Titanium-catalyzed esterification reactions: beyond Lewis acidity

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Esterification is a key reaction and is used in many synthetic and industrial processes, yet the detailed mechanism of operation of often-used (Lewis acid) catalysts is unknown and subject of little research. Here, we report on mechanistic studies of a titanium aminotriphenolate catalyst, using stoichiometric and catalytic reactions combined with kinetic data and density functional theory (DFT) calculations. While often only the Lewis acidity of the Ti-center is taken into account, we found that the amphoteric nature of this catalyst, combining this Lewis acidity with Brønsted basicity of a Ti-bound and in situ formed carboxylate group, is crucial for catalytic activity. Furthermore, hydrogen bonding interactions are essential to pre-organize substrates and to stabilize various intermediates and transition states and thus enhancing the overall catalytic reaction. These findings are not only applicable to this class of catalysts, but could be important for many other esterification catalysis.

Introduction

Esterification is one of the most important reactions in organic synthesis and widely applied in industry, ranging from the production of aspirin to polyesters.[1] Although the direct, uncatalyzed transformation of a carboxylic acid and an alcohol to an ester is possible, it requires temperatures up to 250°C to achieve full conversion under equilibrium conditions.[1]

As early as 1895, Fischer and Speier described the first catalytic esterification reaction using sulfuric acid as a strong Brønsted acid.[2] In general, for Brønsted acid catalyzed esterification the active species is the protonated carboxylic acid and nucleophilic attack by the alcohol and water formation are the rate limiting steps.[3] Despite being very effective esterification catalysts, strong Brønsted acids also give rise to unwanted side reactions such as the dehydrative esterification of alcohols. The activation of the carbonyl function of the carboxylic acid substrate and subsequent nucleophilic attack by the alcohol onto the electron-deficient carbonyl carbon can also be promoted by Lewis acidic metal ions (Scheme 1), which typically allow for milder reaction conditions and a wider substrate scope.[4–9] As such, recent developments in esterification catalysis have relied heavily on optimizing the Lewis acidity of the metal center.[10–14]

This does, however, not need to be the sole factor that controls activity, as mildly Lewis acidic metal alkoxides, carbamates, and oxides are also active esterification catalysts.[15,16] Mechanistic proposals that take other factors besides Lewis acidity into account are scarce. Hydrogen bonding interactions between the hydroxy group of the carboxylic acid and a Lewis basic oxygen bound to the metal center have been proposed, but only in a qualitative description of the reaction mechanism.[17–19] Titanium(IV) compounds, especially titanium alkoxides, are often employed as esterifica-

Scheme 1. Schematic representation for Lewis acid (LA) catalyzed esterification.
ion catalyst due to their inherent Lewis acidity and non-toxic nature.[20–23] Mechanistic insight into the role of these titanium derivatives is, however, hampered by the rapid uncontrolled exchange reactions with carboxylic acids, alcohols and esters (Figure 1).[24,25] In addition, facile hydrolysis leads to very complex reaction mixtures consisting of titanium dioxide, oxoalkoxides and oligomeric structures.[26–28] Here, we report a mechanistic investigation on the use of titanium aminotriphenolate complexes showing the amphoteric nature of the catalyst. Both the Lewis acidity and Brensted basicity are important for the overall performance in esterification reactions. The catalysts based on the tetradeutate aminotriphenolate ligands are robust, display remarkable stability to hydrolysis and are stable under acidic conditions.[29–32] This can be of importance for the application of these complexes, and the stability also allows the isolation of relevant reaction intermediates. The steric and electronic properties of the tetradentate aminotriphenolate ligand can be modified, making it a perfect platform for optimization of catalyst properties and a detailed mechanistic study (Figure 1).[33]

