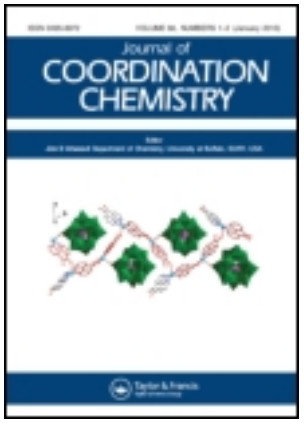

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

A density functional study of the relative stability of intermediates in a McMurry coupling reaction

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Published online: 02 Apr 2012.

To cite this article: Andrew J. Livingston, Harriet A. Lindsay & Maria Clelia Milletti (2012) A density functional study of the relative stability of intermediates in a McMurry coupling reaction, Journal of Coordination Chemistry, 65:9, 1484-1492, DOI: 10.1080/00958972.2012.674113

To link to this article: http://dx.doi.org/10.1080/00958972.2012.674113

Journal of Coordination Chemistry
Vol. 65, No. 9, 10 May 2012, 1484–1492

A density functional study of the relative stability of intermediates in a McMurry coupling reaction

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(*Received 21 December 2011; in final form 28 February 2012*)

The intramolecular McMurry reaction is a relatively common method for assembling carbocycles in organic synthesis. Most typically, this reaction involves a reductive coupling mediated by Ti(II). However, there are few examples of intramolecular McMurry reactions in the presence of Lewis basic heteroatoms. In this work, we investigate the titanium-mediated McMurry coupling leading to a pyrrolidine methoxy keto ester. Specifically, we compare the relative energies of all possible reaction intermediates at the B3LYP/6-31G level of theory. The most stable intermediate is found to be the one resulting from deoxygenation of the α-methoxy ketone. The McMurry product is not predicted to form.

Keywords: McMurry coupling; Pyrrolidine keto ester; Density functional; Titanium

1. Introduction

Pyrrolizidine alkaloids are a very large class of secondary metabolites that are found exclusively in flowering plants [1]. Over 600 members of this class have been identified from more than 6000 plant species [1b]. While some pyrrolizidine alkaloids have exhibited potential therapeutic glycosidase inhibition [1a, c], others have shown potent toxicity [1b], which is thought to be a form of plant predation deterrence [1b].

Hydroxylated pyrrolizidine alkaloids [1c] have garnered significant interest from synthetic chemists because of their ability to inhibit glycosidases. For example, australine (**1**), isolated from *Castenospermine austral* [2], inhibits α-amyloglucosidase, and glycoprotein processing [3]. In addition, it has shown anti-HIV activity [4]. Casuarine (**2**), which has been isolated from both *Casuarina equisetifolia* and *Eugenia jambolana*, has shown potential for the treatment of breast cancer, bacterial infections,

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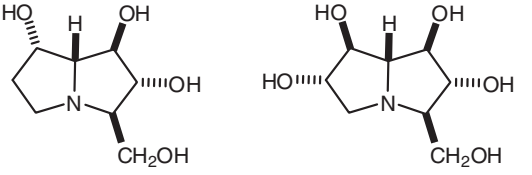
Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online
http://dx.doi.org/10.1080/00958972.2012.674113

and diabetes [5].



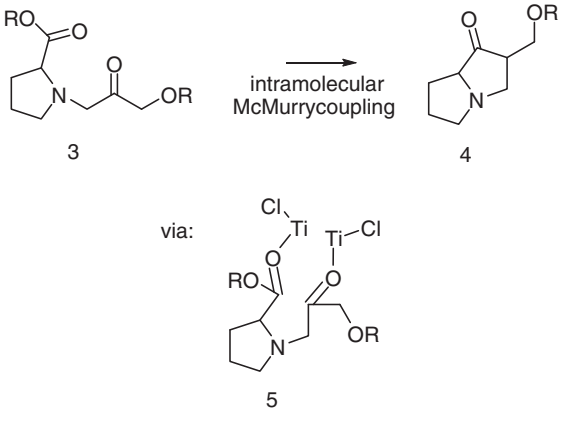
australine (1) casuarine (2)

As part of our ongoing efforts directed toward the syntheses of these and related classes of natural products, we required a reductive cyclization of keto ester (**3**) to generate the functionalizable methoxy alkyl pyrrolizidinone (**4**). We envisioned that this might be accomplished *via* an intramolecular McMurry coupling [6]. However, we were concerned about the viability of this strategy for keto ester (**3**) given its multiple Lewis basic sites present in the substrate and the pronounced affinity of low-valent titanium for oxygen. Indeed, few examples of successful titanium(II)-mediated reductive couplings in the presence of additional Lewis basic sites appear in the literature [7] (cf intermediate **5**, scheme 1).

