

# Probing the Mechanism of the Petasis Olefination Reaction by Atmospheric Pressure Chemical Ionization Mass and Tandem Mass Spectrometry

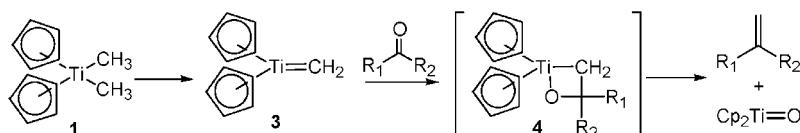
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Received December 9, 2002

## ABSTRACT



Atmospheric pressure chemical ionization mass (APCI-MS) and tandem mass spectrometry (APCI-MS/MS) is used to probe the mechanism of the Petasis olefination reaction. Oxatitanacyclo intermediates **4** were transferred from solution to the gas phase, detected as  $4\text{H}^+$  by APCI-MS with characteristic Ti-isotopic patterns, and structurally characterized by APCI-MS/MS. Detection of  $4\text{H}^+$ , which upon collision activation dissociates to both  $3\text{H}^+$  and  $\text{Cp}_2\text{TiOH}^+$ , fully supports the Hughes mechanism as depicted above.

Several efficient strategies using titanium-based organometallic reagents are available for the olefination of esters, ketones, and amides, such as that which uses Tebbe's reagent derived from titanocene dichloride and  $\text{Me}_3\text{Al}^1$  and the Grubbs' titanocyclobutane modification derived from Tebbe's reagent and olefins.<sup>2</sup> Petasis<sup>3</sup> conceived, however, an attractive and more practical strategy for the titanium-mediated olefination of carbonyl compounds based on the titanium complex  $\text{Cp}_2\text{TiMe}_2$  (**1**). The Petasis reaction using **1** is attractive because it avoids the difficulties of handling organoaluminum compounds whereas Petasis reagent **1** is nonpyrophoric and stable to air and water and, therefore, much easier to handle as compared with Tebbe's and Grubbs

reagents. Additionally, benzyldiene and trimethylsilylmethylene transfer is possible with Petasis reagent **1** while Tebbe's reagent is restricted to simple methylene groups.<sup>4</sup>

Different mechanisms have been proposed for olefinations with Tebbe and Grubbs reagents.<sup>5</sup> Petasis<sup>4</sup> proposed that the reactions involving **1** proceed by methyl transfer via the acyclic intermediate **2** (Scheme 1). The Petasis mechanism was contested, however, by Hughes<sup>6</sup> who, based on kinetic and labeling studies, proposed that olefination of esters using **1** is intermediated by the titanium carbene **3** and the oxatitanacyclo **4** (Scheme 1). From quantitative data gathered from thermal decomposition of methyltitanium(IV) derivatives, the participation of free radicals has been ruled out,<sup>7</sup> at least in noncoordinating solvents.<sup>8</sup>

Decomposition of organotitanium compounds that bear no hydrogen atoms in the organyl group  $\beta$ -position is initiated

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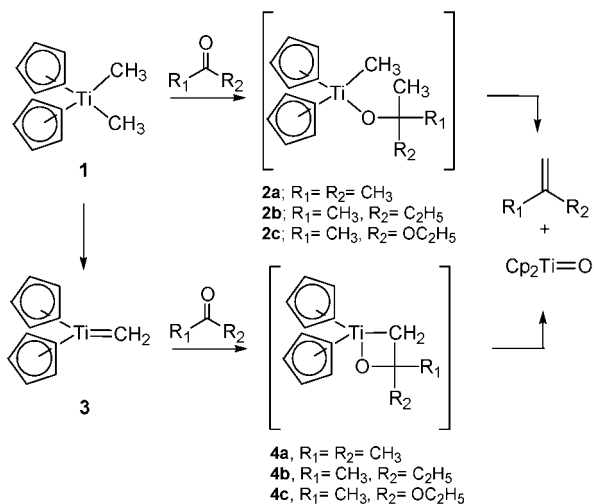
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Scheme 1



