-O(^{i}PrO) 106.5; O(κ^1-COO)-Ti-O(^{i}PrO) 99.5, 106.3; O(κ^1-COO)-Ti-O(κ^2-COO) 84.5, 138.9; O(k^2-COO)-Nb-O(k^2-COO) 61.0. Selected bond lengths (Å) for **4b**: Ti-O(^{i}PrO) 1.738, 1.740; Ti-O(κ^2-COO^{L1}) 2.064, 2.145; Ti-O(κ^2-COO^{L2}) 2.012, 2.309; C-O(κ^2-COO^{L1}) 1.257, 1.266; C-O(κ^2-COO^{L2}) 1.243, 1.281. Selected angles (°) for **4b**: O(^{i}PrO)-Ti-O(^{i}PrO) 102.4; O(k^2-COO^{L1})-Nb-O(k^2-COO^{L1}) 61.9; O(k^2-COO^{L2})-Nb-O(k^2-COO^{L2}) 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 NbX_5 (X = Cl, Br) and $Ti(O^iPr)_4$ 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, O^{i}Pr) are generally lost during the reactions, moreover selective deacetylation of the organic moiety occurs during the interaction NbX_5/aspirin. This latter case traces a clear distinction with the parallel reactivity displayed by the main group homologue PCl_5.



Scheme 5. Overview of the reactivity of $NbCl_5$ with bioactive carboxylic acids.

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.

$TiCl_4$ (99%, Strem), $NbCl_5$ (99+%, Strem), $Ti(OiPr_4)$ (98%, Strem), PCl_5 (>98%, Sigma Aldrich), Ag_2O (99+%, Sigma Aldrich) and organic reactants (highest purity available, from TCI Europe or Sigma Aldrich) were commercial products stored under nitrogen atmosphere as received. $NbBr_5$ 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 ^{1}H 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 $NbX_4[\kappa^2\text{-}C_6H_4(O)(CO_2H)]$ (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_2Cl_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 °C for one week. The product, **1a**, was recovered as a dark red microcrystalline solid. Yield 215 mg, 65%. Anal. Calc. for $C_7H_5Cl_4NbO_3$: 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}. ^{1}H NMR ($CDCl_3$): δ = 11.5 (br, 1 H, OH); 8.28, 7.93, 7.43, 7.15 (m-br, 4 H, arom CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 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 ($CDCl_3$): δ = –271 ($\Delta\nu_{1/2} = 4\cdot10^3$ 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 $C_7H_5Br_4NbO_3$: 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,

1504m, 1481m, 1428w, 1367s 1325w, 1312w, 1228m, 1207m, 1162m, 1098m, 1030w, 898s, 854w-m, 796s, 755vs, 691m, 666vs cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 10.3 (br, OH); 8.53, 8.28, 7.93, 7.58-7.43, 7.34-7.17 (m, arom CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.0 (COO); 161.3 (C-OH); 139.6-138.8, 134.0-132.7, 128.8-127.3, 119.0-118.2 (arom) ppm.

The reactions of NbX_5 with acetylsalicylic acid were also performed in CD_2Cl_2 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 $NbCl_5$ with diclofenac: synthesis of $NbCl_3[\kappa^3_{O,O,N}$-$O_2CCH_2(C_6H_4)N\ C_6H_3Cl_2]$, ***2.***

The reaction of $NbCl_5$ (464 mg, 1.71 mmol) with diclofenac (506 mg, 1.71 mmol) was carried out by a procedure analogous to that described for $NbCl_5$/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 $C_{14}H_9Cl_5NNbO_2$: 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 (ν_{as}COO), 1570m, 1496w, 1458m (ν_sCOO), 1440m, 1398w, 1362m, 1300w, 1262w, 1200m, 1097w, 997w, 943w, 779vs, 750s, 737m-s, 709m, 686s cm^{-1}. ^{1}H NMR (CD_3CN): δ = 7.68, 7.57, 7.47, 7.28, 7.19, 6.52 (m, 7 H, arom CH); 3.86 (s, 2 H, CH_2) ppm. ^{93}Nb NMR (CD_3CN): δ = –564 ($\Delta\nu_{1/2} = 2\cdot10^3$ Hz) ppm.

4.3. Reaction of $NbCl_5$ with ethacrynic acid: synthesis of $NbCl_4(O_2C$-EA), ***3****.*

$NbCl_5$ (141 mg, 0.522 mmol), ethacrynic acid (158 mg, 0.521 mmol) and CH_2Cl_2 (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

$C_{26}H_{22}Cl_{12}Nb_2O_8$: C, 29.08; H, 2.06; Cl (inorganic), 26.42. Found: C, 28.80; H, 2.17; Cl, 28.90. IR (solid state): ν = 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 (ν_{OH}) 1735 ($\nu_{C=O,acid,EACO2H}$) and 1642 cm^{-1} (δ_{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_2Cl_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}. ^1H NMR (CD_3CN): δ = 7.67-6.97 (m, arom CH); 6.54, 6.48 (br); 4.00, 3.80 (br, CH_2) ppm.

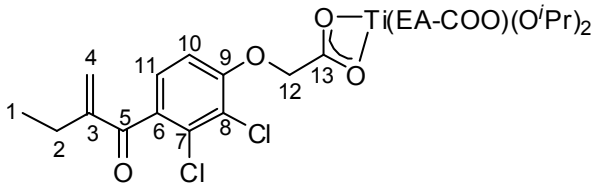
The reaction of $TiCl_4$ (1.00 mmol) with acetylsalicylic acid (1.00 mmol) was carried out by a procedure analogous to that described for $TiCl_4$/diclofenac, and a red solid was finally isolated (yield ca. 150 mg). IR (solid state, cm^{-1}): 1599s, 1575s, 1557m-s, 1489s, 1474s, 1442s, 1377vs, 1313m-s, 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_2O (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**: ethacrynic acid; from **3**:

ethacrynic acid; from $TiCl_4$/diclofenac: diclofenac; from $TiCl_4$/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 $Ti(O^iPr)_2(O_2C\text{-}EA)_2$, **4**.*



A solution of $Ti(O^iPr)_4$ (0.1 ml, 0.33 mmol) in $CHCl_3$ (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 $C_{38}H_{52}Cl_4O_{10}Ti$: 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 (ν_{as}COO), 1583vs, 1574m-sh, 1467s (ν_sCOO), 1455s, 1421s, 1383m, 1339m, 1286s, 1259vs, 1206s 1120m, 1076vs, 1001s, 938m, 894w, 800s, 755vs cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.13 (d, 1 H, $^3J_{HH}$ = 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 + OCHC*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$): 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 (OCH*C*H$_3$); 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 ωB97X [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 ωB97X 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.

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