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Theoretical Investigation of the Oxidative Carbonylation of Toluene to Toluic Acid over Rh(III) and Pd(II), and Theoretical Method Development for the Rapid Identification of ab initio Transition States

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Theoretical Investigation of the Oxidative Carbonylation of Toluene to Toluic Acid over Rh(III) and Pd(II), and Theoretical Method Development for the Rapid Identification of ab initio Transition States

By

Andrew Paul Behn

A dissertation submitted in partial satisfaction of the requirements for the degree of

Doctor of Philosophy

in

Chemical Engineering

in the

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of the

University of California, Berkeley

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Abstract

Theoretical Investigation of the Oxidative Carbonylation of Toluene to Toluic Acid over Rh(III) and Pd(II), and Theoretical Method Development for the Rapid Identification of \textit{ab initio} Transition States

by

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Doctor of Philosophy in Chemical Engineering

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The use of theoretical chemistry techniques in the investigation of catalytic reactions has been able to provide strong insights into the inner workings of various chemical mechanisms. In tandem with experimental results, such studies often provide information by computing reaction rates with transition state theory, predicting and/or confirming various spectroscopic experiments, and elucidating the identities and structures of key stable intermediates and short-lived transition states. The present work is concerned with the application of these techniques to the study of the oxidative carbonization of toluene to toluic acid over Rh(III) and Pd(II), as well as the development of theoretical techniques to efficiently find \textit{ab initio} transition states for use in such studies.

Previous work has shown that the oxidative carbonylation of toluene to form toluic acid is possible with Rh(III) and Pd(II) with acetic acid. These reactions are believed to operate via a rate-limiting electrophilic mechanism in which toluene binds to the metal complex and has a C-H bond activated. Previous works have suggested that the active catalyst for the Rh(III) system is Rh(CF$_3$COO)$_3$(CO)$_2$, and Pd(CF$_3$COO)$_2$ for the Pd(II) system, though these were not rigorously confirmed. In this work, we properly identify the Rh(III) species as the active catalyst through a series of \textit{ab initio} spectroscopic calculations with comparison to experiments. Additionally, an unprecedented interaction between an acetate and carbonyl ligand on the Rh(CF$_3$COO)$_2$(CO)$_2$ catalyst is investigated and found to be the result of an unusual charge balance within the structure. Prior work has shown that using trifluoroacetate acid instead of acetic acid significantly increases the rate of reaction, without investigating further. This work demonstrates that the reaction rate passes through a maximum for intermediate strength acids, which is due to competition between the two sub-steps of the rate-limiting step. Weakly basic anionic ligands increase the positive charge on the metal center and increase the rate of toluene
binding while decreasing the ability of the same ligands to accept the activated proton. A similar trend and explanation were found with a model catalyst for the Pd(II) system as the ligands were varied.

The second part of this work concerns the development of efficient transition state searching algorithms. The calculation of theoretical rate constants often employs transition state theory, but requires the user to possess the transition state structure. The local search for such a structure requires an extremely good guess, and is most practically obtained with the help of an automated guess generator. The most commonly used algorithms operate by optimizing a chain of molecular images connecting known reactant and product structures into the reaction pathway. One such routine, the Growing String Method (GSM), grows a chain of states inward from the known endpoints while optimizing these points. The original GSM algorithm relies upon cartesian coordinates with cubic splines for adding new structures to the chain, however this often leads to unrealistic images which require many steps to relax into the reaction pathway. By replacing the cartesian coordinate interpolation with Linear Synchronous Transit interpolation, the computational cost of optimizing complex reaction pathways may be cut approximately in half. Additionally, by simplifying the algorithm to focus computational effort on the location of just the transition state rather than the entire reaction pathway, the overall cost may be reduced even further. In this new method, the Freezing String Method, nodes are iteratively added to a growing chain, optimized for several steps, and then frozen in place for the remainder of the execution.
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“I can’t believe it! Reading and writing actually paid off!”

-Homer J. Simpson
Chapter 1

Introduction

1.1 Motivation

The application of theoretical chemistry methods to questions of catalyst behavior has recently been an area of great interest. Theoretical methods have been used to predict and understand catalyst structure, calculate rate constants to determine activity, and understand the relationship between the two. While existing methods are capable of describing a wide range of reaction systems, many catalytic systems remain out of practical reach. Thus, the development of more efficient methods for the rapid theoretical screening of catalysts is desirable. With the maturation of these technologies, the ubiquitous use of computational chemistry in fundamental research may be one step closer.

1.2 Oxidative Carbonylation of Toluene

The oxidative carbonylation of arenes with organometallic compounds is a promising synthetic route for a variety of chemicals. In particular, the carbonylation of toluene is of interest as a way to avoid using $p$-xylene in the production of $p$-toluic acid for the synthesis of terephthalic acid (see Scheme 1). High selectivity towards the para isomer is necessary for the practical application to this reaction, since the meta and ortho isomers are industrially undesirable.
Scheme 1.1 Overall reaction for the oxidative carbonylation of toluene to form \( p \)-toluic acid

The first demonstrated oxidative carbonylation of toluene by Pd(II) cations was performed by Fujiwara and co-workers using acetic acid together with carbon monoxide [1-5]. Subsequent work indicated that this system could be made catalytic with the addition of a reoxidation co-catalyst. The Pd(II) systems were reported to have high overall activity but low selectivity towards the \( para \) isomer. Conversely, the analogous Rh(III) systems were reported to have higher selectivity towards the \( para \) isomer while being less active [6-9].

The substitution of acetic acid with trifluoroacetic acid has been found to significantly increase catalyst activity [8-14]. This was attributed to an increased rate of toluene binding to the metal complexes during an electrophilic reaction mechanism. More recent theoretical and experimental work on the Rh(III) with trifluoroacetic acid system has indicated that the specific active catalyst is \( \text{Rh(CF}_3\text{COO)}_3\text{(CO)}_2 \) and that the binding and activation of toluene is the rate limiting step [15-16]. The first step, toluene binding, is reversible while the second step is an irreversible C-H bond activation in which a proton is transferred from toluene to one of the acetate ligands.

The objectives of this study are to advance the understanding of this reaction by creating density function theory (DFT) models of the key reaction structures and reaction pathways. In Chapter 2, the proposed structure of the \( \text{Rh(CF}_3\text{COO)}_3\text{(CO)}_2 \) catalyst is examined, with particular attention to an usual interaction between a carboxyl and acetate ligand. Experimental and theoretical results of a spectroscopic study of the Rh(III) catalyst and other important reaction intermediates is presented in Chapter 3. Chapter 4 examines the effect of Rh(III) catalyst ligand composition on activity through a combination of experimental and theoretical techniques. In Chapter 5, a study of the Pd(II) system is presented which explores the basic reaction mechanism and the effect of ligand composition on a proposed catalyst.

### 1.3 Rapid Identification of Transition States

The reactions discussed above, as well as many others of interest in the study of catalytic systems with theoretical methods largely rely upon transition state theory (TST) for the estimation of kinetic rate constants. The use of this method depends upon the user knowing the proper transition states for the reaction of interest. Even for simple reactions, the location of such transition states can be extremely challenging.
The most widely used methods for isolating transition states are surface walking algorithms. These operate in a very similar manner to traditional minima (stable structure) search algorithms, but with the goal of finding a solution that is maximized along one eigenmode and minimized along all others. Unfortunately, local surface-walking algorithms only work properly when initiated with a very good guess of the final transition state structure. (i.e. close to the TS). Complex reactions involve many internal molecular degrees of freedom, making human estimation of the transition state difficult.

To allow for the reliable use of surface walking techniques to isolate transition states, a number of methods designed to automatically generate transition state guesses have been developed [22-34]. These typically operate by using known reactant and product structures (PES minima), interpolating a chain of molecular images connecting the two, and optimizing this chain to settle into the reaction path. From the final chain, it is straightforward to select the maximum energy node and perform a local surface walking search for the exact transition state.

The most widely used chain of states method is the Nudged Elastic Band (NEB) method [21-25]. After interpolating the initial chain, neighboring nodes are connected with contrived hookian springs to ensure that the nodes remain adequately spaced. The NEB optimization step direction consists of two components. The first is in the downhill direction of the PES to minimize the energy of each node. The second arises from the springs which connect neighboring nodes for proper spacing. Similar to the NEB is a slightly new method, the String Method (SM) [26-31]. In the SM, like the NEB, a “string” (chain) of images is optimized by moving each node in the downhill direction perpendicular to the reaction path on the PES. Instead of connecting imaginary springs to keep the nodes evenly spaced, the SM uses an explicit reparameterization step. This reparameterization is performed by re-interpolating the string nodes using a series of cubic splines over the string’s cartesian coordinates. The Growing String Method (GSM) improves upon the SM by iteratively adding nodes from the reactant and product structures inward towards the transition state [32]. In doing so, expensive calculations of the poorly interpolated interior nodes are avoided before a reasonable guess of this region is developed.

Despite recent advances in the methods used to automatically compute transition state structure estimates, they are still computationally expensive. This is of particular concern in the search for \textit{ab initio} transition states, where calculation of PES gradients with QM methods are expensive and calculations of the PES hessian are prohibitively expensive. Thus, reducing the number of gradient calculations necessary to develop a good guess of the transition state is of interest, and the concern of the present study. Chapter 6 describes our effort to reduce the cost of the GSM by replacing the normal cartesian coordinate with cubic splines interpolation with the more chemically intuitive Linear Synchronous Transit (LST) of Halgren and Lipscomb [33-34]. This has the effect of guessing new nodes that are closer to the final solution and require fewer QM calculations to optimize. In Chapter 7, a modified version of the GSM, the Freezing String Method, is presented. This method aims to reduce overall computational cost by freezing new nodes after
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1.4 References

Chapter 2

Weak interligand interactions with major structural consequences in Rh(CO)$_2$(CF$_3$COO)$_3$

2.1 Abstract

A theoretical study was conducted to investigate the chemical nature of an unusual interaction observed between carbonyl and acetate ligands in the Rh(CO)$_2$(CF$_3$COO)$_3$ complex. This interaction is intriguing because it is only nominally longer (0.1-0.2 Å) than a typical carbon-oxygen sigma bond, yet is only associated with a modest (~10 kcal/mol) energy lowering of the complex. A localized bonding molecular orbital which promotes the notion of charge sharing is present between the interacting ligands. Constrained geometry optimizations in tandem with Mulliken population analyses indicate that the interaction stems from the inability of Rh(III) with highly electron withdrawing ligands to back donate properly into the carbonyl ligands. This produces a charge imbalance in the ligands which sets the stage for nucleophilic attack by the acetate oxygen to the carbonyl carbon. This interaction causes a shift in the predicted values of both IR and $^{13}$C NMR signals, which are compared to experiment. For a full explanation of the $^{13}$C NMR shifts, two explicit solvent molecules were added to the model and found to induce interaction of both carbonyls with acetate ligands. The chosen density functional (B3LYP) and basis set were validated by comparing theoretically predicted structures and vibrational frequencies with experimentally determined values for several complexes.
2.2 Introduction

Transition metal carbonylation chemistry plays a prominent role in the synthesis of many chemicals, including aldehydes, ketones, carboxylates, acid anhydrides [1]. As a result, the structure and properties of transition metal carbonyl complexes have been investigated extensively [2-5]. These studies have shown that ligand composition has a profound impact on the electronic structure of the complex and can influence the geometry and reactivity of the complex.

Carbonyl ligands are notable for their susceptibility to both nucleophilic and electrophilic attack when bound to a transition metal. Such attacks are rationalized by the competing effects of forward donation to, and back donation from the metal [3, 6]. These interactions do not prohibit further interaction of the carbonyl ligand with other metal-complexes, solvent molecules, or even other ligands of the same complex [7-11]. It is the last of these three, and in particular intramolecular carbonyl-ligand interactions which is of interest for the present study. The literature is generally sparse in the area of inter-ligand interactions; however there is precedent to believe such interactions should exist.

While bridging carbonyl ligands have long been established, it took until 1961 for Hock to document the first instance of so-called semi-bridging carbonyl ligands [7]. Subsequent work by Cotton isolated several other structures which exhibited semi-bridging carbonyls, and in particular for this study, Fe2(CO)2dipy [8-9]. The structure of this complex, determined by x-ray crystallography, possesses a carbonyl ligand which is attributed primarily to one of the iron atoms but is made non-linear by a weak donation of charge from the d-orbitals of the second iron atom into the π* orbital of the carbonyl. This interaction causes the carbonyl to become bent with respect to its parent iron. Subsequent studies have found a variety of semi-bridging carbonyl compounds exhibiting the full range of behavior between completely bridging and completely non-bridging [10]. Simpson and Hall have carried out a theoretical study of the special case of linear semi-bridging carbonyls [11]. They concluded that such structures are the result of steric hindrance, and would prefer to exist as terminal groups. The electronic structure of non-linear bridging carbonyls was not discussed in depth in their work.

Compounds which possess interaction of a carbonyl ligand with a second ligand of the same metal complex have also been synthesized [12]. For example, Chetcuti and co-workers have reported a complex formed by cyclometallation of highly substituted metal (specifically Rh(III)) carbonyls with aryl N-oxides. These reactions produce five membered interligand rings wherein the nitrile oxygen binds to the carbonyl carbon that have been likened to a 1,3-dipolar addition, which normally open carbon-carbon double and triple bonds [13]. As a result of charge donation in the carbonyl from the nitrile, the carbonyl becomes highly non-linear. This fact is apparent not only from the x-ray crystal structure, but also from the severely red-shifted carbonyl stretching frequencies.