by intramolecular  $\alpha$ -hydrogen abstraction from the alkyl group to afford the corresponding alkylidene titanium species.<sup>7f,9</sup> The agostic interactions between titanium and the C $\alpha$ -H bond may assist  $\alpha$ -elimination, which possibly proceeds either via a 1,2-hydrogen shift to the metal atom to form a hydridotitanium species or in a concerted manner via a four-center transition state with direct elimination of an alkane molecule.<sup>8</sup> An analogy between  $\alpha$ -agostic interactions and hyperconjugative stabilization of carbenium ions by  $\beta$ -hydrogen has been proposed<sup>8,10</sup> and used to explain the kinetic isotope effects observed in olefin insertion reactions involving metallocene-*d*<sub>0</sub> complexes.<sup>8</sup>

The methylenetitanocene intermediate **3** has never been isolated,<sup>11</sup> but its phosphine complex is known and has been spectroscopically characterized.<sup>12</sup> According to theoretical considerations, **3** is a 16-electron species with an empty orbital on titanium lying in the plane bisecting the Cp-Ti-Cp bond angle. Any ligand with nonbonding electrons, such as a carbonyl group, may coordinate to **1**, thus affording **2a-c** (Scheme 1).<sup>13</sup>

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Atmospheric pressure ionization (API) techniques such as electrospray (ESI)<sup>14</sup> and atmospheric pressure photon (APPI)<sup>15</sup> and chemical ionization (APCI)<sup>16</sup> have revolutionized the way molecules are ionized and transfer to mass spectrometers for mass and structural analysis and have greatly expanded the applicability of mass spectrometry for a variety of new classes of molecules including amino acids, proteins, sugars, oligonucleotides, salts, and inorganic and organometallic compounds. Such new MS techniques are also beginning to be used to probe mechanisms of reactions of fundamental importance and practical applications.<sup>17</sup> In this study, we use APCI and both mass (MS) and tandem mass spectrometry (MS/MS) to transfer the Petasis reaction intermediates directly from solution to the gas phase. Then, for the first time, these intermediates were intercepted, isolated, detected, and then structurally characterized. The results support the mechanism of the titanium-mediated Petasis olefination of carbonyl compounds as proposed by Hughes.<sup>6</sup>

Acetone, 2-butanone, and ethyl acetate were commercially available whereas the Petasis reagent was prepared according to literature procedure.<sup>4</sup> All the chemicals used were of HPLC grade. The water was purified in a Milli-Q water purification system. The Petasis reagent **1** (20  $\mu\text{g/mL}$ ) was dissolved directly in the reactant carbonyl compounds. A microsyringe pump was used to deliver the reagent solution to the APCI source at flow rates of 0.01 mL/min. The mass spectrometer was a high-resolution (7.000) hybrid double quadrupole (Qq) and orthogonal time-of-flight (Tof) mass spectrometer (Qtof, Micromass UK). The temperature of the nebulizer was 50 °C. The mass spectrometer was operated in the positive-ion mode using APCI pin potential of +3500 V for the corona discharge. The cone and extractor potential were set to 30 and 0 V, respectively. The scan range was  $m/z$  50–1000.

Tandem mass spectrometric (MS/MS) experiments were performed using the product ion scan mode via Q1 mass-selection of the desirable product ion, q2 collision-induced dissociation (CID) with N<sub>2</sub>, and orthogonal Tof mass analysis of the CID ionic fragments. The collision energy ranged from 5 to 25 eV, depending on the dissociation lability of the precursor ion.