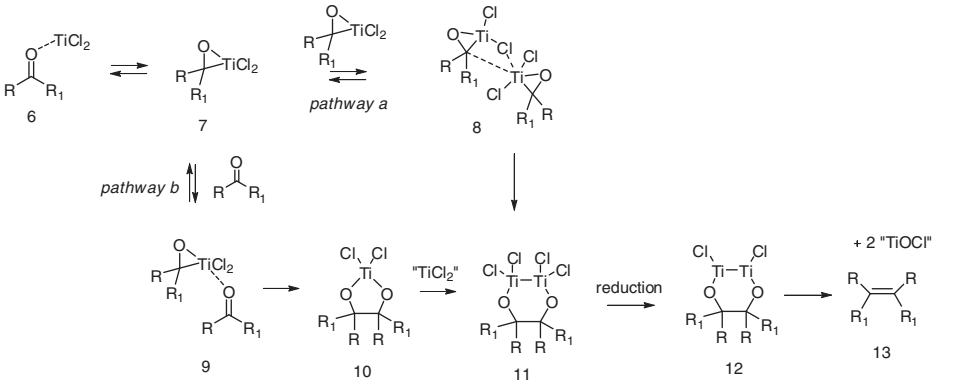
Here, we describe a computational analysis of a portion of the titanium(II)-mediated cyclization reaction of keto-ester ligand **5** to determine whether intermediate **5**, required for formation of pyrrolizidinone (**4**), is energetically favored. Specifically, we will focus on this intermediate since its formation is required regardless of the mechanistic pathway of the McMurry reaction (*vide infra*).

Intramolecular McMurry coupling reactions have seen significant use in organic synthesis because they are an efficient method of generating medium-to-large cycloalkanes and cycloalkenes [6]. However, theoretical and experimental mechanistic investigations have thus far focused on intermolecular reductive coupling reactions, and have been further limited to those involving ketones and aldehydes.

Earlier theoretical work has shed light on the nature of the intermediate species. Frenking modeled the McMurry reaction between two molecules of formaldehyde by comparing the two pathways shown in scheme 2 [8]. Both pathways begin with the



Scheme 1. Intramolecular McMurry coupling of keto ester (**3**) leading to pyrrolizidinone (**4**).



Scheme 2. Two possible pathways for the McMurry reaction leading to the formation of an alkene.

formation of a η^1 complex **6** between Ti(II) and a carbonyl compound. This complex then forms η^2 titanaoxacyclopropane (**7**). Experimental evidence has been found for the existence of these η^2 intermediates in the McMurry sequence [6c]. In pathway a, coordination of a second titanaoxacyclopropane results in **8**, which undergoes C–C bond formation to produce titanium pinacolate (**11**). By contrast, in pathway b, a second carbonyl coordinates to the titanaoxacyclopropane to form **9**, which undergoes a similar C–C bond formation to form titanium pinacolate (**11**). Reduction and elimination lead to alkene (**13**). According to Frenking's calculations, both pathways a and b are energetically accessible.

As **11** (scheme 2) is required for both pathways a and b, and because of our concern that other Lewis acids present in our McMurry precursors might form more stable complexes, we focus our efforts on determining the relative energies of productive *versus* nonproductive coordination complexes required for intramolecular McMurry reaction of keto-esters. This work complements existing theoretical studies in that it represents the first computational examination of intramolecular McMurry reactions and the first examination of keto-ester couplings [8].

2. Details of the calculations

The Gaussian 03 suite of programs was used to perform all density functional calculations [9]. Structures were optimized to a minimum using the Berny algorithm; force constants and resulting vibrational frequencies were computed analytically [10]. For both the capnellene and pyrrolidine systems, we constructed all possible metallacyclic intermediates by attaching one titanium in the dimer to one of the three electronegative atoms in the pyrrolidine keto-ester ligand. We ensured that the bond lengths in the metallacycle of these initial structures conformed as much as possible to those calculated by Frenking for the optimized pinacolate intermediate complex of CH_2O and $TiCl_2$ [8]. We performed the optimization and frequency calculations using