**Results and Discussion**

Aminotriphenols 1–5 (Scheme 2) are readily available via electrophilic aromatic substitution of the corresponding phenol with hexamethylenetetramine or reductive amination of the electrophilic aromatic substitution of the corresponding phenol molecule. The reaction of Ti(OPr)i4 with one equiv. of 1–5 yielded the mononuclear, C2-symmetric complexes 6–10.[34–36] Ligand exchange of the apical isopropoxide group is facile under acidic conditions.[37] Reaction of complex 6 with 20 equivalents of acetic acid resulted in complex 11, which was isolated as an orange powder. 1H NMR analysis revealed a sharp singlet corresponding to the six methylene hydrogens in the ligand framework, a broad singlet corresponding to six hydrogens of two acetate fragments and also a strongly deshielded signal at 14.5 ppm, integrating for one hydrogen (Figure S7). This indicates that besides apical exchange of the isopropoxide for an acetate ligand, an intact acetic acid molecule has also entered the coordination sphere of TiIV, resulting in an overall octahedral coordination. Upon addition of D2O to species 11, the strongly downfield signal disappeared, demonstrating facile exchange of the acidic hydrogen of acetic acid (Figure S8). The singlet for the methylene hydrogens is remarkable, as it reveals that the barrier for inversion of the rotor-shaped ligand is significantly lower than in complex 6.[37]

In addition, a variable temperature 1H NMR experiment further supported that both an acetate and an acetic acid group are coordinated to the titanium center: Six doublets corresponding to three different methylene groups are observed at –65 °C, indicating loss of C2 symmetry of this complex (Figure S11). Suitable crystals for single crystal X-ray diffraction were obtained via slow evaporation of a benzene solution of complex 11. The molecular structure (Figure 2) displays a slightly distorted octahedral complex with an O1–Ti–O2 angle of 98.13(5)°. The difference in C–O bond lengths of the two carboxylate moieties indicates coordination of both an acetate and an acetic acid group to titanium, with the proton (H1) sandwiched between both groups.

To demonstrate that the apical exchange of the isopropyl group is also possible for sterically less encumbered ligands, the unsubstituted complex 10 was treated with an excess of acetic acid. Attempts to isolate the newly formed complex proved to be cumbersome, but in situ formation of the acetic acid/acetate complex 12 was demonstrated by 1H NMR spectroscopy (Figure S12).

We studied the catalytic activity of complexes 6–10 (1 mol%) in a model esterification reaction between benzoic acid and heptanol in a 1:10 ratio (Table 1). An excess of the alcohol was used in order to drive the reaction to completion without the need for dehydrating agents or azeotropic distillation, and a reaction time of 6 h was used to enable the observation of distinct differences in catalytic activity. The uncatalyzed reaction hardly provided any heptylbenzoate (entry 1), while the presence of catalytic amounts of complexes 6–8 gave a moderate increase in the efficiency of the reaction.
(entries 2–4). The reaction with the sterically less hindered complexes 9–10 resulted in a further increase in yield (48% and 62%, entries 5 and 6), although they could not match the activity of Ti(OPr)₄ (79% yield, entry 7). The trend in activity for catalysts 6 (B > 6 > 7), related to the electronic properties of the phenox ligands (OMe > H > NO₂), suggesting that a more Lewis acidic titanium center leads to higher activity. In addition, the steric bulk in the ortho-position of the phenol motif of complexes 6 and 9 clearly impedes activity in catalysis (entries 2 and 5). In separate experiments complex 10 and Ti(OPr)₄ provided full conversion of benzoic acid after 24 h reaction time (> 99% yield of heptyl benzoate, Figure S1). Furthermore, the addition of molecular sieves as dehydrating agent had a marginal influence on the rate of formation of heptylbenzoate (Figure S1). To investigate the reaction mechanism underlying the titanium aminotriphenolate-catalyzed esterification, initial kinetic and stoichiometric experiments were performed. For complex 10 an order in catalyst of 0.80 was found in the concentration range 1.56 to 9.33 mM (0.25 to 1.5 mol%) (Figure S2, Table S1), which lends support to a mononuclear mechanism. The activation energy was experimentally determined via an Arrhenius plot of the different rates of the reaction between 150–180 °C (Figure S3, Table S2). We found an energy of 20.1 kcal mol⁻¹, which is in good agreement with other titanium based esterification catalysts.