The Petasis reactions were performed by dissolving Cp<sub>2</sub>TiMe<sub>2</sub> (**1**) directly into the pure carbonyl compounds

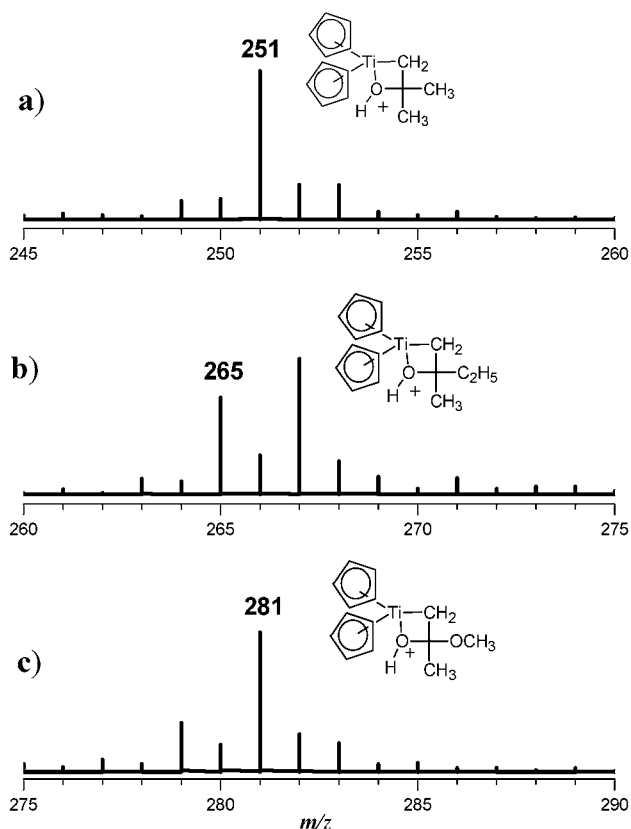
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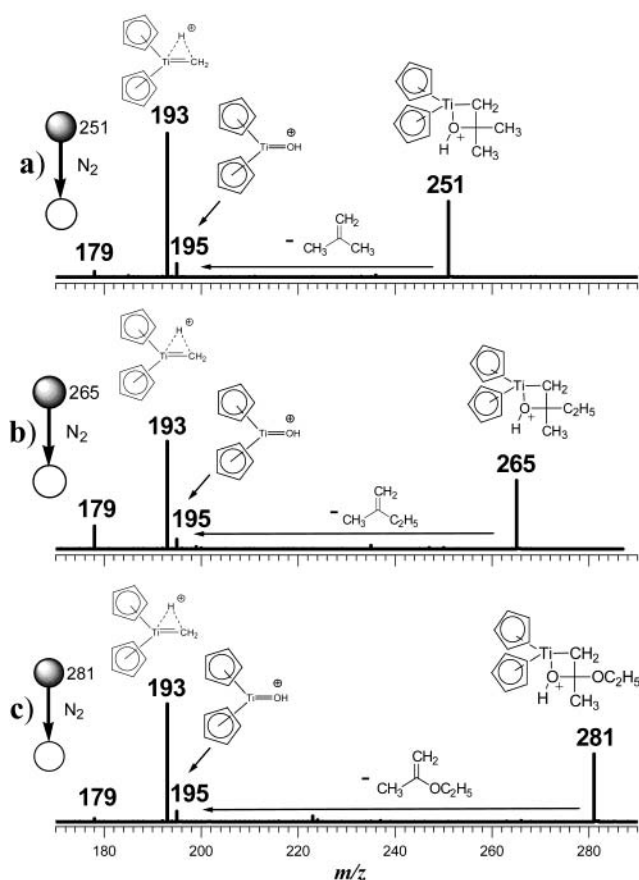
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**Figure 1.** APCI-MS partial mass spectrum for the Petasis reaction of **1** with (a) acetone, (b) 2-butanone, and (c) ethyl acetate.

(acetone, 2-butanone, and ethyl acetate) and then by spraying the solution through the heated APCI source. No solvents were used so as to concentrate possible transient intermediates, particularly **2** or **4**, or both, conceivably present in the reaction mixture in very low concentrations. In APCI, neutral molecules are transferred from the solution of the drying spray droplets to the gas phase, where these molecules are ionized at atmospheric pressure via either electron abstraction, protonation, or deprotonation promoted by a series of ion–molecule reactions initiated by the action of a corona discharge ( $\sim 3500$  V). Therefore, the mass spectrometric detection is expected to closely reflect the solution composition. Moreover, the metal coordination spheres are also expected to be fully preserved. Reagents, intermediates, and products present in solution should therefore all be transferred directly to the gas phase and then ionized and mass analyzed. As the postulated intermediates in both mechanisms (Scheme 1) have basic sites (oxygen), we selected the positive mode of ion detection to monitor protonated molecules,  $\text{MH}^+$ , formed in the gas phase.