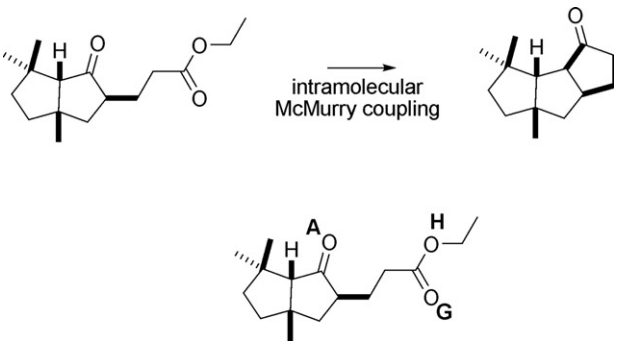


Figure 1. The McMurry coupling precursor for the synthesis of capnellene shown below the relevant reductive coupling [14]. Electronegative atoms where Ti centers can bond are labeled on the precursor.

spin-unrestricted B3LYP hybrid functionals and the 6-31G basis set [11, 12]. Analyses of the electron density distributions were done using the Mulliken approximation [13].

3. Results and discussion

3.1. *McMurry cyclization of a keto ester*

The general approach used in determining whether the coordination complex required for the keto-ester McMurry cyclization is most energetically favored is to consider all possible intermediates and compare their relative energies.† To validate this approach, we first test it on a system that is known to undergo keto-ester McMurry cyclization. Oda *et al*. [14] used such a reductive coupling as a key step in the synthesis of capnellene, a sesquiterpene natural product. For this keto-ester, there are three possible coordination complexes where each titanium in the dimer is coordinated to one of the three oxygen atoms in the ligand, labeled A, G, and H in figure 1. Geometry optimization calculations on all three intermediates resulted in the formation of the desired McMurry product only in the case where Ti initially bonded at the A and G positions. Figure 2 shows the optimized structure of this intermediate. Note that the Ti dimer optimized such that there is no bond between the two titaniums; rather, they are bridged by chlorides. Other investigators have noted bridging chloride in titanium complexes. Frenking *et al*. [8] found that a single chloride bridged the titanium centers in the intermediate of their model system. Titanium cluster compounds with bridging chlorides have also been confirmed experimentally. Cotton *et al*. [6c, 15] isolated $[Ti(\mu\text{-}Cl)Cl(dmpe)]_3$ in which three chlorides bridge three titanium centers; polymer-like chains containing a repeated structure in which two chlorides bridge two titaniums have also been observed.

† A note about nomenclature: we label intermediates based on the ligand atoms bonding in the initial, pre-optimization structure. Intermediates are labeled [X,Y] to indicate that the titanium centers are bonded to atoms X and Y on the keto-ester.

In addition to being the only intermediate leading to the McMurry product, [A,G] is also the most stable configuration, as the other two lead to optimized structures that are 22 kcal mol^{-1} ([G,H]) and 61 kcal mol^{-1} ([A,H]) higher in energy. Additionally, the optimized bond lengths in the [A,G] metallacycle are very similar to those found by Frenking for the pinacolate intermediate complex formed from two equivalents of CH_2O and two equivalents of $TiCl_2$ [8]. We conclude that the computational approach we have chosen leads to the correct structure for the McMurry intermediate in the case of the capnellene precursor and can therefore be applied to the pyrrolidine keto ester system of interest.

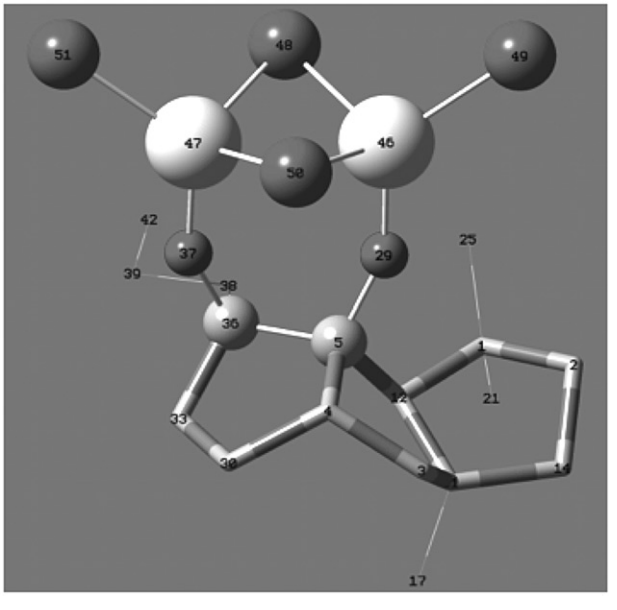


Figure 2. Optimized structure of the [A,G] capnellene intermediate. Atoms 29 and 37 are labeled A and G, respectively, in figure 1. Atoms 46 and 47 are Ti; atoms 48–51 are Cl.