In the present study we report a novel example of interligand interaction arising from the interaction of the carbonyl and acetate ligands in the lowest energy isomer of Rh(CO)2(CF3COO)3. Some of the properties of this complex have been reported as a part of our investigations of its catalytic properties for the oxidative
carbonylation of toluene to toluic acid [14-16]. The remarkable feature of the complex is the close proximity of the carbonyl and acetate ligands, which structurally indicates a chemically bonded interaction. However, the energetics of this interaction are far too modest (~10 kcal/mol) to be a conventional bond, and suggests instead that due to the role of the metal, the bonding geometry is only marginally favored over a non-bonded interaction.

2.3 Theoretical Methods

All calculations were performed with the Q-Chem 3.1 software package [17]. Constrained geometry optimizations, non-constrained geometry optimizations and IR frequency calculations were all performed with Density Functional Theory [18] (with the B3LYP functional) and the 6-31G* basis set for all non-metal atoms. Rhodium was described in these calculations using the LANL2DZ effective core potential in order to save computational cost and include relativistic effects. Reported energies were refined with the 6-311G**/LANL2DZ basis set and effective core potential.

Computed IR frequencies were scaled by a factor of 0.9614 to correct for systematic overestimation at the 6-31G*/B3LYP level of theory [19]. NMR shielding constant calculations were performed with Hartree-Fock wavefunctions and gauge invariant atomic orbitals [20]. The 6-31G* basis set for all atoms except rhodium, which was described by the all-electron 3-21G basis set. To correct for systematic overestimation of the $^{13}$C NMR shifts, 65 ppm were subtracted from the raw values in a manner similar to that done in reference 16. This calibration for theoretical values is also the source of an estimated ± 8 ppm uncertainty in the computed shifts. All species were found to be singlet molecules in the gas phase, and solvent effects were ignored except where noted. Molecular orbital localization was carried out in Q-Chem using the Boys method [21-23]. JMol and MacMolPlt [24] were used for orbital, electron density, and normal mode visualization.

2.4 Results and Discussion

2.4.1 Validation of theoretical methods

Several test molecules were optimized with the same level of theory employed in the rest of this study in order to validate the ability of DFT models to accurately compute molecular structures and vibrational frequencies of complexes with both weakly and strongly interacting carbonyl ligands. The three test structures considered were Fe$_2$(CO)$_2$-dipy [9] and the [closo-2-(PPh$_3$)-2-{$\eta^2$-C(m-FC$_6$H$_4$)NOC(=O)-}]-2,1,7-Rh$_2$B$_3$H$_{11}$] anion and ({$\eta^2$-C$_5$Me$_5$}-PMe$_3$)-Rh[{$\eta^2$-C(p-FC$_6$H$_4$)NOC(=O)-}] aryl N-oxide structures [12].

The Fe$_2$(CO)$_2$-dipy complex contains a semibridging carbonyl, as shown in the picture of our computed structure, Figure 1. The two iron to bridging carbon distances obtained from the DFT calculations are 2.40Å and 1.80Å, which agree closely with those determined by x-ray crystallography, 2.37 Å and 1.80 Å. Likewise, the calculated Fe-C-O angle was 160.1°, agreeing closely with the
measured value of 160.5°. DFT calculations generally give poorer agreement with observed metal-metal distances than with observed C-O and M-C distances, but are still able to reproduce the system geometry rather well. The calculated Fe-Fe distance of 2.745 Å is to be compared with the experimental distance of 2.611 Å.

The DFT models of the \([\text{closo-2-}(\text{PPh}_3)\cdot 2-\{\eta^2-\text{C}(\text{m-FC}_6\text{H}_4)\text{NOC}(=\text{O})\}\cdot 2,1,7-\text{RhC}_2\text{B}_9\text{H}_{11}\}\) anion and \(\{\eta^5-\text{C}_5\text{Me}_5\}-(\text{PMe}_3)\text{Rh}\{\eta^2-\text{C}(\text{p-FC}_6\text{H}_4)\text{NOC}(=\text{O})\}\), shown in Figure 2, also agree well with experimental measurements. These structures are highly substituted Rh(III) complexes. The computed nitrile oxygen to carbonyl carbon interligand distances for the two structures are 1.394 Å and 1.395 Å (for a and b) respectively. These values compare well with the distances determined experimentally from x-ray crystallography, 1.390 Å and 1.399 Å. The computed carbonyl frequencies of 1700 cm\(^{-1}\) and 1712 cm\(^{-1}\) agree reasonably well with the experimental values of 1670 cm\(^{-1}\) and 1689 cm\(^{-1}\).

### 2.4.2 The structure and energetics of Rh\((\text{CF}_3\text{COO})_3(\text{CO})_2\)

The Rh\((\text{CO})_2(\text{CF}_3\text{COO})_3\) complex can form three distinct isomers as shown in Figure 3. These isomers are named according to the location of the carbonyl ligands relative to the plane of the bidentate acetate with \(e\) denoting an equatorial carbonyl and \(a\) denoting an axial carbonyl. In each isomer the carbonyl ligands can be said to form associations with a unidentate acetate, in that the unbound oxygen on the acetate will point towards the carbon atom of the carbonyl. This association does not mean that the two ligands are chemically interacting, but it will be convenient to think of them as pairs. The \(a\text{e}\) isomer (which contains one axial and one equatorial carbonyl) is lowest in energy and stands out from the other isomers because of its asymmetric carbonyls. Inspection of the carbonyls (Figure 4) shows that the equatorial carbonyl interacts very closely with the neighboring acetate. This equatorial carbonyl and its associated acetate, with an interligand distance of 1.53 Å, resemble an ether linkage. While typical hydrocarbon carbon to oxygen sigma bond lengths are roughly 0.1-0.2 Å shorter, this is very unusual in a metal complex. Unlike the equatorial carbonyl, the axial carbonyl of the \(\text{a}\text{e}\) isomer does not closely interact with its associated acetate. Cutouts of the electron isodensity surface, shown in Figure 4, depict a sharing of electron density between the equatorial carbonyl/acetate pair, and a lack of sharing for the axial carbonyl/acetate. Molecular orbital localization with the Boys method produced a bonding orbital between the oxygen of the acetate and the carbon of the carbonyl as depicted in Figure 5. This orbital is comprised mainly of \(p\)-orbital character and represents a sharing of charge between the two ligands.

To determine the strength of interaction between the acetate and carbonyl ligands a series of constrained dihedral angle optimizations was performed. In these calculations, two planes are defined by three atoms each. They are forced to sit relative to one another with a specified dihedral angle while all other degrees of freedom relax. In Rh\((\text{CO})_2(\text{CF}_3\text{COO})_3\) the first plane is defined by Rh-C-O (of a carbonyl), and the second by Rh-O-C (of an acetate). Thus, constraining the dihedral angle between these planes causes the ligands to twist away from one another. Two sets of optimizations were performed – one with the constraint between equatorial
carbonyl and its acetate, and the other with the axial carbonyl and its acetate. The final energies of these constrained structures as a function of dihedral angle are shown in Figure 6. This plot clearly shows that the equatorial carbonyl sits in a much steeper potential well than the axial carbonyl. This supports the notion that the equatorial carbonyl is chemically interacting with the acetate, while the axial carbonyl is not. Although the equatorial carbonyl is relatively hard to separate from the axial carbonyl, the energetic penalty of dihedral angle rotation is extremely mild for true bond breaking, which should be ~100 kcal/mol. This observation is surprising due to the presence of a localized bonding orbital between the equatorial carbonyl and acetate. It demonstrates that the truly surprising aspect of this interaction is not the proximity of the ligands, but rather the incredible flexibility of this complex to redistribute charge with only modest energetic penalty.

The interaction of the equatorial carbonyl can be rationalized by recognizing the influence that rhodium in the +3 oxidation state has on the electronic structure of the carbonyl. Because it is so electron deficient, rhodium is prevented from back donating into the carbonyl π* orbital, creating a structure of predominantly Rh-C=O δ− character rather than Rh=C=O δ− character. As a result, the carbon is susceptible to nucleophilic attack by the acetate group. Donation of charge from the acetate group to the carbon atom causes the carbonyl to become bent. This is similar to the case of Fe₂(CO)₉, discussed above.

To test this proposal, the equatorial (interacting) carbonyl and its associated acetate were separated forcibly through another set of constrained optimizations. In these calculations, the structure was fully optimized with the sole exception of the specified carbonyl carbon to acetate oxygen inter-atomic distance. Figure 7 illustrates the geometry of the equatorial carbonyl (and associated acetate) as a function of interligand distance. The carbonyl becomes linear as the ligands are separated, implying that the interaction causes the distortion. The Rh-C bond distance simultaneously becomes shorter due to the slightly greater ability of the carbonyl to accept back donation from rhodium when the acetate is not interacting. Mulliken population analysis of these constrained complexes (Figure 7) shows that the rhodium becomes more positive and the carbonyl carbon more negative as the ligands are separated. At the same time, the acetate oxygen becomes more negative due to its inability to shed charge through interaction.

Assuming that the acetate-carbonyl interactions results from the electron poor nature of rhodium, one might expect metals with similar electronic structures to yield similar interactions. Specifically, octahedral complexes with the transition metal in the 3+ oxidation state that are either more or less electron poor than rhodium should posses stronger or weaker interligand interactions, respectively. In the case of Ir(CO)₂(CF₃COO)₃, the Ir atom is more electron rich than Rh, and produces a complex that lacks an interligand (i.e., carbonyl-acetate) interaction. Conversely, for Co(CO)₂(CF₃COO)₃ the cobalt atom is less electron rich than Rh, and produces a complex which exhibits an interligand interaction very to similar to Rh. The acetate-carbonyl distance in the Co complex is 1.57 Å, compared to 1.54 Å in the case of Rh. The energetics of forming the interland interaction in Co again seem very modest when compared to the extreme structural distortion. The overall
structures of the Ir, Rh and Co complexes are very similar, as may be seen from the information given in the supplemental information.

The ligand in the position trans to the carbonyl ligands should have the greatest impact on the ability of Rh to back-donate into the equatorial carbonyl. Thus, placing a more electron withdrawing ligand in this position should strengthen the equatorial carbonyl/acetate interaction by decreasing the electron density of Rh. In the ace isomer of the Rh(CO)₂(CF₃COO)₃ complex, the ligand trans to the equatorial carbonyl is a bidentate acetate. Changing the composition of this acetate group in the model and re-optimizing the entire structure had a strong influence on the carbonyl-acetate interligand distance. A plot of this distance versus the pKa of the conjugate acid of the acetate group (a measure of electron withdrawing ability) is shown in Figure 8. It is clearly evident from this plot that more electron withdrawing ligands (lower pKa) shorten the interligand distance and strengthen the interaction.

Along with geometric and charge distortions, the equatorial carbonyl/acetate interaction lowers the carbonyl stretching frequency to a predicted 1892 cm⁻¹, compared to 2121 cm⁻¹ for the axial (non-interacting) carbonyl. Unfortunately, this lowering of the IR frequency for the equatorial carbonyl places it into the broad absorbance of the trifluoroacetic acid needed to prepare this structure experimentally, thus hiding it from direct observation. The distortion of the equatorial carbonyl also changes its electronic environment and alters the predicted ¹³C NMR shift. The ¹³C shift of the axial (non-interacting) carbonyl is predicted to be 164.7 ± 8 ppm, while the equatorial (interacting) carbonyl is predicted to be 134.6 ± 8 ppm. This reduction is consistent with the gain of negative charge on the carbon atom.

Zakzeski et al. have recently shown that the Rh(CO)₂(CF₃COO)₃ complex exhibits a single carbonyl ¹³C NMR shift at 130 ppm [16]. The authors propose that the observation of a single NMR resonance, rather than two, may be a consequence of solvent interactions, which induce the second carbonyl group to interact with a nearby acetate ligand. To explore the role of solvent molecules in the interaction of the equatorial and axial carbonyls, two explicit CF₃COOH molecules were added to the model. One of the viable structures obtained for the Rh(CO)₂(CF₃COO)₃ + 2CF₃COOH system possesses the desired interaction of both carbonyls with their associated acetates, as depicted in Figure 9. In this structure, the first CF₃COOH attaches to Rh in the first coordination sphere by displacing one of the bidentate acetate ligands Rh-O bonds. The second CF₃COOH interacts with the axial carbonyl through its proton. This draws charge away from the axial carbonyl, and allows the nearby acetate to perform a nucleophilic attack on the carbon atom in a similar manner to the equatorial carbonyl. In this configuration, the predicted ¹³C NMR shift of the axial carbonyl is 156.1 ± 8 ppm, while the predicted shift of the equatorial carbonyl is 136.7 ± 8 ppm. These values are more consistent with the experimental observation than the predicted shifts of the isolated Rh(CO)₂(CF₃COO)₃ complex and suggest that the interaction of multiple CF₃COOH molecules with Rh(CO)₂(CF₃COO)₃ could result in interactions of both carbonyl ligands with the acetate ligands, and thereby explain the observation of a single ¹³C NMR peak when this complex is formed in the presence of excess CF₃COOH.
2.5 Conclusions

The results of this study indicate that the Rh(CO)$_2$(CF$_3$COO)$_3$ complex in its most stable isomer possesses a novel interaction between acetate and carbonyl ligands. The chemical nature of this interaction was investigated through a series of combined geometry optimization and Mulliken population analyses. These calculations showed that the interaction occurs because of a nucleophilic attack on the carbonyl carbon by the neighboring unidentate acetate. Furthermore, the interaction is rationalized by considering the poor ability of Rh in the +3 oxidation state with several highly electron withdrawing ligands, to back donate charge into the $\pi^*$ orbital of the carbonyl. This creates a partial positive charge on the carbonyl carbon which is necessary to induce the interaction. By artificially changing the electron withdrawing nature of the complex, it was shown that more electron rich rhodium complexes will produce weaker carbonyl-acetate interactions.