The Hughes mechanism for Petasis  $\text{Cp}_2\text{TiMe}_2$  (**1**) olefination postulates that the titanocene intermediate **3** participates, which would react with acetone, 2-butanone, and ethyl acetate to form the oxatitanacycle intermediates **4a–c** (Scheme 1). Because titanium displays five isotopes,  $^{46}\text{Ti}$  (8.0%),  $^{47}\text{Ti}$  (7.3),  $^{48}\text{Ti}$  (73.8),  $^{49}\text{Ti}$  (5.5), and  $^{50}\text{Ti}$  (5.4), the



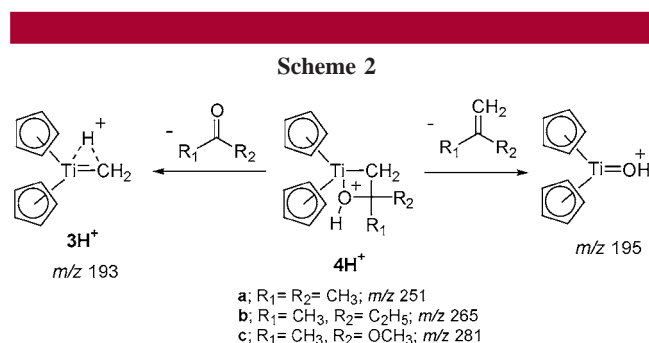
**Figure 2.** APCI-MS/MS mass spectra for low energy (near 15 eV) collision-induced dissociation of the mass-selected gaseous intermediates  $4\mathbf{a}\text{-cH}^+$  of the Petasis reaction of **1** with (a) acetone, (b) 2-butanone, and (c) ethyl acetate. Note that the relative abundance of  $\text{Cp}_2\text{TiOH}^+$  of  $m/z$  195 (a minor fragment at 15 eV) increases substantially at higher collision energies and that the ions of  $m/z$  193 and 195 are formed at nearly equal abundances at 60 eV collisions.

protonated intermediates  $4\mathbf{H}^+$  should be mass detected as clusters of isotopomeric ions centered (for the most abundant  $^{48}\text{Ti}$  isotope) at  $m/z$  251 (**4a**), 265 (**4b**), and 281 (**4c**). Alternatively, the mechanism proposed by Petasis<sup>4</sup> assumes the intermediacy of the oxytitanium **2**, which in the reaction with acetone, 2-butanone, and ethyl acetate should be detected in their protonated forms  $2\mathbf{H}^+$  as clusters of isotopomeric ions centered (for  $^{48}\text{Ti}$ ) at  $m/z$  267 (**2a**),  $m/z$  281 (**2b**), and  $m/z$  297 (**2c**).

APCI monitoring of the Petasis reaction of **1** detects ionic clusters centered at  $m/z$  251 ( $4\mathbf{aH}^+$ ) for acetone (Figure 1a), at  $m/z$  265 ( $4\mathbf{bH}^+$ ) for 2-butanone, and at  $m/z$  281 ( $4\mathbf{cH}^+$ ) for ethyl acetate. These ions are likely the protonated oxatitanacycle intermediates  $4\mathbf{H}^+$  postulated in the Hughes mechanism. Note that this assignment is based on both the  $m/z$  ratios and the characteristic Ti-isotopic patterns of the protonated oxatitanacycle intermediates  $4\mathbf{H}^+$ , which nicely fit the five-component theoretical isotopic patterns predict for such Ti-containing ions.<sup>18</sup> In contrast, no ionic clusters centered at  $m/z$  267, 281, and 297 expected for the protonated

intermediates  $2\text{H}^+$  of the mechanism proposed by Petasis were detected.