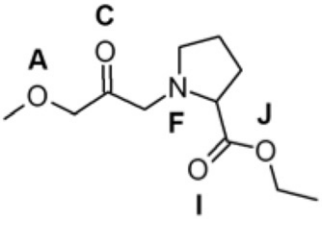


Figure 3. The pyrrolidine keto-ester; atoms where Ti can bond are labeled.

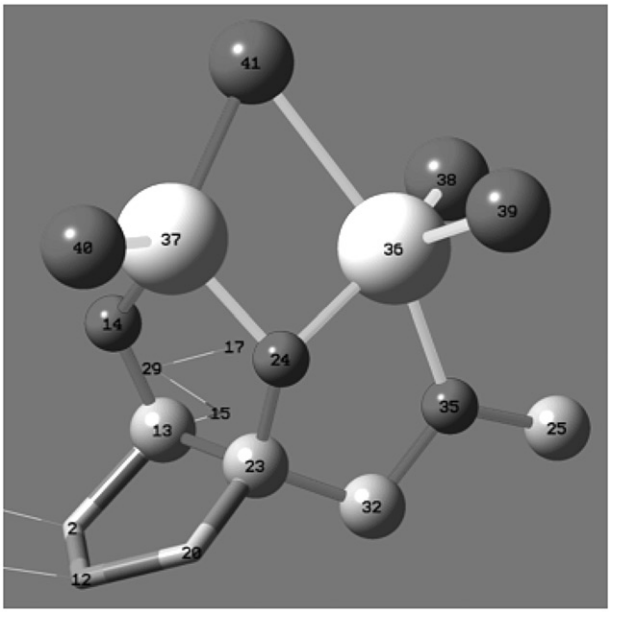


Figure 4. Optimized structure of the [A,I] intermediate. Here a new C–C bond between atoms 13 and 23 is formed in the course of optimization, as expected in a successful McMurry coupling.

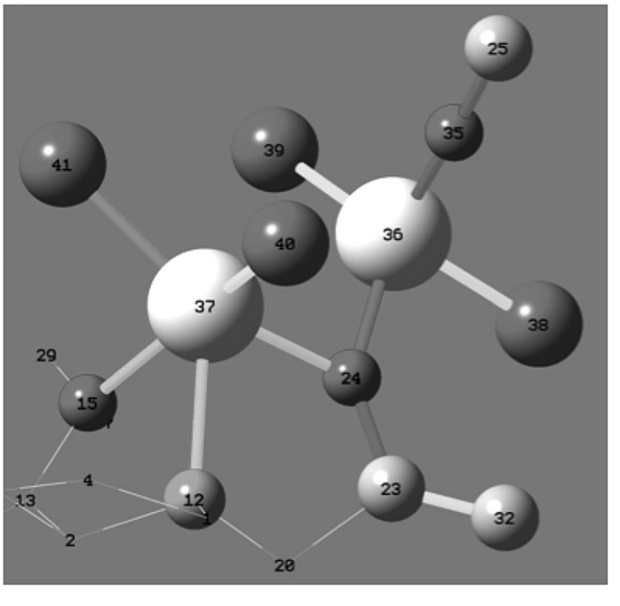


Figure 5. Optimized structure of the [A,J] intermediate. Deoxygenation of the methoxy ketone (breaking of the C-32–O-35 bond) occurs during optimization [16].

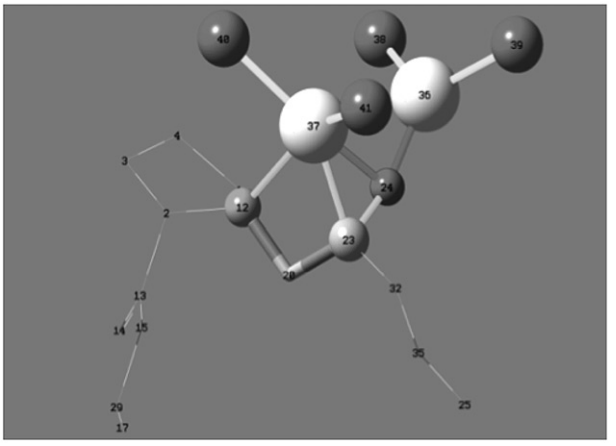


Figure 6. Optimized structure for intermediate [C,F]. In this case, a η^2 titanaoxacyclopropane is formed, a complex that has been previously proposed based on both experimental and theoretical evidence [6c, 8] (cf scheme 2). However, coordination of the proximal amine to the complex seems to preclude McMurry coupling.