Similarly to those seen in experimental studies of rhodium carbonyl complexes with more strongly interacting ligands, a red shift in the carbonyl stretching frequencies of Rh(CO)$_2$(CF$_3$COO)$_3$ is predicted as a result of the interaction. Additionally, this interaction causes a lowering of the predicted $^{13}$C NMR shift which was previously seen experimentally. When two explicit CF$_3$COOH molecules were added to the model of Rh(CO)$_2$(CF$_3$COO)$_3$, the axial carbonyl was induced to also interact with its associated acetate and shifted the predicted $^{13}$C NMR signal to be more consistent with experimental observations.
2.6 Figures

![DFT molecular structure of Cotton's Fe2(CO)7dipy structure with the semi-bridging carbonyl in the top middle. Hydrogen omitted for clarity.](image)

Figure 2.1 DFT molecular structure of Cotton's Fe2(CO)7dipy structure with the semi-bridging carbonyl in the top middle. Hydrogen omitted for clarity.
Figure 2.2 DFT models of the Chetcuti structures, a) \([\text{closo-2-}(\text{PPh}_3)\text{-}2\text{-}\{\eta^2\text{-}C(m-}\text{FC}_6\text{H}_4)\text{NOC(=O)}\text{-}2,1,7\text{-}\text{RhC}_2\text{B}_9\text{H}_{11}\}\text{ anion and b) }\{\eta^5\text{-}C_5\text{Me}_5\}\text{-}(\text{PMe}_3)\text{Rh}\{\eta^2\text{-}C(p}\text{-}\text{FC}_6\text{H}_4)\text{NOC(=O)}\text{-}\}. \) Hydrogen omitted for clarity.
Figure 2.3 Isomers of the Rh(CF₃COO)₃(CO)₂ complex. The a:e isomer is lowest in energy.

Figure 2.4 Electronic isodensity surface (ρ=0.8 au) for the equatorial carbonyl and associated acetate (left) and axial carbonyl and associated acetate (right). The electron density on rhodium and extraneous ligands are omitted for clarity.
Figure 2.5 Localized bonding molecular orbital between the interacting acetate and carbonyl ligands comprised primarily of p-type Gaussian basis functions.

Figure 2.6 Energy vs. dihedral angle for the two sets of constrained dihedral angle optimizations. The two curves correspond to separately perturbing the equatorial and axial carbonyl from their associated acetates.
Figure 2.7 Geometric parameters and Mulliken charges for the constrained interligand distance (equatorial carbonyl to acetate) optimizations.
Figure 2.8 Equatorial carbonyl to acetate interaction distance (carbonyl carbon to acetate oxygen) vs. pKa of the conjugate acid for the bidentate ligand. Points included are CCF3COOH (pKa = 0), CClF2COOH (pKa = 0.35), CCl3COOH (pKa = 0.63), CCIH2COOH (pKa = 2.86) and CH3COOH (pKa = 4.76).

Figure 2.9 Structure of the Rh(CF3COO)3(CO)2 complex interacting with two explicit CF3COOH solvent molecules. The first CF3COOH binds directly to the metal center, while the second CF3COOH interacts with the axial carbonyl, inducing it to interact with the nearby acetate anion.
2.7 References


Chapter 3

Spectroscopic investigation of the species involved in the rhodium-catalyzed oxidative carbonylation of toluene to toluic acid

3.1 Abstract

A spectroscopic investigation was conducted of complexes used to catalyze the oxidative carbonylation of toluene to para-toluic acid was conducted. Rhodium complexes were analyzed by $^{103}$Rh and $^{13}$C NMR, UV-visible spectroscopy, and infrared spectroscopy. In the presence of vanadium and oxygen, the resting state of the Rh catalyst was found to exist as a Rh(III) complex with carbonyl and trifluoroacetate ligands, consistent with the structure Rh(CO)$_2$(TFA)$_3$. The $^{13}$C NMR spectrum of Rh($^{13}$CO)$_2$(TFA)$_3$ complex exhibited a carbonyl peak with an unusual degree of shielding, which resulted in the appearance of the carbonyl peak at an unprecedented upfield position in the $^{13}$C NMR spectrum. This shielding was caused by interaction of the carbonyl group with the trifluoroacetate ligand. In the absence of oxygen, the Rh(III) complex reduced to Rh(I), and the reduced form exhibited properties resembling the catalyst precursor. Structures and spectroscopic properties calculated using density functional theory agreed closely with the experimental results. The vanadium co-catalyst used to reoxidize Rh(I) to Rh(III) was similarly characterized by $^{51}$V NMR and UV-visible spectroscopy. The oxidized species corresponded to [(VO$_2$(TFA))$_2$, whereas the reduced species corresponded (VO)(TFA)$_2$. The spectroscopic results obtained in this study confirm the identity of the species that have been proposed to be involved in the Rh-catalyzed oxidative carbonylation of toluene to toluic acid.
3.2 Introduction

The oxidative carbylation of toluene represents a potentially useful route to synthesis para-toluic acid, which is an intermediate used in the production of terephthalic acid. Terephthalic acid reacts with ethylene glycol to form polyethylene terephthalate (PET), a compound used extensively in plastics and resins.

Several studies have demonstrated that p-toluic acid can be synthesized by oxidative carbylation of toluene catalyzed by Rh(III) cations in the presence of trifluoroacetic acid (TFAH) and its anhydride (TFAA) together with a vanadium oxo co-catalyst and molecular oxygen [1-2]. The active center in this system is thought to be \(\text{Rh(CO)}_x\text{(TFA)}_3\) \(x = 1\) or 2 [1-4]. Kalinovskii and coworkers have proposed that \(\text{Rh(CO)}_x\text{(TFA)}_3\) reacts with toluene to form an aryl-rhodium complex \(\text{Rh(CO)}\text{(TFA)}_3\text{(Ph)}\) [3]. Migratory insertion of CO into the arene-metal bond forms \(\text{PhCO-Rh(TFA)}_3\), which then undergoes reductive elimination to form the mixed anhydride of toluic and trifluoroacetic acids [3]. Upon release of this product, the Rh cation is reduced from Rh(III) to Rh(I). The VO\(_x\) species in the reaction mixture then oxidize Rh(I) back to Rh(III). The basic features of this mechanism have been supported by subsequent experimental work carried out by Zakzeski and Bell [2] and theoretical work reported by Zheng and Bell [5]. The results of these studies indicated that the resting state of the catalyst is most likely to be \(\text{Rh(CO)}_2\text{(TFA)}_3\), a structure satisfying the 18-electron rule, and that the overall reaction mechanism is that shown in Scheme 1. This scheme also provides a detailed picture of the mechanism by which Rh(I) is reoxidized to Rh(III) by VO\(_x^+\) cations and the mechanism by which O\(_2\) participates in the reoxidation of VO\(_2^+\) cations to VO\(_2^+\) cations. While Scheme 1 captures all of the features of the reaction system observed experimentally, to the best of our knowledge, little experimental evidence exists to support the structures and identities of the rhodium and vanadium complexes present in the proposed catalytic cycles. The objective of this investigation was to obtain direct spectroscopic evidence for these complexes, namely \(\text{Rh(CO)}_2\text{(TFA)}_3\), \(\text{Rh(CO)}_2\text{(TFA)}\), VO\(_2\)TFA and VO\(_2\text{(TFA)}_2\), using infrared, UV-Visible, and \(^{13}\text{C}\) and \(^{108}\text{Rh}\) NMR spectroscopy.

3.3 Experimental

\([\text{Rh(CO)}_2\text{Cl}]_2\) (Alfa Aesar), the precursor to the active form of the catalyst, and the \(\text{NH}_4\text{VO}_3\) (Aldrich, 99+%), the precursor to the oxidant used to reoxidize Rh(I) to Rh(III), were dissolved in a mixture of trifluoroacetic acid (TFAH) (Aldrich, 99%), trifluoroacetic anhydride (TFAA) (≥99%, Aldrich), and toluene (99.8%, Aldrich). Room temperature experiments were conducted in glass vials, whereas high temperature and pressure reactions were conducted in stirred, 50 mL Parr autoclaves made of Hastelloy C. Between runs, each type of reactor was washed thoroughly with water and acetone and then dried in a vacuum oven overnight to avoid contamination. The reaction temperature in the autoclaves was monitored using a thermocouple placed in a Hastelloy C thermowell. The autoclave headspace
was purged four times with helium. After purging, the autoclave was pressurized at 293K with 0.345 MPa O₂ (99.993%, Praxair) and 0.345 MPa CO (99.5%, Praxair).

¹³C NMR experiments carried out by placing the solution of interest in a Wilmad Labglass, high pressure NMR tube, and then pressurizing the tube to 0.345 MPa with ¹³CO (Isotec, min 99% ¹³CO). The tube was then inverted several times to enhance mixing. ¹³C NMR measurements were made on a Bruker DRX-500 or a Bruker AV-600 spectrometer without lock using a 5mm ZBO probe with proton decoupling. Chemical shifts were assigned relative to the methyl peak of toluene at 20.4(7) ppm. ¹⁹F NMR spectra were obtained on a Bruker AVQ-400 using a standard glass NMR tube with D₂O contained in a capillary tube as the lock source. Chemical shifts were measured relative to CFCl₃ at 0 ppm. ⁵¹V NMR measurements were conducted on a Bruker AVB-400 spectrometer using a standard glass NMR tube with D₂O in a capillary tube as a lock source. Chemical shifts in this case were referenced to VOCl₃ at 0 ppm. ¹⁰³Rh NMR measurements were obtained on a 499.803 MHz Varian Unity+ spectrometer equipped with a Varian 10 mm HX probe. The frequencies used for the ¹⁰³Rh transmitter frequencies ranged from 15.7 to 15.9 MHz. The δ(¹⁰³Rh) values were calculated by determining the absolute frequency of the cross peak and relating it to the arbitrary reference frequency (Σ = 3.16 MHz at 100.00 MHz), which is 15.800 for operation at 500 MHz. Since the operating frequency of 499.803 MHz differed from 500 MHz, a 394.4 ppm correction was added to all ¹⁰³Rh chemical shifts. Analysis of a sample of Rh(acac)₃ and [Rh(CO)₂Cl]₂ resulted in peaks at 8349 and 118 ppm, respectively, in good agreement with literature values of 8358 for Rh(acac)₃ and 84 [Rh(CO)₂Cl]₂ [6]. For analysis by ¹⁰³Rh NMR, the solutions were concentrated to 0.1M Rh and analyzed in 10mm diameter tubes to aid in detection.

UV-Visible spectroscopy was conducted using a Varian Cary 400 Bio UV-Visible spectrophotometer. Solutions were placed in 10mm standard quartz spectroscopic cells and analyzed from 900 to 300 nm with a scan rate of 600 nm/min. The solvent, typically a mixture of toluene, trifluoroacetic acid, and trifluoroacetic anhydride, was used for baseline correction.

IR spectroscopy measurements were conducted using a Nicolet 6700 FT-IR equipped with a demountable liquid cell (Harrick, Inc.), which is equipped with 13 mm CaF₂ windows from. Analyses were made by transferring the liquid contained in an autoclave to the demountable liquid cell and immediately acquiring a spectrum. Baseline correction was conducted using a mixture of toluene, trifluoroacetic acid, and trifluoroacetic anhydride.

### 3.4 Theoretical

Computed structures, normal modes, and NMR shifts were determined using density functional theory (DFT) as implemented in Q-Chem [7]. Geometry optimizations and vibrational analyses were performed using the B3LYP density functional with the 6-31G* basis set applied to all atoms except rhodium which was described by the LANL2DZ pseudopotential [8-10]. Vibrational frequencies were scaled by 0.9614 to correct for systematic overestimation [11]. Calculated energies were refined with the 6-
311G** basis set for all non-rhodium atoms. NMR shifts were calculated using the Hartree-Fock wavefunction of the B3LYP equilibrium geometry, and rhodium was described using the all electron 3-21G basis set. To correct for the systematic overestimation of NMR shifts, a small library of rhodium carbonyl shifts were calculated (compounds and theoretical shifts in ppm: \( \text{Rh}(\text{Py})(\text{CO})_2\text{Cl} \), 185.6 and 181.3; \( \text{Rh}(\text{Acac})(\text{CO})_2 \), 183.8; \( \text{Rh}(\text{Acac})(\text{Ph}_3\text{P})\text{CO} \), 190.4; and \( \text{Rh}(\eta_5\text{-C}_5\text{H}_5)(\text{CO})_2 \), 190.9) and compared to published experimental values [12]. The mean and standard deviation of the theoretical-experimental offset was found to be 65 ± 8 ppm. This value was then used as a general correction to our calculations.

### 3.5 Results and Discussion

Analysis of the solvent in the absence of Rh or V species was conducted in order to establish a background for each analytical method. A mixture consisting of toluene, trifluoroacetic acid, and trifluoroacetic anhydride, did not exhibit UV-visible bands in the range 900 to 300 nm. When a portion of this mixture was placed in a high-pressure NMR tube and exposed to 0.35 MPa \(^{13}\text{CO} \), a carbonyl peak associated with free CO appeared at 184 ppm [13]. Peaks from the solvent were also clearly identifiable: two quartets attributable to trifluoroacetic acid were observed at 160.8 and 114.2 ppm, and two quartets attributable to trifluoroacetic anhydride were observed at 149.2 and 113.0 ppm. In addition, strong peaks associated with the toluene solvent were observed at 137.5, 128.7, 127.9, and 125.0, and 20.5 ppm. The IR spectrum of the solution exhibited strong absorbances in the range of 1950-500 cm\(^{-1}\) characteristic of trifluoroacetic acid, trifluoroacetic anhydride, and toluene.