In order to establish the resting state during catalysis, an aliquot was taken from the model esterification reaction catalyzed by complex 6 after 30 minutes reaction time, and studied with mass spectrometry. The two observed species have an experimental mass of 669.3291 m/z and 663.4111 m/z which correlates to complexes where the apical isopropoxide group is exchanged for a heptoxy or a benzoate group (Figure S22). To further deduce the exact structure of the resting state, complex 6 was treated with 10 equiv. of acetic acid and 100 equiv. of ethanol in toluene at 110 °C. After 24 h, at which point the reaction had not yet reached completion, the mixture was evaporated and complex 11 was isolated with only minor impurities, suggesting that in the resting state both a carboxylate and a carboxylic acid are coordinated to titanium.

To demonstrate the facile formation of the alkoxy-substituted complex, complex 11 was dissolved in an excess of dry ethanol and stirred for 15 min. at RT. After evaporation of the solvent the new complex 13 was isolated (Scheme 2), bearing an ethoxy group in the apical position, as determined by NMR spectroscopy and mass spectrometry. Given these results, we conclude that complex 11 is the resting state during catalysis, while complex 13 is the end-of-catalysis state when an excess of alcohol is used, and possibly also an off-cycle complex.

The reaction mechanism for the most active titanium aminotriphenolate complex 10 was further examined with DFT-D3 calculations at the BP86/TZ2P level of theory (Figure 3, see Supporting Information for other, energetically less favorable calculated reaction pathways (Figure S24). The reaction starts with the acetic acid/acetate complex A, which is an analogue of the well characterized complex 11, followed by transition state TS₁, involving a rotation of the acyclic carboxylic acid. Intermediate B is significantly higher in energy than complex A (ΔG = 7.6 kcal mol⁻¹), due to the loss of the favorable hydrogen bonding interaction between the acetic acid and the acetate group. Nucleophilic attack of the alcohol is facile with a ΔΔG of 6.9 kcal mol⁻¹ for TS₂. This step is favorable because the alcoholic hydrogen is hydrogen bonded to the acetate group that can also accept the proton and thus acts as an internal base. The combined action of a Brønsted basic acetate group and a Lewis acidic titanium center, results in overall amphoteric character for this catalyst. The beneficial effect of using an amphoteric catalyst for esterification reactions has already been observed for metal hydroxides and alkoxides in the 1960s, but is rarely mentioned in more recent studies. The next transition state, TS₃, involves a rotation which requires the cleavage of two hydrogen bonds, in order to pre-

Table 1. Catalyst screening in model esterification reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Complex</th>
<th>Conv. [%]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no cat.</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
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<td>4</td>
<td>8</td>
<td>19</td>
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<td>5</td>
<td>9</td>
<td>48</td>
<td>48</td>
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<tr>
<td>6</td>
<td>10</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>Ti(OPr)₄</td>
<td>79</td>
<td>79</td>
</tr>
</tbody>
</table>

[a] All reactions were performed with benzoic acid (5 mmol), heptanol (50 mmol), and Ti catalyst (1 mol%, 0.05 mmol), at 150 °C for 6 h. Yield and conversion were determined by GC analysis with pentadecane as internal standard.
organize intermediate E for water formation. The third transition state, TS_{EF}, concerns the actual cleavage of the carbon-hydroxyl oxygen bond in structure E in order to form the ester. Consecutive loss of water and the ester product results in an overall slightly exergonic process ($\Delta G = -2.0$ kcal mol$^{-1}$). The total energy profile shows that two transitions states (TS_{de} and TS_{EF}) are close in free energy (1.3 kcal mol$^{-1}$), showing that both these transitions state can be the rate determining transition state.

The optimized structures for the transition states TS_{de} and TS_{EF} reveal the presence of hydrogen bonding interactions (Figure 4). During TS_{de}, hydrogen bonds are formed between H$_A$ and O$_2$ of the ligand framework as well as between the acetic acid hydrogen (H$_B$) and O$_2$. These interactions pre-organize the complex for water formation (intermediate E) and are thus necessary to enhance the next step in the reaction, where water is expelled. Hydrogen bonding interactions between both water hydrogens (H$_A$ and H$_B$) and the ligand oxygen (O$_2$) and the substrate oxygen (O$_3$) respectively, remain in TS_{EF}, showing that these contribute to a lower energy of this rate determining transition state, thus enhancing the overall reaction rate.