To structurally characterize the protonated oxatitanacycle intermediates  $4\text{H}^+$  via CID, MS/MS experiments were performed (Figure 2). The tandem mass spectrum of Figure 2a shows for  $4\text{aH}^+$  of  $m/z$  251 a predictable and highly structurally diagnostic gas-phase dissociation behavior which, interestingly, closely matches the solution equilibrium involving reagents and products of the Petasis reaction. The oxatitanacycle  $4\text{aH}^+$  loses neutral 2-methylpropene (the major olefinic product expected for the Petasis reaction), thus forming the protonated Ti-complex of  $m/z$  195 (Scheme 2).



Additionally,  $4\text{aH}^+$  also dissociates to the protonated methylenetitanocene intermediate  $3\text{H}^+$  of  $m/z$  193 via retro-addition. Similar CID behavior is observed for  $4\text{bH}^+$  ( $m/z$  265, Figure 2b) and  $4\text{cH}^+$  ( $m/z$  281, Figure 2c), that is, dissociation by both the loss of the neutral carbonyl compound and the corresponding neutral olefin to form the respective fragment ions of  $m/z$  195 and 193 (Scheme 2). The additional, and minor, fragment ion of  $m/z$  179 corresponds to  $\text{Cp}_2\text{TiH}^+$ . This characteristic CID behavior provides therefore secure structural characterization of intermediates  $4\text{a-cH}^+$ . Additionally, increasing the collision energy for dissociation of all three protonated intermediates  $4\text{H}^+$  increases substantially the relative abundance of  $m/z$  195 (a minor fragment ion at low energy collisions, Figure 2), hence favoring the Petassis olefination route (Scheme 2).<sup>19</sup> Another analogy to the solution behavior is therefore observed as higher collision energy increases the internal

(18) Note that the disturbed isotopic pattern observed for  $4\text{bH}^+$  is likely due to an interference ion of  $m/z$  267, an effect hard to avoid for such low abundance, transient intermediates.

energy of the dissociating ion thus favoring the olefination product by increasing<sup>4</sup> the (effective) temperature of the gas-phase intermediates  $4\text{H}^+$ . In solution, higher temperatures also favor the Petassis olefination products.<sup>3</sup>

In conclusion, the APCI-MS and APCI-MS/MS experiments described herein have proved the mechanism of the Petasis olefination reaction by mass spectrometric characterization of its key oxatitanacycle reaction intermediates **4**. The neutral **4** for the reaction of the Petasis reagent **1** with acetone, 2-butanone, and ethyl acetate have been transferred to the gas phase, ionized by protonation, isolated by mass selection, and for the first time detected and then structurally characterized by MS and MS/MS experiments. Mass detection of  $4\text{H}^+$ , which upon collision activation dissociate to both the protonated methylenetitanocene  $3\text{H}^+$  and  $\text{Cp}_2\text{TiOH}^+$  (together with the neutral olefin, that is, the two final Petassis olefination products), fully supports the mechanism proposed by Hughes for the Petasis reaction (Schemes 1 and 2). Intermediates  $4\text{H}^+$  display characteristic Ti-isotopic patterns and collision-induced dissociation behavior analogous to the reagent-product equilibrium expected to operate in solution.

This work on the Petassis reaction illustrates the suitability of API-MS<sup>n</sup> techniques to isolate and characterize key but transient organometallic reaction intermediates which are directly transferred from solution to the gas phase,<sup>17b</sup> a vast but still little explored field.<sup>20</sup> Similar application of modern MS techniques is likely to find broad use in organic<sup>21</sup> and organometallic chemistry,<sup>22</sup> probing many of its reaction and catalysis mechanisms.

**Acknowledgment.** This work has been supported by the São Paulo State Research Foundation (FAPESP) and the Brazilian National Research Council (CNPq).

OL027439B

(19) Dissociation of  $4\text{H}^+$  to  $\text{Cp}_2\text{TiOH}^+$ , much more pronounced at higher collision energies, seems to eliminate an alternative route to formation of these ions via gas-phase  $R_1R_2\text{CO}$  coordination to  $\text{Cp}_2\text{TiCH}_3^+$ .

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