Dissolution of \( \text{NH}_4\text{VO}_3 \) in a mixture of trifluoroacetic acid and trifluoroacetic anhydride produced an orange-colored solution, which exhibited a ligand-to-metal charge transfer band below 300 nm, but no bands were observable in the visible region. When toluene was added to this solution, it turned orange/brown in color and new transitions appeared at 410 and 455 nm, which are discussed later. When this sample was pressurized to 0.35 MPa \(^{13}\text{CO} \) a \(^{13}\text{C} \) NMR, a peak associated with free CO was observed at 184 ppm; however, neither \(^{13}\text{C} \) NMR nor IR spectroscopy showed any evidence for carbonyl groups associated with the dissolved V(V) species. These results suggest that vanadium-carbonyl complexes do not form under the conditions used to obtain the spectroscopic data.

\([\text{Rh}(\text{CO})_2\text{Cl}]_2\), the catalyst precursor used in these studies, was characterized after dissolving it in a solution containing trifluoroacetic acid, trifluoroacetic anhydride, and toluene. Analysis of this solution by \(^{103}\text{Rh} \) NMR resulted in a single peak at 118 ppm, which lies in the range expected for Rh(I) complexes [14]. \(^{13}\text{C} \) NMR analysis of this solution after pressurization with 0.35 MPa \(^{13}\text{CO} \) produced a doublet at 177.8 and 177.2 ppm \((J_{103\text{Rh}-13\text{C}} = 76.7 \text{ Hz}) \) attributable to a Rh(I) carbonyl peaks [15]. The infrared spectrum of the solution taken in the absence of \(^{13}\text{CO} \) exhibited strong carbonyl stretches at 2090, and 2034 cm\(^{-1}\) and a weaker carbonyl feature at 2107 cm\(^{-1}\). The UV-Visible spectrum of the resulting yellow-colored solution showed no bands in the region of 900 to 500 nm and only a peak at 325 nm. The observed \(^{13}\text{C} \) chemical shift and the \(^{103}\text{Rh}-^{13}\text{C} \) coupling constant agree very closely with of the values reported for \([\text{Rh}(\text{CO})_2\text{Cl}]_2 \) dissolved in CD\(_2\)Cl\(_2\).
The oxidative carbonylation of toluene was conducted under the reaction conditions described in the Experimental section for 0.5 h, after which the reaction mixture was analyzed at room temperature to identify Rh species present. The color of the solution after reaction was emerald-green/brown as compared to yellow prior to reaction and a peak appeared at 600 nm in the UV-Visible spectrum characteristic of Rh(III) cations. The presence of Rh(III) was also confirmed by $^{103}$Rh NMR, which showed a single peak at 6322 ppm characteristic of a Rh(III) complex [14] with a relatively de-shielded metal center. Pressurization of the reaction mixture with 0.35 MPa $^{13}$CO and subsequent $^{13}$C NMR showed carbonyl peaks broadened extensively by the presence of a high concentration of paramagnetic and quadrapolar V(IV) species (see below). Therefore, a second 0.5 h reaction was conducted with a lower concentration of vanadium (approximately 24 μmol/mL). The full $^{13}$C NMR spectrum is presented in Figure 1a and the region between 140 and 120 ppm is presented in Figure 1b. A doublet attributable to a carbonyl species was observed at 130.0 ppm ($J_{103\text{Rh}-13\text{C}} = 194.8$ Hz) a shift not typically characteristic for Rh(I) or Rh(III) carbonyls [17]. To ascertain that the new $^{13}$C peaks were not due to organic species, a proton-coupled spectrum was acquired. Neither peak-splitting or shift was observed in the proton-coupled spectrum, consistent with the assignment of these peaks to rhodium-carbonyl groups. Moreover, no peaks were observed in the absence of Rh or $^{13}$CO. To rule out the possibility that the new $^{13}$C NMR peaks might be due to CO$_2$, the liquid was pressurized with $^{13}$CO$_2$. This led to the observation of a peak at 124.5 ppm. Analysis of the isotopically unlabeled solution by infrared spectroscopy with higher vanadium concentrations (approximately 93 μmol/mL) revealed two strong peaks of roughly equal intensity at 1714 and 1684 cm$^{-1}$ and two weak peaks at 2122 and 2113 cm$^{-1}$. In the absence of CO, no significant peaks occur above 1600 cm$^{-1}$. The UV-Visible spectrum of the reaction solution containing CO, which was an emerald-green/brown color, is shown in Figure 2a. The UV-Visible spectrum exhibits broad, overlapping bands at 317, 410, 455, and 600 nm.

The evidence presented above shows that after 0.5 h of reaction all trace of [Rh(CO)$_2$Cl$_2$] have disappeared and, hence, all of the Rh(I) complex was oxidized to a Rh(III) complex in the course of reaction. Of further note, the position of the $^{103}$Rh NMR peak suggests that the cation is highly de-shielded, as would occur if the Rh(III) cations were coordinated with highly electron withdrawing anions, such as trifluoroacetate. The coordination of CO with Rh(III) is clearly indicated by the data obtained from $^{13}$C NMR and IR; however the $^{13}$C chemical shift of coordinated $^{13}$CO is uncharacteristic for terminal rhodium carbonyls. The infrared bands at 1684 and 1714 cm$^{-1}$ are consistent with CO vibrations within a unidentate trifluoroacetate...
ligand. The observation of two bands is consistent with the structure of Rh(CO)₂(TFA)₃, which possesses one bidentate and two unidentate trifluoroacetate ligands. In the absence of CO these peaks are not observed for Rh(TFA)₃, which does not contain bidentate ligands. As discussed below, the unusual ¹³C NMR and IR characteristics of the CO ligands can be attributed to interaction of the carbonyl groups with the trifluoroacetate ligands coordinated with the Rh(III) cation.

The two very small IR peaks of roughly equal intensity detected at 2122 and 2113 cm⁻¹ are likely due to the decomposition of the Rh(III) dicarbonyl complex to two monocarbonyl isomers. In fact, loss of CO was evident by the decrease in intensity of both IR carbonyl signals and the ¹³C NMR peaks with time when the complex was not under CO pressure. Under CO pressure, however, the dicarbonyl-rhodium complex was stable. Because the NMR spectra were recorded using a pressurizable NMR tube under a ¹³CO atmosphere, the di-carbonyl species was stable, and there was no evidence for a Rh(III) mono-carbonyl species under these conditions.

As shown in Scheme 1, the Rh (III) complex assumed to be active for the activation of toluene and its subsequent oxidative carbylation to toluic acid undergoes reduction to Rh(I) at the end of the reaction sequence. The mechanism presented in Scheme 1 suggests that in the absence of O₂, needed to re-oxidize the vanadium species involved in the oxidation of Rh(I) to Rh(III), all of the Rh will accumulate in the Rh(I) state. The following experiments were, therefore, conducted in order to characterize the the Rh(I) complex. After 0.5 h of reaction the autoclave headspace was flushed free of O₂ using dry He, re-pressurized with CO, and the reaction was then continued for an additional hour. The resulting solution was light green/yellow in color. ¹³C NMR analysis of the solution after pressurizing it with ¹³CO revealed a broad doublet at 177.2 ppm. To obtain better ¹³C NMR spectra, the experiment was repeated with a higher Rh loading (120 μmol/mL) and the reduction in the presence of CO (and the absence of O₂) was conducted for 3 h. Figure 3 shows the resulting ¹³C NMR spectrum. A doublet was again observed at 177.2 ppm (J¹³Rh-¹³C = 79.2 Hz). The IR spectrum of the solution exhibited a weak band at 2106, and strong bands at 2090 and 2033 cm⁻¹. Comparison of this UV-visible spectrum (Figure 2b) with the spectrum taken after 0.5 h of reaction in the presence of CO and O₂ (Figure 2a) showed that the reaction in CO alone resulted in the disappearance of the absorption band near 600 nm attributed to Rh(III) cations and a reduction in the intensities of the bands appearing below 500 nm. The ¹³C NMR and IR spectra of the complex strongly resemble those of the [Rh(CO)₂Cl]₂ precursor (see above), suggesting that the Rh(I) species reverts to the chlorine-bridged dimer upon reduction; however, it is also possible that the Rh(I) cations are now present as [Rh(CO)₂TFA]₂ complexes or a combination of this complex and [Rh(CO)₂Cl]₂. These alternatives are discussed more fully below.

Density functional theory calculations were conducted in order to aid in interpretation of the experimental results obtained under reaction conditions and presented in the preceding paragraphs. Earlier DFT calculations reported by Zheng and Bell [5] have suggested that the active form of Rh(III) under the conditions used in the present study is Rh(CO)₂(TFA)₃. Additional analysis of this complex was undertaken in the course of the present investigation with the aim of establishing
whether the experimentally observed characteristics of the Rh(III) complex reported here are consistent with the assignment of this complex as is \( \text{Rh(CO)}_2(\text{TFA})_3 \).

Figure 4a depicts the optimized geometry of the lowest energy isomer of \( \text{Rh(CO)}_2(\text{TFA})_3 \), assuming that it is in the gas phase. The other two isomers (not shown) possess trans carbonyls out of plane with the bidentate acetate, and cis carbonyls in plane with the bidentate acetate. The lowest energy isomer (shown) is the species of interest and adopts a pseudo-octahedral configuration with two cis-located carbonyls, one axial and one equatorial relative to the plane of the bidentate trifluoroacetate. One of the three trifluoroacetate ligands differs significantly from the others by bonding with Rh via both the O1 and O2 atoms, whereas the remaining two trifluoroacetate ligands bond to Rh through a single oxygen atom (O3 and O5, respectively). It is noted that the carbonyl ligands display a large degree of angular distortion relative to most terminal carbonyl ligands. The angle between the first carbonyl and the Rh (O7-C3-Rh1) is approximately 137 degrees, whereas Rh-C-O bond angles of approximately 180 degrees are usually observed. The origin of this distortion is the close interaction between the carbonyl ligand and the trifluoroacetate bound to Rh by a single oxygen atom. Indeed, the distance between the O4 oxygen atom of the trifluoroacetate and the C3 carbon atom of the carbonyl is unusually short, only 0.153 nm, which closely resembles the C1-O4 distance of 0.130 nm found in the trifluoroacetate ligand itself. These factors, taken together, suggest that a bonding interaction occurs between the carbonyl ligand and the trifluoroacetate ligand to form a five-membered ester-resembling ring with the Rh metal center. Since acetate ligands normally act as versatile bridging ligands [18,19], this interaction stabilizes the trifluoroacetate ligands in the complex and significantly alters the electronic and vibrational characteristics of the carbonyl. A similar interaction is also observed between the second trifluoroacetate ligand and the second carbonyl ligand, but the extent to which the interaction occurs is reduced, as indicated by the Rh1-C4-O8 and of approximately 165 degrees and a C4-O8 bond distance of 0.234 nm.

The \(^{13}\text{C}\) NMR chemical shift for the carbonyl groups present in \( \text{Rh(CO)}_2(\text{TFA})_3 \) were determined and then adjusted downwards by 65 ± 8 ppm to account for a systematic over prediction of the shift relative to measured \(^{13}\text{C}\) shifts for various Rh carbonyls. The corrected calculated chemical shift for C3 is 134.6 ± 8 ppm and that for C4 is 164.7 ± 8 ppm. The corresponding IR frequencies for the C3-O and the C4-O bonds calculated with standard correction are 1893 and 2121 cm\(^{-1}\), respectively. We note that the CO ligand that exhibits the unusually low \(^{13}\text{C}\) NMR shift and low C-O vibrational frequency is the one that interacts with one of the trifluoroacetate ligands. This type of inter-ligand interactions is similar to that reported by Chetcuti and coworkers for Rh aryl nitrile N-oxide complexes [20]. The crystal structure of this complex clearly shows that the carbonyl group interacts with the aryl nitrile N-oxide ligand in a manner very similar to that found in the calculations for \( \text{Rh(CO)}_2(\text{TFA})_3 \) (see Figure 5). Furthermore, the strong interaction of the CO ligand in Rh aryl nitrile N-oxide complexes with the aryl nitrile N-oxide ligand causes a red-shift in the C-O stretching frequency to between 1700 and 1640 cm\(^{-1}\).
In contrast to the $^{13}$C NMR shifts calculated for $\text{Rh(CO)}_2(\text{TFA})_3$, the experimental results show only a single $^{13}$CO peak at 130.0 ppm. The absence of a $^{13}$C NMR peak near 165 ppm, suggests that both CO ligands interact the with trifluoroacetate ligands. By separately constraining the carbonyl-acetate interaction distance for each pair (O4-C3 and O6-C4) $^{13}$C NMR shifts for each carbonyl ligand were computed over a range of interaction distances. These shifts (see Figure 6) were found to be almost entirely a function of interaction distance, rather than of placement of CO in the complex (axial or equatorial). Based on this information, a proposed structure for $\text{Rh(TFA)}_3(\text{CO})_2$ is shown in Figure 4b, for the case in which both CO ligands exhibit identical $^{13}$C NMR shifts at 130.0 ppm. This configuration of the complex shown in Figure 4b does not represent an equilibrium structure of this complex, since calculations were made assuming that the complex was in the gas phase. It is possible, however, that specific solvent interactions, which cannot be handled because of excessive computational cost, stabilize the structure of the complex shown in Figure 4b when it is in the liquid phase.