Additional DFT calculations were performed to evaluate the catalytic activity of Ti complexes based on the C$_3$-symmetric tetradentate ligand with different para-substituents on the aromatic rings (Table 2). These calculations show that for the transition states TS_{CD}, TS_{DE} and TS_{EF} the relative barrier, $\Delta\Delta G^\ddagger$ (the free energy difference between the transition state and its preceding intermediate), is indeed lowered by an electron-withdrawing nitro-substituent (entry 1), which leads to a more Lewis acidic metal center. However, the effect of a para-substituent on the overall activation energy of the reaction is small, with only 0.6 kcal mol$^{-1}$ difference between the methoxy- or nitro-substituted versions and the unsubstituted ligand, thus showing that here the Lewis acidity of the metal center is only a minor factor to modulate the overall activation energy and reaction rate.

Based on these kinetic experiments and DFT calculations, we propose a catalytic cycle as depicted in Figure 3. In all geometries, including transition states, hydrogen bonding interactions are present between the ligand, the acetate/acetic acid group and the alcohol. Nucleophilic attack by the alcohol has a moderate energy barrier due to favorable preorganization of both the alcohol and the titanium-bound acetic acid via hydrogen bonding interactions with the acetate group and an oxygen of the ligand framework. As a result, proton transfer from the alcohol to the acetate group, which acts as a proton reservoir for water formation, is facile. TS_{de} is a rotation, which requires the breakage of a hydrogen bond, in order to have the adequate geometry for water formation. The subsequent carbon-oxygen bond breaking, TS_{EF}, therefore has a notably low

Table 2. Influence of the para-substituent of the ligand on the relative barrier and the overall barrier of transition states TS_{CD}, TS_{DE}, TS_{EF}, and TS_{EF}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Para-substituent</th>
<th>$\Delta\Delta G^\ddagger$</th>
<th>$\Delta G^\ddagger$</th>
<th>$\Delta\Delta G^\ddagger$</th>
<th>$\Delta G^\ddagger$</th>
<th>$\Delta\Delta G^\ddagger$</th>
<th>$\Delta G^\ddagger$</th>
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<tr>
<td>1</td>
<td>$\text{NO}_2$</td>
<td>6.1</td>
<td>16.4</td>
<td>5.1</td>
<td>21.2</td>
<td>3.5</td>
<td>22.6</td>
</tr>
<tr>
<td>2</td>
<td>$\text{H}$</td>
<td>6.8</td>
<td>16.8</td>
<td>5.3</td>
<td>21.9</td>
<td>3.7</td>
<td>23.2</td>
</tr>
<tr>
<td>3</td>
<td>$\text{OMe}$</td>
<td>7.5</td>
<td>16.1</td>
<td>6.1</td>
<td>22.6</td>
<td>4.0</td>
<td>22.6</td>
</tr>
</tbody>
</table>

(a) Values are given in kcal mol$^{-1}$.  

Figure 3. Proposed reaction pathway for the esterification reaction catalyzed by complex 10 (in the catalytic cycle hydrogen bonds are indicated with black dashed lines).

Figure 4. Calculated transition states TS_{de} and TS_{EF} (optimized with DFT-D3 at the BP86/def-TZ2P level of theory) and ChemDraw representations thereof. All hydrogen atoms have been omitted for clarity (except hydrogens A and B involved in hydrogen bonds, indicated with black dashed lines).
barrier for a bond-breaking step. Overall, this mechanism shows that there are three essential prerequisites for an active catalyst: Lewis acidity of the Ti metal, favorable hydrogen bonding interactions between both reactants and the ligand, and a Brønsted basic group to facilitate proton transfer. This is in strong contrast with the common assumption that the Lewis acidity of the metal is the sole crucial (rate determining) factor for catalytic activity. The generality of our findings is demonstrated by the fact of many esterification catalysts under reaction conditions. The acidic reaction medium results in ligand exchange reactions, leading to the in situ formation of amphoteric metal carboxylates,[24] which could well have a similar mode of operation as the titanium aminotriphenolates presented in this study.