Table 1. Energies of pyrrolizidine intermediates optimized at the B3LYP/6-31G level of theory.

Intermediate	Total energy (a.u.)	Energy relative to [A,I] (kcal mol^{-1})
[I,J]	−4326.0571	−20.72
[A,J]	−4326.0541	−18.82
[A,I]	−4326.0241	0
[A,C]	−4326.0206	2.169
[C,J]	−4326.0063	11.16
[A,F]	−4325.9864	23.65
[C,I]	−4325.9770	29.52
[C,F]	−4325.9363	55.06
[F,I]	−4325.9291	59.58
[F,J]	−4325.9175	66.87

3.2. *Pyrrolidine keto-ester*

To determine the likelihood of successful McMurry coupling using the pyrrolidine keto-ester required to access pyrrolizidine alkaloids, we used a similar procedure to evaluate whether the coordination complex necessary for coupling was likely to form. For this keto-ester, there are five electronegative centers to which Ti can bond (labeled A, C, F, I, and J in figure 3), thus producing 10 different intermediate coordination complexes.

Optimization of the 10 coordination complexes yields three kinds of structures: (1) McMurry intermediates ([A,I], [C,J], [C,I]), in which a new C–C bond is formed; (2) intermediates in which deoxygenation of the methoxy ketone occurs ([A,J], [I,J], [F,J], [A,C]); and (3) intermediates in which no significant change to the keto-ester

structure occurs ([A,F], [C,F], [F,I]). Optimized structures from each category are shown in figures 4–6. All stable intermediates are in a singlet spin state.

The energy ordering of the 10 optimized coordination complexes is shown in table 1. Energies in $kcal\,mol^{-1}$ are calculated relative to that of [A,I], the most stable complex that would presumably lead to McMurry coupling. In general, structures in which no significant change to the ligand occurred during the optimization process (category 3) tend to have higher energy than structures in categories 1 or 2. Furthermore, the most stable intermediate is a product of deoxygenation, while complexes leading to C–C bond formation are not predicted to be thermodynamically favored.

As for the capnellene-precursor McMurry product [A,G], the structures of McMurry products [A,I] and [C,I] are very similar to that of Frenking's Ti(II) intermediate [8]. In addition, the pinacolic C–C bond distance in these structures (1.57 Å and 1.58 Å, respectively) is similar to that of another titanapinacolate complex (1.610 Å) [17].

Now we turn to possible steric factors affecting the relative stability of the intermediates. The two most stable structures, [A,J] and [I,J], are also the two in which the Ti dimer is initially bonded to the oxygen atoms furthest out on the ligand's "arms." This is corroborated by experimental evidence, indicating that the yield of ketone-ester cyclization is strongly influenced by the "chain length" of the ligand [16b]. The two structures that are next lowest in energy, ([A,I] and [A,C]), also contain dimer–ligand bonds relatively far out on the arms. The structures higher in energy than these four, with one exception, begin with one titanium attached to atom F. Given the location of atom F in the ligand, it would be reasonable to expect a fair amount of steric strain in the formation of a bond between one titanium center and its associated chlorides and the ligand nitrogen.

4. Conclusions

In this work, we investigated the relative stability of a number of pyrrolidine keto-ester coordination complexes as possible McMurry cyclization precursors. We used the results of geometry optimization calculations at the B3LYP/6-31G level of theory and Mulliken population analyses to determine the structure and bonding of these complexes.

We first validated our approach by performing an analogous set of calculations on a keto-ester known to undergo McMurry cyclization en route to the capnellene sesquiterpene; the results predicted formation of the coordination complex required for the McMurry reaction. In addition, the optimized structures we obtained for the known keto-ester as well as the pyrrolidine keto-ester are largely consistent with the results of a computational study on an intermolecular version of the McMurry reaction, further validating our methodology.

As for the proposed pyrrolidine keto-ester cyclization we investigated, we conclude that McMurry cyclization of this substrate may prove difficult. Even though this work does not address kinetic considerations such as activation barriers, we observe that the requisite coordination complex for McMurry coupling is much higher in energy than other optimized complexes resulting from deoxygenation of the methoxy ketone. Both McMurry and Furstner have observed such titanium-mediated C–O bond cleavages, although those reactions have occurred at more substituted carbons [16]. Nonetheless,

this work suggests that the deoxygenation process should compete significantly with the desired McMurry cyclization.

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