Additional DFT analysis was conducted to aid in characterization of the rhodium complex observed after reduction of the Rh(III) complex to a Rh(I) complex. The DFT calculations of Zheng and Bell [5] and those carried out in the context of the present study suggest that the Rh(I) complex is $\text{Rh(CO)}_2(\text{TFA})$, a 16-electron, d$^8$ complex with a pseudo-square planar geometry, in which the two carbonyl groups are cis-coordinated and the trifluoroacetate ligand is bonded to Rh by both oxygen atoms. As noted above, the experimental evidence indicates that the stable form of the Rh(I) complex exists as a dimer and consequently calculations were carried for both $[\text{Rh(CO)}_2(\text{TFA})]_2$ and the catalyst precursor, $[\text{Rh(CO)}_2\text{Cl}]_2$. Figure 7 depicts the calculated structure for $[\text{Rh(CO)}_2(\text{TFA})]_2$. The calculated $^{13}$C chemical shift for $[\text{Rh(CO)}_2(\text{TFA})]_2$ after correction is 184 ± 8 ppm, and the calculated IR frequencies are 2102, 2085, and 2049 cm$^{-1}$, whereas the calculated $^{13}$C chemical shift for $[\text{Rh(CO)}_2\text{Cl}]_2$ after correction is 182 ± 8 ppm, and the calculated IR frequencies are 2101, 2089, and 2045 cm$^{-1}$. These calculated values are to be compared with the experimentally observed $^{13}$C carbonyl shift for the Rh(I) complex of 177.2 ppm, and observed IR frequencies of carbonyl stretching frequencies of 2106, 2090, and 2033 cm$^{-1}$. The closeness of the observed $^{13}$C shifts and the IR band frequencies to those calculated for $[\text{Rh(CO)}_2(\text{TFA})]_2$ and $[\text{Rh(CO)}_2\text{Cl}]_2$ makes it impossible to say unambiguously whether one or both of these species is present once the active catalyst has been reduced from the Rh(III) to the Rh(I) state.

Additional calculations were carried out to determine the thermodynamics of converting $[\text{Rh(CO)}_2\text{Cl}]_2$ to $[\text{Rh(CO)}_2(\text{TFA})]_2$ via the reaction:

$$[\text{Rh(CO)}_2\text{Cl}]_2 + 2 \text{TFAH} \rightleftharpoons [\text{Rh(CO)}_2(\text{TFA})]_2 + 2 \text{HCl} \quad (1)$$

The Gibbs free energy change for this process at 298 K is +13 kcal/mol, which suggests that for a TFAH/Cl ratio of concentrations of approximately 2000 $[\text{Rh(CO)}_2\text{Cl}]_2$ would be favored by about 8 to 1 over $[\text{Rh(CO)}_2(\text{TFA})]_2$. The thermodynamics for dissociating the dimeric species $[\text{Rh(CO)}_2(\text{TFA})]_2$ to the monomeric species $\text{Rh(CO)}_2(\text{TFA})$ was also examined. The Gibbs free energy change for the reaction:
\[ \text{[Rh(CO)\textsubscript{2}(TFA)\textsubscript{2} \rightleftharpoons 2 \text{Rh(CO)\textsubscript{2}(TFA)} \quad (2) \]

was found to be approximately \(+15\) kcal/mol, indicating that formation of the monomeric species is highly unfavorable. However, in the presence of the oxidizing species (see Scheme 1), the Rh(I) complex is converted completely to the Rh(III) complex as shown by the experimental evidence presented above.

The identity of the vanadium complexes formed in solution was investigated in the following manner. \(\text{NH}_4\text{VO}_3\) was dissolved in trifluoroacetic acid and the resulting orange-colored solution was then dried in a vacuum oven to yield an orange-colored powder. This product was then dissolved in D\textsubscript{2}O and analyzed by \(^{51}\text{V}\) and \(^{19}\text{F}\) NMR. The results are depicted in Figure 8a and Figure 8b, respectively. The chemical shift of the vanadium species, which appeared at -545 ppm is assigned to \(\text{VO}_2^+\) species [21]. A strong fluorine peak was observed at -75 ppm characteristic of trifluoroacetate anions [22,23]. Taken together, these results suggest that the \(\text{NH}_4\text{VO}_3\) reacts with trifluoroacetic acid to form the vanadium species \((\text{VO}_2)(\text{TFA})\) via the following reaction:

\[
\text{NH}_4\text{VO}_3 + \text{TFAH} \rightarrow (\text{VO}_2)(\text{TFA}) + \text{NH}_3 + \text{H}_2\text{O} \quad (3)
\]

As indicated above, when a sample of this vanadium complex was added to toluene, a color change occurred associated with the appearance of two peaks at 410 and 455 nm in the UV-visible spectrum. Analysis of the toluene phase by GC/MS indicated trace quantities of toluene oxidation products, such as benzaldehyde and the ester of benzyl alcohol and trifluoroacetic acid, suggesting that the observed color change from yellow to orange/brown is associated with the reduction of the \(\text{V(V)}\) species to \(\text{V(IV)}\) species, a process known to occur with vanadyl compounds and arenes [24]. In the presence of a water, \((\text{VO}_2)(\text{TFA})\) dissociates to form \(\text{VO}_2^+\) and TFA\(_3^-\), as suggested by the chemical shifts observed in the \(^{51}\text{V}\) and \(^{19}\text{F}\) NMR spectra. In the presence of toluene, trifluoroacetic acid, and trifluoroacetic anhydride, \((\text{VO}_2)(\text{TFA})\) is most likely present as cation anion pair because of the low di-electric constant of the solution. Our DFT calculations show that the stable form of this ion pair is a dimer, \([(\text{VO}_2)(\text{TFA})\text{]}_2\), rather than a monomer, as shown in Figure 9a. This complex resembles vanadium (V) complexes, which have been shown to form stable 5-coordinate dimeric species [25].

The V complexes present during the oxidation of Rh(I) to Rh(III) were analyzed by \(^{51}\text{V}\) NMR. Figure 10 depicts the results of \(^{51}\text{V}\) NMR of \(\text{NH}_4\text{VO}_3\) dissolved in toluene, trifluoroacetic acid, and trifluoroacetic anhydride, where a broad peak appeared at -634 ppm which we attribute to \([(\text{VO}_2)(\text{TFA})\text{]}_2\) species. The difference in chemical shift from this peak and the peak at -545 ppm when this compound is dissolved in D\textsubscript{2}O is attributable to solvent effects [26]. When \([\text{Rh(CO)\textsubscript{2}Cl}]_2\) was added to this solution at room temperature, the color of the solution changed rapidly from orange to green/brown, and the intensity of the \(^{51}\text{V}\) peak associated with \([(\text{VO}_2)(\text{TFA})\text{]}_2\) diminished. Increasing the concentration of Rh(I) caused the peak associated with \(\text{VO}_2^+\) to disappear entirely, but no other peaks appeared in the \(^{51}\text{V}\) NMR spectrum. The observed change can be attributed to the reaction:
Rh(CO)$_2$(TFA) + [VO$_2$(TFA)]$_2$ + 4TFAH $\rightarrow$ Rh(CO)$_2$(TFA)$_3$ + 2VO(TFA)$_2$ + 2H$_2$O (4)

The calculated structure for VO(TFA)$_2$ is given in Figure 9b. The V(IV) species formed as a result of this reaction could not be observed by $^{51}$V NMR because of the quadrupolar relaxation of the paramagnetic V(IV) species, which caused the peaks to broaden extensively precluding their detection. The V(IV) species could, however, be observed by UV-visible spectroscopy. Addition of a small quantity of [Rh(CO)$_2$Cl]$_2$ to a solution containing NH$_4$VO$_3$ dissolved in trifluoroacetic acid and water resulted in an immediate color change from orange to blue/green. The resulting UV-visible spectrum is shown in Figure 11 [2], exhibited $^2$B$_{2g}$ $\rightarrow$ $^2$E$_g$, $^2$B$_{2g}$ $\rightarrow$ $^2$B$_{1g}$, and $^2$B$_{2g}$ $\rightarrow$ $^2$A$_{1g}$ transitions at 760, 620, and 520 nm, similar to those reported in the literature for VO$_2^+$ ions upon tetragonal distortion [27,28]. Thus, UV-visible and $^{51}$V NMR spectroscopy provide evidence that the active form of the oxidant is VO$_2^+$, and that this species reduces to VO$_2^+$ upon oxidation of Rh(I) to Rh(III) via the reaction shown above.

3.6 Conclusions

Evidence accumulated from experiments and theory provides strong support for the composition and structures of the rhodium and vanadium complexes involved in the mechanism for the oxidative carbonylation of toluene to toluic acid depicted in Scheme 1. The active form of the Rh complex is Rh(CO)$_2$(TFA)$_3$. The cis-positioned carbonyl groups in this complex are found to exhibit unusual interactions with the trifluoroacetate ligands, which give rise to a five-membered ring involving the central rhodium atom. In the course of the reaction, Rh(CO)$_2$(TFA)$_3$ reduces to Rh(CO)$_2$(TFA), which, in turn, readily dimerizes to form [Rh(CO)$_2$(TFA)]$_2$, which exists in equilibrium with the more stable dimer species, [Rh(CO)$_2$Cl]$_2$. The vanadium species involved in the reoxidation of Rh(I) to Rh(III) (see Scheme 1) is identified as [VO$_2$(TFA)]$_2$. Reoxidation of Rh(I) by this V(V) species is very rapid and leads to the formation of the paramagnetic species VO(TFA)$_2$. 


3.7 Figures

Figure 3.1 a) Full 13C NMR spectrum (0 – 200 ppm) of the reaction solution. b) view of spectrum from 120 to 140 ppm. Toluene (12.4 mmol), trifluoroacetic acid (4.2 mmol), and trifluoroacetic anhydride (1.3 mmol) [Rh(CO)2Cl]2 (14.4 μmol), NH4VO3 (44 μmol), 0.345 MPA O2, 0.345 MPa CO, T = 353K, t = ½ h.
Figure 3.2  a) Reaction solution after $\frac{1}{2}$ hour. Toluene (12.4 mmol), trifluoroacetic acid (4.2 mmol), and trifluoroacetic anhydride (1.3 mmol) [Rh(CO)$_2$Cl]$_2$ (5 μmol), NH$_4$VO$_3$ (170 μmol), 0.345 MPa O$_2$, 0.345 MPa CO, $T = 353K$, $t = \frac{1}{2}$ h. b) Reaction solution after exposure to CO for 3 hours. 0.345 MPa CO, $T = 353K$, $t = 3$ h.
Figure 3.3 $^{13}$C NMR spectra of Rh the reaction solution after 3 h in absence of O$_2$. Toluene (49.5 mmol), trifluoroacetic acid (17.2 mmol), and trifluoroacetic anhydride (4.9 mmol), [Rh(CO)$_2$Cl$_2$] (219.7 μmol), NH$_4$VO$_3$ (1 mmol), 0.345 MPa CO, T = 353K, t = 3 h.
Figure 3.4  a) Computed geometry for the Rh(CO)$_2$(TFA)$_3$ complex.  b) Computed geometry for Rh(CO)$_2$(TFA)$_3$ showing the interaction of both carbonyl ligands with trifluoroacetate ligands.
Figure 3.5 Comparison of structures of Rh(CO)(TFA) interaction with Rh(CO)(C(Ar)NO) interaction proposed by Chetcuti and coworkers [17]. Extraneous ligands were omitted for clarity.

Figure 3.6 Computed $^{13}$C NMR chemical shifts as a function of constrained carbonyl-acetate distance for axial and equatorial CO.
Figure 3.7 Computed geometry for [Rh(CO)$_2$(TFA)]$_2$. 
Figure 3.8 0.138 mmol NH₄VO₃, 26.2 mmol TFAH. a) $^{51}$V NMR spectrum of (VO₂)(TFA) dissolved in D₂O. b) $^{19}$F NMR spectrum of (VO₂)(TFA) dissolved in D₂O.
Figure 3.9  a) Computed geometry for [VO$_2$(TFA)]$_2$.  b) : Computed geometry for VO(TFA)$_2$. 
Figure 3.10 $^{51}$V NMR spectra of NH$_4$VO$_3$ (69 $\mu$mol) dissolved in TFAH (12.9 mmol).

Figure 3.11 UV-Visible spectrum of a solution of NH$_4$VO$_3$ taken before and after addition of Rh(I).
Scheme 3.1 Proposed mechanism for Rh and V catalyzed toluene oxidative carbonylation.
3.9 References and Notes


$^{51}$V NMR of the vanadium complex indicated a strong interaction with the solvent as indicated by a change in chemical shift when the acid was changed from acetic acid ($^{51}$V $\delta$ = -545 ppm), dichloroacetic acid ($^{51}$V $\delta$ = -574 ppm), chlorodifluoroacetic acid ($^{51}$V $\delta$ = -625 ppm), pentafluoropropionic acid ($^{51}$V $\delta$ = -630 ppm), trifluoroacetic acid ($^{51}$V $\delta$ = -634 ppm), methanesulfonic acid ($^{51}$V $\delta$ = -685 ppm).


Chapter 4

Effects of ligand composition on the oxidative carbonylation of toluene to toluic acid catalyzed by Rh(III) complexes

4.1 Abstract

Experimental and theoretical studies were conducted to investigate the influence of anionic ligands (e.g. CF$_3$COO$^-$, CH$_3$SO$_3^-$) on the catalytic activity and selectivity of Rh(III) for the oxidative carbonylation of toluene to toluic acid. The catalyst activity is found to pass through a maximum as the pKa of the conjugate Brønsted acid decreases from 4.63 to -2.00, with the maximum activity occurring at pKa = 0.35, corresponding to CClF$_2$COOH. Theoretical analysis shows that the strength of toluene coordination increases with decreasing basicity of the anion, i.e., decreasing pKa of the corresponding acid. By contrast, the activation barrier for C-H activation increases with decreasing ligand pKa. The experimentally observed effect of anion composition on catalyst activity can be explained from calculations of the apparent rate coefficient for toluene activation based on DFT and transition state theory. The ratio of para to meta toluic acid formed increases with decreasing acid pKa and passes through a maximum for pKa = 0, corresponding to CF$_3$COOH. The effect of anion composition on the isomer selectivity is attributed to changes in the charge density on the Rh(III) cation, which, in turn, affect the distribution of charge on the para and meta carbon atoms on the aromatic ring.