Conclusion

In summary, we have shown that the amphoteric nature of Ti-aminotriphenolate complexes, combining a Lewis acidic metal center with a Brønsted basic ligand site, in combination with preorganization via hydrogen bonding interactions, is essential for the catalytic activity of titanium aminotriphenolate complexes in the esterification reaction. Experimental and computational findings demonstrate that Lewis acidity is not the only key factor for catalytic activity, contrary to what often is assumed in literature. DFT calculations support favorable preorganization via hydrogen bonding interactions with the ligand and elucidate the role of the additional acetate group as internal base. This acetate group enhances the nucleophilicity of the alcohol and subsequently stores the proton of the alcohol, which later on in the reaction is expelled in the form of water. We believe that these insights do not only apply to this particular class of titanium complexes, but are also important for other esterification catalysts, including often-used titanium alkoxides, and as such can help the rational design of new catalysts for esterification reactions.

Experimental Section

General Experimental Details

Dichloromethane and acetonitrile were distilled from CaH2, n-pentane and Et2O from sodium/benzophenone and toluene from sodium under argon atmosphere. Ethanol was degassed and dried over 3 Å molecular sieves. All other chemicals were obtained from Merck or Fluorochem and were used without further purification. All air-sensitive materials were manipulated using standard Schlenk techniques or by the use of an argon-filled glovebox (MBraun Unilab). The NMR solvents CDCl3, toluene-d8, and CD3OD were dried over molecular sieves and degassed via three cycles of freeze-pump-thaw.1H and 13C NMR spectra were recorded on a 300 or 400 MHz Bruker AVANCE spectrometer. Spectra were referenced against residual solvent signal. FD-MS spectra were recorded on an AccuTOF GC v 4 g, JMS-T100GCV Mass spectrometer (JEOL, Japan) equipped with a Carbotec emitter. A typical current rate of 51.2 mA min–1 over 1.2 min and a flashing current 40 mA on every spectra of 30 ms was used. High resolution ESI-MS spectra were recorded on a JEOL AccuTOF LC-Plus JMS-T100LP spectrometer in CH3CN. IR spectra were recorded on a Bruker Alpha FTIR machine. GC analysis for heptylbenzoate and benzoic acid was performed on a Thermo Scientific Trace GC Ultra equipped with a Restek Stabilwax-DA column (30 m x 0.25 mm x 0.25 μm). Temperature program: initial temperature 50 °C, heat to 200 °C with 20 °C min–1, hold for 10 min, heat to 250 °C with 50 °C min–1, hold for 3 minutes. Inlet temperature 250 °C, split ratio of 30, 1.0 mL min–1 helium flow, FID temperature 250 °C. Esterification reactions were performed in a Radley Discoveries 12 plus reaction station allowing a maximum of 12 simultaneous reactions under a nitrogen atmosphere.

Single crystal X-ray diffraction

X-ray Crystal Structure Determination of complex 11: X-ray intensities were measured on a Bruker D8 Quest Eco diffractometer equipped with a Triumph monochromator (λ = 0.71073 Å) and a CMOS Photon 100 detector at a temperature of 150(2) K. Intensity data were integrated with the Bruker APEX3 software.[43] Absorption correction and scaling was performed with SADABS.[44] The structures were solved using intrinsic phasing with the program SHELXT.[45] Least-squares refinement was performed with SHELXL-2014[46] against F2 of all reflections. Non-hydrogen atoms were refined with anisotropic displacement parameters. The H atoms were placed at calculated positions using the instructions AFIX 13, AFIK 43 or AFIK 137 with isotropic displacement parameters having values 1.2 or 1.5 times Ueq of the attached C atoms. CCDC 1941519 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational details

Geometry optimizations were carried out with the Amsterdam Density Functional (ADF) program package using version 2017.2.01.[40,41] We used the BP86 functional in combination with the TZ2P basis set and a large frozen core.[42,43] Grimme’s dispersion corrections (version 3, disp3) were used to include Van der Waals interactions.[10] All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by calculating the Hessian matrix. ZPE and gas-phase thermal corrections (enthalpy, 298 K) from these analyses were calculated.

Synthesis and catalysis

The triphenolamines 1–5 and titanium complexes 6–10 were synthesized via literature procedures.[14–17]

Complex 7

Under nitrogen atmosphere ligand 2 (100 mg, 0.16 mmol) was dissolved in 10 mL dry Et2O. This solution was slowly added to Ti(OMe)4 (46 μL, 0.16 mmol) in 5 mL dry Et2O. The reaction mixture immediately changed to orange and over a period of 12 h a pale yellow precipitate formed. After filtration the solid material was dissolved in a minimum amount of DCM and precipitated with Et2O (15 mL). Subsequent filtration afforded complex 7 (76 mg, 64 %). 1H NMR (300 MHz, CDCl3): δ 8.19 (d, J = 2.8 Hz, 3H, H2a), 8.01 (d, J = 2.8 Hz, 3H, H2b), 3.58 (br s, 6H, NC6H5), 1.58 (d, J = 6.2 Hz, 6H, OCH3), 1.51 (s, 27H, Tbu), the OCH3(CH3)2 proton overlaps with the solvent peak (δ 5.32). 13C NMR (300 MHz, CDCl3): δ 83.2 (d, J = 2.8 Hz, 3H, H2b), 7.77 (d, J = 2.7 Hz, 3H, H1a), 5.18 (s, J = 6.0 Hz, 1H, OCH (CH3)2), 2.88 (br s, 3H, NCH3), 2.19 (br s, 3H, NCH3), 1.47 (d, J = 6.1 Hz, 6H, OCH3(CH3)2), 1.35 (s, 27H, Tbu). 11C NMR (100 MHz, CDCl3): δ 167.20
Complex 11

Under nitrogen atmosphere Complex 6 (100 mg, 0.165 mmol) was dissolved in 5 mL dry toluene and 20 equivalents of acetic acid (188 μL, 3.29 mmol) were added dropwise to give an orange reaction mixture. After stirring at room temperature for 10 min the solvent was removed in vacuo. The remaining orange powder was triturated three times with 10 mL dry acetonitrile and dried under nitrogen atmosphere to give a yellow suspension after 30 minutes of stirring at room temperature. Removal of ethanol and acetic acid group were not observed due to their fluxional character. Procedure for esterification of benzoic acid and heptanol

In a carousel reaction station under a nitrogen atmosphere benzoic acid (610.6 mg, 5 mmol) was dissolved in heptanol (7.14 mL, 50 mmol). The catalyst (1 mol%) was added as a powder, except from Ti(OTf)4 and pentadecane (0.41 mL, 1.5 mmol) as internal standard. The reaction mixture was heated up to 150 °C. After 6 h the conversion and yield were determined with GC analysis via the integration of the peak area of benzoic acid and heptyl benzoate. In order to achieve full conversion the reaction time was extended to 24 h for a selection of catalysts. The effect of a dehydrating agent was studied via the addition of 1 g of activated powder molecular sieves (4 Å).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Homogeneous Catalysis · Esterification · Titanium · Amphoteric · Hydrogen bonding interactions

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Given the catalyst order of 0.8, we believe that the system is primarily catalyzed by mononuclear titanium complexes, although a minor contribution of dimeric species that dissociate during the rate-determining step, lowering the reaction order, cannot be excluded. In addition, the order in carboxylic acid and alcohol are outside the scope of this research, since the very high concentrations of both reactants makes order determination cumbersome. Moreover, a considerable Brønsted acid-catalyzed (background) reaction also takes place, making both reactant orders non-informative for the titanium-catalyzed reaction, see reference (34).

For all octahedral complexes with a carboxylate and a carboxylic acid group coordinated to titanium, the carboxylic acid group was not observed with mass spectrometry.


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Bruker APEX2 software, 2016.

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