4.2 Introduction

The oxidative carbonylation of aromatic hydrocarbons to produce carboxylic acids was first demonstrated by Fujiwara and coworkers using Pd(II) cations in acetic acid [1-5]. In subsequent work, it was shown that oxidative carbonylation of
aromatic hydrocarbons, particularly benzene and toluene, could also be catalyzed by Rh cations, and that for both Pd(II) and Rh(III) cations, the use of trifluoroacetic acid resulted in significantly higher reaction rates than the use of acetic acid [6-17]. In their investigation of the oxidative carbonylation of alkanes, Fujiwara and coworkers [6] noted that acids more or less acidic than trifluoroacetic acid, such as trifluoromethanesulfonic and methanesulfonic acids or dichloroacetic and acetic acid are ineffective in promoting the formation of carboxylic acids in the presence of Pd cations. Zakzeski and Bell have recently demonstrated that acid composition has a considerable effect on the activity and selectivity of Rh(III) and Pd(II) for the oxidative carbonylation of benzotri fluoride to trifluoromethylbenzoic acid [18]. Attempts to explain the effect of acid composition on the catalytic activity of Rh(III) and Pd(II) complexes on the oxidative carbonylation of arenes have focused on the impact of the anionic ligands derived from acids on the electrophilicity of the cation. Thus, for example, Fujiwara and coworkers [8] and Kalinovski and coworkers [13] have attributed the higher rate of oxidative carbonylation in trifluoroacetic acid than in acetic acid to the higher electrophilicity imparted to the metal cation by trifluoroacetate than by acetate anions. Implicit in this interpretation is the assumption that the rate-limiting step in oxidative carbonylation of aromatic compounds is electrophilic activation of a C-H bond on the aromatic ring. Recent theoretical work indicates that C-H activation of aromatic compounds can also occur by other mechanisms. For example, Ziatdinov and coworkers have concluded that the C-H bond activation of benzene by the complex Pt(pic)(TFA)$_2$ (pic = picolinate) is best described as an electrophilic substitution proceeding via addition of the Pt center to the arene ring as opposed to σ-bond metathesis [19]. Work by Davies et al. on the cyclometallation of dimethyl benzylamine (DMBA-H) with Pd(OAc)$_2$ and Ir(OAc)Cp (OAc = acetate) shows that C-H bond activation in the case of Pd(OAc)$_2$ proceeds via an agostic C-H complex [20], whereas in the case of Ir(OAc)Cp, C-H bond activation proceeds by an electrophilic mechanism [21].

The objective of the present investigation was to develop a systematic understanding of the effects of ligand composition on the oxidative carbonylation of toluene to toluic acid catalyzed by Rh(III) complexes. Previous investigations of the mechanism and kinetics of this reaction have suggested that when the solvent is the reactant itself, the Rh(III) cation is stable as a cation-anion pair [8,18,22]. This view is supported by a theoretical study of the oxidative carbonylation of toluene by Rh(III) cations in the presence of trifluoroacetic acid (TFAH) [23]. This work suggests that the species responsible for the activation of toluene is Rh(CO)$_2$(TFA)$_3$. In the course of the reaction Rh(III) is reduced to Rh(I) and the latter cation must be reoxidized in order to complete the catalytic cycle. If NH$_4$VO$_3$ is used as the oxidant, the rate of reoxidation is much more rapid than the rate of reduction and, hence, Rh in its resting state is present as Rh(III) [22]. The composition and structure of the catalytically active species have been investigated recently by combined spectroscopic and theoretical work, and this effort has confirmed that the resting state of the catalyst is Rh(CO)$_2$(TFA)$_3$ [24].

Scheme 1 illustrates the mechanism for the oxidative carbonylation of toluene to toluic acid catalyzed by Rh(CO)$_2$(TFA)$_3$ when [VO$_2$]$^+$ cations serve as the
oxidizing agent for the reoxidation of Rh(I) to Rh(III) [23-24]. Both experimental and theoretical studies suggest that the first step in the oxidative carbonylation of toluene is the coordination of the toluene by Rh(III) followed by C-H bond activation of the arene to produce a Rh-arene complex and TFAH. Theoretical and experimental analysis of the process suggests that the coordination of toluene to the Rh complex, \( \text{Rh(CO)}_2(\text{TFA})_3 + \text{C}_6\text{H}_5\text{CH}_3 \leftrightarrow \text{Rh(CO)}_2(\text{TFA})_3(\text{C}_6\text{H}_5\text{CH}_3) \), is equilibrated and that C-H bond activation is the rate-limiting step [23-24]. Thus, it is of interest to establish the roles of anion composition in promoting the coordination of toluene and the activation of the C-H bond associated with the aromatic ring. With this aim in mind, we have investigated the effects of ligand composition on the rate of oxidative carbonylation of toluene both experimentally and theoretically.

### 4.3 Experimental

Reactions were conducted in a stirred, 50 mL Parr autoclave made of Hastelloy C. Between runs, the reactor was washed thoroughly with water and acetone and then dried in a vacuum oven. The reaction temperature was monitored using a thermocouple located inside a Hastelloy C thermowell. During a typical reaction, 3.46 g of anhydrous toluene (99.8%, Aldrich), 13 mmol of either \( \text{CF}_3\text{COOH} \) (99%, Aldrich), \( \text{CF}_2\text{ClCOOH} \) (98%, Aldrich), \( \text{C}_2\text{F}_5\text{COOH} \) (97%, Aldrich), \( \text{CCl}_3\text{COOH} \) (99%, Aldrich), \( \text{CCl}_2\text{HCOOH} \) (99%, Aldrich), \( \text{CCIH}_2\text{COOH} \) (99%, Aldrich), \( \text{CH}_3\text{COOH} \) (99.7%, EMD), \( \text{CF}_3\text{SO}_3\text{H} \) (98%, Aldrich), or \( \text{CH}_3\text{SO}_3\text{H} \) (≥99.5%, Aldrich), 3.8 mmol of either \( \text{CF}_3\text{CO}_2\text{O} \) (≥99%, Aldrich), \( \text{CF}_2\text{ClCO}_2\text{O} \) (98%, Aldrich), \( \text{C}_2\text{F}_5\text{CO}_2\text{O} \) (99%, Aldrich), \( \text{CCl}_3\text{CO}_2\text{O} \) (96%, Aldrich), \( \text{CCl}_2\text{HCO}_2\text{O} \) (Aldrich, 96%), \( \text{CCIH}_2\text{CO}_2\text{O} \) (Alfa Aesar, 96%), \( \text{CH}_3\text{CO}_2\text{O} \) (99%, EM Science), \( \text{CF}_3\text{SO}_2\text{O}_2\text{O} \) (99+, Aldrich), or \( \text{CH}_3\text{SO}_2\text{O}_2\text{O} \) (97%, Aldrich), 0.0039 g of \( \text{Rh(acac)}_3 \) (97%, Aldrich), and 0.0604 g of \( \text{NH}_4\text{VO}_3 \) (99+, Aldrich) were placed into the autoclave, which was then sealed and purged four times with nitrogen. After purging, the reactor was pressurized at 293 K with 0.345 MPa \( \text{O}_2 \) (99.993%, Praxair) and 0.345 MPa \( \text{CO} \) (99.5%, Praxair). The reactor was then heated to 353 K in approximately 10 min and then held at this temperature for 4 h. Upon the completion of the reaction, the reactor was quenched with ice water to 308 K and vented. The quantity of toluic acid was determined by gas chromatography using an Agilent Technologies 6890N gas chromatograph equipped with an HP-1 capillary column coated with crosslinked methyl siloxane and an FID detector.

### 4.4 Theoretical

Electronic structures and energies of reactants, products, and transition states were determined using density functional theory (DFT) implemented in Q-Chem [25]. The B3LYP functional was used to describe electron exchange and correlation, and the 6-31G* basis set was used to locate optimized ground-state and transition-state structures. The LANL2DZ effective core potential was used to describe the Rh atom. After a particular molecular structure was optimized to a stationary point (transition state or
minimum energy structure), its energy was further refined at a higher level of theory using the 6-311G**/LANL2DZ basis set (see also Supporting Information). All stationary and transition state points were found on the basis of gas-phase calculations. The Growing String Method (GSM) was used to locate the transition state (TS) connecting two minimum energy structures [26]. In this method a minimum energy path connecting the reactant and product is estimated without making an initial guess for the reaction path. The point with highest energy on this reaction path is taken as an estimate of the transition state geometry, which is then converged to the exact saddle point by the transition state finding algorithm implemented in Q-Chem. Vibrational analysis was performed to ensure the nature of energy minima and transition states, as well as to generate thermochemical data. All energies and free energies are reported for the gas phase at 353 K, the experimental reaction temperature. Vibrational, rotational, and translational entropy values were computed using standard statistical mechanical methods within the rigid rotor–harmonic oscillator approximation. The energetics of toluene binding were BSSE corrected using the counterpoise method. Equilibrium constants were calculated at a standard state of 1 bar, and adjusted to molar concentration units according to Equation 1

\[
K = \left( \frac{RTc^o}{P^o} \right)^{-\nu} \exp\left( -\frac{\Delta G^o}{RT} \right)
\]

where \( K \) is the equilibrium constant, \( R \) is the gas constant, \( c^o \) is the standard state concentration in the liquid phases (1 mol/L), \( P^o \) is standard state pressure, \( \nu \) is the stoichiometric coefficient, \( \Delta G^o \) is Gibbs free energy of reaction at the reaction temperature, and \( T \) is temperature. Rate coefficients constants were computed from transition state theory, as described by Equation 2

\[
k = \frac{k_B T}{h} \exp\left( \frac{\Delta S^i}{R} \right) \exp\left( -\frac{\Delta H^i}{RT} \right)
\]

where \( k \) is elementary rate constant, \( k_B \) is Boltzmann’s constant, \( h \) is Planck’s constant, and \( \Delta S^i \) and \( \Delta H^i \) are the entropy and enthalpy of activation at the reaction temperature, respectively. Energy decomposition analysis (EDA) was performed using the method of Khaliullin et al., as implemented in Q-Chem [27].

4.5 Results and Discussion

Figure 1 shows the effect of acid pKa on the number of turnovers obtained for Rh(III) at various reaction times. The reactions for \( t = 4 \) h were repeated in triplicate. Comparison of the turnover numbers for reactions at different times indicates that the relative order of catalytic activity with respect to acid pKa remained constant. In each case, the total reaction time includes the time required to heat and cool the autoclave (see Supporting Information). As indicated by Figure 1, only acids with pKa’s between -2 and 3 were effective in producing toluic acid, and the most effective acids were those with pKa’s between 0 and 0.5 [28-30].
Within this range, CClF2COOH (pKa = 0.35) yielded the highest number of turnovers. Reduced catalytic activity was observed for acids with higher pKa values relative to CClF2COOH, such as CCl3COOH, CCl2HCOOH, CClH2COOH, and CH3COOH, as well as acids with pKa’s lower than CClF2COOH, such as C2F5COOH and CH3SO2OH. The data shown in Figure 1 also confirms that both very strong and very weak acids are ineffective in promoting the oxidative carbonylation of toluene to toluic acid consistent with the observations of Fujiwara and coworkers for the oxidative carbonylation of alkanes [6].

The oxidative carbonylation of toluene to toluic acid involves several important steps in which ligands play an integral role. These include the coordination of toluene to the Rh complex and subsequent C-H bond activation, the reductive elimination of toluic-trifluoroacetic mixed anhydride, and the re-oxidation of Rh(I) species to complete the catalytic cycle [12,22]. In the case of trifluoroacetic acid, the rate of re-oxidation is rapid and C-H bond activation is the rate limiting step [22,24]. To ascertain that the reduced activity observed with acids more or less acidic than CClF2COOH resulted from toluene C-H bond activation rate and not from a decrease in Rh re-oxidation rate, experiments were conducted to determine the resting state of the catalyst in a manner similar to that used for the case of trifluoroacetic acid [24]. In all cases except for CH3COOH, the rate of re-oxidation was rapid, and the resting state of the catalyst was found to be Rh(III). Spectroscopic analysis suggests that in the presence of acetic acid, the majority of Rh was present as Rh(I).

The kinetics for the oxidative carbonylation of toluene can be represented in terms of the two reactions shown below, illustrated for the case in which trifluoroacetate (TFA) anions, derived from trifluoroacetic acid (TFAH), serve as the ligands:

\[
\text{Rh(CO)}_2(\text{TFA})_3 + \text{C}_6\text{H}_5\text{CH}_3 \rightleftharpoons \text{Rh(CO)}_2(\text{TFA})_3(\text{C}_6\text{H}_5\text{CH}_3) \quad \text{Reaction 1}
\]

\[
\text{Rh(CO)}_2(\text{TFA})_3(\text{C}_6\text{H}_5\text{CH}_3) \rightarrow \text{Rh(CO)}_2(\text{TFA})_2(\text{TFAH})(\text{C}_6\text{H}_4\text{CH}_3) \quad \text{Reaction 2}
\]

Reaction 1 represents the reversible coordination of toluene to the complex Rh(CO)$_2$(TFA)$_3$ and Reaction 2 represents the irreversible activation of the para C-H bond in the coordinated toluene to form the complex Rh(CO)$_2$(TFA)$_2$(TFAH)(C$_6$H$_4$CH$_3$). The rate of toluene activation, \( r \), can then be written as:

\[
r = k_{app}[\text{Rh}][\text{CH}_3\text{C}_6\text{H}_5] \quad (3)
\]

where

\[
k_{app} = K_{coord}k_{act} \quad (4)
\]

In equations 3 and 4, \( k_{app} \) is the apparent rate coefficient for the oxidative carbonylation of toluene, \( k_{act} \) is the intrinsic rate coefficient for activation of the C-H bond, \( K_{coord} \) is the equilibrium constant for the coordination of toluene to the
complex Rh(CO)$_2$(TFA)$_3$, and [Rh] and [CH$_3$C$_6$H$_5$] are the concentrations of Rh(CO)$_2$(TFA)$_3$ and toluene, respectively. The turnover number based on the formation of toluic acid, TON, can then be expressed as follow, assuming that the reaction occurs in a well-stirred batch reactor:

$$TON = \frac{[CH_3C_6H_4COOH]}{[Rh]_0} = \frac{[CH_3C_6H_5]_0}{[Rh]_0} (1 - \exp(-k_{app}[Rh]_0 t))$$  \hspace{1cm} (5)$$

In this expression [Rh]$_0$ and [CH$_3$C$_6$H$_5$]$_0$ represent the concentrations of Rh and toluene loaded into the reactor, and $t$ is the reaction time. Since the rate of reoxidation of Rh(I) to Rh(III) is very rapid compared to the rate of reduction of Rh(III), the concentration of Rh(III) is assumed to be equivalent to the concentration of Rh placed into the reactor at the start of an experiment.

Equation 4 suggests that ligand composition can affect the kinetics of toluic acid formation in two ways. The first is through the effect of the anion in ligands on the coordination of toluene and the second is through the effect of the ligands on C-H bond activation. As suggested by earlier work, weakly basic anions promote the coordination of toluene by enhancing the electrophilicity of the Rh(III) cation [12]; however, the anions must be sufficiently basic to accommodate the proton from the aromatic ring of toluene in the rate-limiting step of C-H activation. This interpretation is supported by our quantum chemical calculations discussed below.

Figure 2 shows the number of turnovers predicted from Equation 4 after 4 h of reaction. Consistent with experimental observations, the highest turnover number occurs for CClF$_2$COOH and the value of the turnover number for this acid is in good agreement with that observed experimentally (see Figure 1). It is noted, though, that the decrease in turnover number for acids with higher or lower pKa’s than CClF$_2$COOH (pKa = 0.35) is more rapid than that observed in Figure 1. The variation in the number of turnovers with the pKa of the acid from which the anionic ligands derive can be interpreted in terms of the value of $\Delta G_{app}$, defined as $\Delta G_{app} = \Delta G_{\text{coord}} + \Delta G_{\text{act}}^{\text{app}}$ since $k_{app}$ is exponentially dependent on $\Delta G_{app}$. The dependence of $\Delta G_{app}$ on the pKa of the acid from which the anionic ligand is derived is shown in Figure 3. This figure shows that the lowest value of $\Delta G_{app}$ is for CClF$_2$COOH. Consistent with this, the value of $k_{app}$ is largest for CClF$_2$COOH and, likewise, so is the turnover number determined from Equation 5 (see Figure 2). The sharpness of the change in the turnover number with acid pKa can be ascribed to the degree of change in the value of $\Delta \Delta G_{app}$, the difference in apparent Gibbs free energy of activation relative to that calculated for CClF$_2$COOH, with acid composition. For example, the value of $\Delta \Delta G_{app}$ is 3.9 kcal/mol for CCl$_3$COOH and $\Delta \Delta G_{app}$ is 1.7 kcal/mol for CF$_3$COOH compared to CClF$_2$COOH. Reference of Figure 1 suggests that $\Delta \Delta G_{app}$ should be $\sim \pm 1$ to obtain the experimentally observed results. Thus, while the theoretically derived values of $\Delta G_{app}$ reproduce the trends seen experimentally, the differences in the value of this quantity are not calculated accurately enough to capture the magnitude of the observed changes in the turnover numbers. Solvent interactions with the catalyst may also contribute to charge delocalization, which could result in the gradual decrease observed experimentally.
The cause of the variation in the magnitude of $\Delta G_{\text{app}}$ with pKa can be understood more completely by examining the effects of anionic ligand composition on the component part of $\Delta G_{\text{app}}$, specifically $\Delta G_{\text{coord}}$ and $\Delta G_{\text{act}}^\dagger$. As seen in Figure 3, the magnitude of $\Delta G_{\text{coord}}$ goes through a minimum at a pKa of ~0, corresponding to CF$_3$COOH, but the effect of pKa on $\Delta G_{\text{act}}^\dagger$ is more complex. This component of $\Delta G_{\text{app}}$ tends to increase with decreasing pKa of the acid from which the anionic ligand derives; however, this trend is not completely monotonic in the pKa range of 1 to 0. It is as a consequence of these small variations that the minimum value of $\Delta G_{\text{app}}$ occurs for CClF$_3$COOH.

Figure 4 shows the internal energetics of toluene coordination and C-H bond activation, $\Delta E_{\text{coord}}$ and $\Delta E_{\text{act}}^\dagger$ respectively, as well as $\Delta E_{\text{app}}$, defined as $\Delta E_{\text{app}} = \Delta E_{\text{coord}} + \Delta E_{\text{act}}^\dagger$. The value of $\Delta E_{\text{coord}}$ decreases more or less monotonically with decreasing pKa down to pKa = 0, corresponding to CF$_3$COOH, but then suddenly increases for CH$_3$SO$_2$OH, which has a pKa of -2. The decreases in the magnitude of $\Delta E_{\text{coord}}$ with decreasing pKa for the carboxylate anions is a direct consequence of the increasing electronegativity of the anion, which causes the positive charge on the Rh cation to increase. The latter effect makes the cation more electrophilic and, hence, strengthens the coordination of toluene (see below for further details). By extension of this logic one would expect the value of $\Delta E_{\text{coord}}$ for CH$_3$SO$_3$O$^-$ anions derived from CH$_3$SO$_2$OH to be lower than that for C$_2$F$_5$COO$^-$ anions derived from C$_2$F$_5$COOH; however, Figure 4 shows that this is clearly not the case. The reason for the anomalous behavior of CH$_3$SO$_2$OH is discussed below. Figure 4 also shows that $\Delta E_{\text{act}}^\dagger$ increases when the pKa decreases from 5 to 3, but thereafter the value of this component of $\Delta E_{\text{app}}$ decreases slightly. Finally, it is interesting to observe that $\Delta E_{\text{app}}$ is smallest for C$_2$F$_5$COOH, from which it might be concluded based purely on energetic considerations that the anionic ligands derived from this acid (C$_2$F$_5$COO$^-$) should produce the highest catalyst activity. That this is not the case is a result of the variations in $\Delta S_{\text{app}}$, the apparent entropy of activation, on $\Delta G_{\text{app}}$ arising from differences in composition of the anionic ligands. Thus, to summarize, the minimum in the $\Delta G_{\text{app}}$ with pKa, seen in Figure 3, is a consequence of the combined effects of anionic ligand composition on the apparent energy and entropy of activation.

The abnormally high toluene coordination energy, $\Delta E_{\text{coord}}$, for the case of CH$_3$SO$_2$OH, can be understood by carrying out an energy decomposition analysis (EDA) $\Delta E_{\text{coord}}$ [27]. EDA represents $\Delta E_{\text{coord}}$ as the sum of four terms - $\Delta E_{\text{GD}}$, $\Delta E_{\text{FRZ}}$, $\Delta E_{\text{POL}}$, and $\Delta E_{\text{CT}}$. $\Delta E_{\text{GD}}$ is the geometric distortion contribution, which accounts for the energy required to take the reactants from their equilibrium geometries (i.e. free toluene and free Rh complex) to the geometry they assume in the complex (in this case, the state in which toluene is coordinated to the rhodium complex). $\Delta E_{\text{FRZ}}$, the frozen density interaction, is defined as the electrostatic repulsion of the reactants, viz., the toluene and the Rh complex. $\Delta E_{\text{POL}}$ is the polarization energy lowering attributed to relaxation of the molecular orbitals due to the presence of toluene coordinated to the Rh complex. Finally $\Delta E_{\text{CT}}$, the charge transfer energy lowering, is defined as the stabilization that results from moving charge from one reactant to the other (in this case, primarily from toluene to the Rh complex).

The results of EDA are shown in Figure 5. Trend lines are fitted to the ligands derived from carboxylic acids and then extrapolated to methanesulfonic
acid. This analysis provides general insight into the effect of ligands on toluene binding. $\Delta E_{\text{FRZ}}$ tends to increases as pKa decreases. The slightly negative slope of this trend indicates that the electrostatic repulsion of the electrons in the Rh complex increases as the electron density on the complex increases. The value of $\Delta E_{\text{POL}}$ tends to decrease as pKa decreases, indicating that as the pKa of the acid used to derive the ligands decreases the complex is better able to redistribute charge. The trend in $\Delta E_{\text{POL}}$ strongly resembles that for $\Delta E_{\text{FRZ}}$. The value of $\Delta E_{\text{CT}}$ also tends to decrease with decreasing pKa. This trend is a consequence of the increase in the electropositive character of the Rh cation which, in turn, increases the extent of charge transfer from the coordinated toluene. The magnitude of $\Delta E_{\text{GD}}$ results from distortions in both complex and toluene but is dominated by the distortion of the complex, and it tends to increase with decreasing pKa. Specifically, in the course of coordinating toluene the catalyst must break one of the Rh-O bonds associated with a bidentate ligated acetate anion to accommodate toluene into the coordination sphere [22-23]. The increase in $\Delta E_{\text{GD}}$ shows that ligands derived from acids with lower pKa require more energy to make the transition from bidentate to monodentate ligation of an anion.

The EDA for methanesulfonic acid shows that while most terms follow the trends with pKa seen for the carboxylic acids, there are some notable differences. The value of $\Delta E_{\text{FRZ}}$ for CH$_3$SO$_2$OH is consistent with that for the carboxylic acids, which indicates that the electrostatic repulsion of the electrons in the complex does not contribute disproportionately to the higher value of $\Delta E_{\text{coord}}$. The $\Delta E_{\text{POL}}$ for CH$_3$SO$_2$OH is slightly above the carboxylic acid trend line, indicating that methanesulfonate anion cannot redistribute charge quite as well as carboxylate anions. The value of $\Delta E_{\text{CT}}$ for CH$_3$SO$_2$OH is again slightly higher than that projected by the trend line for carboxylic acids, indicating that the ability of methanesulfonic acid to accept and redistribute charge contributes to its weak binding. However, most importantly, the magnitude of $\Delta E_{\text{GD}}$ for CH$_3$SO$_2$OH lies considerably above the trend line for the carboxylic acids. This deviation indicates that the energy required to convert bidentate to monodentate ligated CH$_3$SO$_2$O$^-$ required for the Rh cation to coordinate toluene is notably higher than that projected for an carboxylate anion of equivalent basicity, and it is this effect that reduces the overall binding strength of toluene when the anions coordinated to Rh are CH$_3$SO$_2$O$^-$. The combined influence of the four terms comprising $\Delta E_{\text{coord}}$ results in a less favorable binding energy for the Rh methanesulfonate complex than expected for a Rh complex involving a carboxylate anion derived from an acid with a pKa equivalent to CH$_3$SO$_2$OH.

Examination of the geometry of the coordinated toluene complex and transition state involved in the activation of the C-H bond at the para position provide additional insights into the chemistry by which the oxidative carboxylation of toluene occurs. Figure 6 shows the geometries of coordinated toluene and the relevant bond distances for the various ligands. Since methanesulfonate ligands have two oxygens with which to receive the abstracted H atom, each methanesulfonic acid catalyst reaction possesses two possible transition states. Only the lower energy transition state of methanesulfonic acid was considered in this study. In the minimum-energy configuration for coordinated toluene, two of the three anions and the two CO ligands lie in the equatorial plane, whereas toluene and
the third anion are axially coordinated. As the pKa of the conjugate acid decreases, going from CH$_3$COOH to CH$_3$SO$_2$OH, the length of the Rh-C bond tends to decrease, the most dramatic shortening occurring when progressing from CH$_3$COOH to CClH$_2$COOH. The decrease in the Rh-C distance is a consequence of the increasing electropositive character of the Rh cation as the pKa of the conjugate acid decreases, which leads to tighter coordination of the arene. Similarly, the decrease in H-O1 distance occurs because the more basic acetate ligand is better able to interact with the proton at the *para* position of toluene. The electronegativity of the anionic ligand, however, has no effect on the length of the C-H bond. The length of the Rh-H bond is greater than 2.64 Å in all cases and, hence, there is no evidence for the formation of an agostic C-H interaction with the Rh cation, which would be characterized by a Rh-H distance of 1.9 Å or less [20].

Figure 7 shows the geometry of the transition-state for the C-H bond activation step (Reaction 2) and the associated table gives the interatomic bond distances as a function of the anion composition. In all cases, the length of the C-H bond undergoing activation increases from 1.09 Å in the coordinated toluene to 1.26 Å or greater in the transition state, the length of this bond decreasing with increasing pKa of the associated acid. The increased basicity of the ligand results in an earlier transition state during the C-H bond activation step, and, hence, a smaller C-H bond distance is observed with more basic ligands. It is also evident that the distance between the activated Rh cation and the H atom decreases from 2.42 Å to 2.23 Å with increasing pKa. Again, the possible contribution of agostic interactions to C-H bond activation can be eliminated because the Rh-H distance is large (2.23-2.53 Å) relative to that seen in agostic interactions (~ 1.9 Å) [20]. These results suggest that the activation of the C-H bond in the systems studied is best described as electrophilic activation or, alternatively, as oxidative hydrogen transfer [19].

Further evidence for the structure of the arene intermediate is that the strong preference for C-H activation at the *para*-position of toluene. Charge stabilization by the electron-donating methyl substituent on the aromatic ring favors C-H bond activation at the *ortho*- and *para*-positions; however significant formation of the *ortho*-isomer is precluded by the steric bulk of the Rh complex. Consistent with this reasoning, the major reaction products were *p*-toluic and *m*-toluic acid, and only traces of *o*-toluic acid were observed. The ratio of *p*/*m* toluic acids is shown in Figure 8 as a function of acid pKa. As the pKa decreases, the *p*/*m* isomer ratio increases from 1.5 to 3.8 and then decreases to 2.3. The overall trend in selectivity reflects the inverse of the trend for ∆$G^\circ_{\text{coord}}$ shown in Figure 3. The maximum in the *p*/*m* ratio occurs for CF$_3$COOH, which also binds toluene most strongly. It has been shown previously that the preferred formation of *p*-toluic acid when the anionic ligand is CF$_3$COO$^-$ can be attributed to the stronger coordination of toluene via the *para* than the *meta* position on the benzene ring. Calculations of the Mulliken charge on the C atoms at the *para* and *meta* position on the benzene ring indicate that coordination of toluene to the Rh(III) cation in the complex enhances the difference in negative charge on the *para* position relative to the *meta* position more than is observed for uncoordinated toluene. Similar calculations done for ligands derived from CH$_3$COOH and CF$_3$CF$_2$COOH show a smaller difference in the Mulliken charge on the C atoms in the *para* position relative to the *meta*
position, suggesting that the difference in energies for the coordination of toluene via the \textit{para} versus the \textit{meta} C atom will be smaller for catalysts that bind toluene more weakly. This reasoning leads to the conclusion that the maximum in \textit{p/m} ratio of toluic acid observed CF$_3$COOH can be ascribed to the effect of the anion composition on the electrophilicity of the Rh cation and, in turn, the effect of the cation charge on the relative energies of toluene coordination via the \textit{para} versus the \textit{meta} C atom of the benzene ring.

\subsection*{4.6 Conclusions}

The results of this investigation demonstrate that the composition of the anion associated with Rh(III) can be tuned to obtain an optimum activity of the cation for oxidative carbonylation of toluene. Anions derived from acids with pKa's between 0.0 and 0.5 exhibit the highest activities. Theoretical analysis of the reaction for Rh(III) cations reveals that the coordination of toluene is favored by decreasing the acid pKa; however, the activation energy and free energy for aromatic ring C-H bond activation are only weakly affected over the same range of pKa. The difference in toluene binding strength for methanesulfonic and carboxylic acids was attributed mostly to the geometric effects with smaller contributions from polarization and charge transfer. Bond distances during the toluene-Rh coordination and transition state indicate the absence of an agostic interaction in the course of the reaction, which proceeds instead through an electrophilic mechanism. The identity of the ligands influences the charge density of the metal complex, which slightly alters the selectivity of the rhodium complex in favoring coordination in the \textit{para}-position over the \textit{meta}-position. Altering the characteristics of the ligands on the Rh complex, therefore, influences not only the activity by balancing the ability of the complex to coordinate toluene, activate the C-H bond, and abstract the activated proton, but also influences isomer selectivity by altering the charge on the metal center relative to the carbon atoms in free toluene.
4.7 Figures

Figure 4.1 Turnover numbers for Rh-catalyzed oxidative carbonylation of toluene to toluic acid versus pKa of designated acid. Reaction conditions: 37.5 mmol toluene (3.46 g); 13.0 mmol designated acid; 3.8 mmol corresponding anhydride; 10μmol Rh(acac)₃ (0.0039g), 0.5163 mmol NH₄VO₃ (0.0604 g); P₆O = 0.345 MPa; P₀₂ = 0.345 MPa; T = 353 K.

Figure 4.2 Turnover numbers calculated from equation 4 using apparent rate coefficients determined theoretically.
Figure 4.3 Gibbs free energy of toluene coordination and C-H bond activation and apparent Gibbs free energy of activation as a function of the pKa of the acid from which the anionic ligand was derived.

Figure 4.4 Energy of toluene coordination and C-H bond activation and apparent Energy of activation as a function of the pKa of the acid from which the anionic ligand was derived.
Figure 4.5 Values of $\Delta E_{GD}$, $\Delta E_{FRZ}$, $\Delta E_{POL}$, and $\Delta E_{CT}$ for toluene coordination derived from EDA as a function of the pKa of the acid from which the anionic ligand was derived.
Figure 4.6 Structure of coordinated toluene. Selected bond distances are shown in the table.

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</table>
Figure 4.7 Structure of transition state for C-H bond activation in coordinated toluene. Selected bond distances are shown in the table.
Figure 4.8 Dependence of the $p/m$ ratio of toluic acid observed for the Rh-catalyzed oxidative carbonylation of toluene to toluic acid on the pKa of the acid used. Reaction conditions: 37.5 mmol toluene (3.46 g); 13.0 mmol designated acid; 3.8 mmol corresponding anhydride; 10 $\mu$mol Rh(acac)$_3$ (0.0039 g), 0.5163 mmol NH$_4$VO$_3$ (0.0604 g); $P_{CO} = 0.345$ MPa; $P_{O2} = 0.345$ MPa; $T = 353$ K; $t = 4$ h.
Scheme 4.1 Proposed mechanism for the oxidative carbonylation of toluene by Rh(III) in the presence of trifluoroacetic acid. Reoxidation of Rh(I) to Rh(III) is illustrated for the case where VO$_2^+$ serves as the oxidizing agent.
4.9 References


Chapter 5

Experimental and theoretical investigation of the oxidative carbonylation of toluene to toluic acid catalyzed by Pd(II) in the presence of vanadium and molecular oxygen

5.1 Abstract

The mechanism and kinetics of the liquid-phase, oxidative carbonylation of toluene to toluic acid over Pd(II) in the presence of trifluoroacetic acid (TFAH), trifluoroacetic anhydride (TFAA), and molecular oxygen were investigated through a combination of experimental and theoretical approaches. The experimental results are consistent with the previously proposed mechanism for the oxidative carbonylation of arenes. The reaction is initiated by coordination of toluene to the Pd(II) complex and activation of a C-H bond in the benzene ring. This initial step becomes rate limiting when a sufficiently high (NH₄VO₃)/Pd ratio is used for the reoxidation of Pd(0) to Pd(II). Both process are found to be depend on the electron withdrawing and donating capability of the anionic ligands. Overall catalyst activity peaks for ligands of intermediate basicity, and diminishes for both more and less basic ligands. Theoretical analysis of the coordination of toluene and activation of the C-H bond on the benzene ring reveals that the basicity of the ligands affects the two processes in opposite ways. Weakly basic ligands promote the coordination of toluene but have the opposite effect on the activation of the C-H bond. The tradeoff in these two effects leads to a maximum in the apparent rate coefficient with pKₐ of the conjugate acid of the anionic ligands. The absence of significant product stereoselectivity is due to a lack of steric hindrance in the binding of toluene to the Pd(II) complex.
5.2 Introduction

The oxidative carbonylation of arenes to the corresponding aryl carboxylic acid can be catalyzed by Pd(II) in the presence of acetic acid and CO [1-10]. Early studies of this reaction revealed that in the course of this reaction Pd(II) is reduced to Pd(0) and hence, in the absence of an oxidizing agent the yield of products is stoichiometric in the initial concentration of Pd(II) [1]. The process can be made catalytic by adding an oxidant to convert Pd(0) to Pd(II) [2]. If BuOOH or K$_2$S$_2$O$_8$ is used as the oxidant, this component is consumed in the course of the reaction [2, 3, 8]. Molecular oxygen can also be used as the oxidant provided that a co-catalyst is added to promote the activation of O$_2$. Examples of such co-catalysts include Cu(acetate)$_2$ [4], MnO$_2$ [6] and NH$_4$VO$_3$ [10].

A reaction mechanism has been proposed to rationalize the oxidative carbonylation of toluene to toluic acid [5]. It involves coordination of toluene to the Pd(II) center, activation of a C-H bond in the coordinated toluene at the para, meta, or ortho position of the benzene ring, electrophilic activation of the arene C-H bond, and subsequent insertion of CO into the Pd-C bond of the Pd-toluyl species formed in the preceding step. The resulting acyl species is envisioned to undergo reductive elimination to form a mixed anhydride of the desired aryl acid and the acid that was used in the reaction system to provide anionic ligands (e.g., trifluoroacetic acid). Pd(0) formed in this latter process is then re-oxidized to close the catalytic cycle. The observation that formation of toluic acid is faster when trifluoroacetic acid is used in place of acetic acid suggests that the activation of the arene C-H bond occurs via an electrophilic mechanism [9]. While the proposed mechanism is plausible, definitive evidence for electrostatic activation of the C-H bond of toluene is very limited as are the effects of changing the electrophilicity of the anionic ligand.

In recent studies of the oxidative carbonylation of toluene catalyzed by Rh(III) complexes involving acetate ligands, it was demonstrated that the activity of the catalyst can be tuned through a maximum by substitution of the H atoms of the methyl group in the acetate ligands by Cl or F, or combinations of the elements [11-13]. Experimental studies of the reaction have demonstrated that under conditions where most of the Rh is present as Rh(III), the rate-limiting step is the electrophilic activation of the C-H bond on the benzene ring of coordinated toluene. Theoretical analysis of the process shows that coordination of toluene is a reversible process that is sensitive to the composition of the acetate ligand, as is the activation of the C-H of the benzene ring. In the present study we show that the oxidative carbonylation of toluene to toluic acid catalyzed by Pd(II) also proceeds via electrophilic activation and that the catalyst activity is affected by the composition of the acetate ligand. Theoretical analysis of the coordination of toluene to Pd(II) and the activation of the benzene C-H bond explains why Pd(II) complexes are more active than Rh(III) complexes but less stereoselective towards the formation of p-toluic acid.
5.3 Experimental

Reactions were conducted in a stirred, 50 mL Parr autoclave made of Hastelloy C. Between experiments, the reactor was washed thoroughly with water and acetone and then dried in a vacuum oven overnight to avoid contamination. The reaction temperature was monitored using a thermocouple located inside a Hastelloy C thermowell. During a typical reaction, 3.46 g of anhydrous toluene (99.8%, Aldrich), 1.48 g of CF₃COOH (99%, Aldrich), 1.48 g of (CF₃CO)₂O (≥99%, Aldrich), 0.0016 g of Pd(TFA)₂ (Aldrich) and 0.0604 g of NH₄VO₃ (99+, Aldrich) were placed into the autoclave, which was then sealed and purged four times with nitrogen or helium. After purging, the reactor was pressurized at 293 K with 0.345 MPa O₂ (99.993%, Praxair) and 0.345 MPa CO (99.5%, Praxair). The reactor was then heated to 353 K in approximately 10 min and then held at this temperature for 4 h. Upon the completion of the reaction, the reactor was quenched with ice water to 308 K and vented.

The contents of the reactor were emptied into a vial and weighed, after which approximately 12 g of deionized H₂O was added to organic phase in order to extract the trifluoroacetic acid from it. The vial was inverted 20 times and the aqueous and organic phases were allowed to separate completely. After inverting the vial containing the mixture of aqueous and organic phases 20 times, the two phases were allowed to separate and the aqueous phase was discarded. Solids produced by the reaction were separated from the organic phase by centrifugation and dried overnight in a vacuum oven at 313K.

The concentration of toluic acid in the organic phase was determined by gas chromatography using an Agilent Technologies 6890N gas chromatograph equipped with an HP-1 capillary column coated with crosslinked methyl siloxane and an FID detector. After washing with H₂O and drying, the product solids were dissolved in toluene and similarly analyzed by gas chromatography. The solid lines shown in all figures represent the average over all replicas.

5.4 Theoretical Methods

Molecular structures, energies, vibrational modes, and rotational constants were calculated with Density Functional Theory [14] in Q-Chem [15]. Geometry optimization of minimum energy structures and vibrational analysis were performed with the B3LYP density functional [16-19] and the 6-31G* basis set. Electronic structure energies of the optimized molecular structures were also computed with the B3LYP density functional, and then refined at the 6-311++G** level. For all calculations, the core basis functions for palladium were replaced with the LANL2DZ effective-core potential [20]. Estimates of transition state structures were obtained with the Growing String Method [21] and refined within the normal geometry optimization functionality of Q-Chem. All calculations were performed in the gas phase. Thermochemical calculations were performed at the experimental reaction temperature of 353K, and invoked the rigid-rotor—harmonic oscillator approximation. The energetics of toluene binding were basis set superposition-
error corrected using the counterpoise method. Equilibrium constants were calculated at a standard state of 1 bar and adjusted to molar concentration units according to eq 1:

\[ K = \left( \frac{RTc^o}{P^o} \right)^{-\Delta v} \exp \left( \frac{-\Delta G^o}{RT} \right) \] (1)

where \( K \) is the equilibrium constant, \( R \) is the gas constant, \( T \) is the absolute temperature, \( c^o \) is the standard-state concentration in the liquid phase (1 mol/L), \( P^o \) is the standard-state pressure (1 bar), \( \Delta v \) is the difference between the sums of the stoichiometric coefficients of he products and reactants, and \( \Delta G^o \) is the Gibbs free energy of reaction at the reaction temperature. Rate constants were computed from transition state theory, eq 2:

\[ k = \frac{k_BT}{h} \exp \left( \frac{\Delta S^+}{R} \right) \exp \left( \frac{-\Delta H^+}{RT} \right) \] (2)

### 5.5 Results and Discussion

A proposed mechanism for the oxidative carboxylation of toluene to toluic acid is shown in Scheme 1. This scheme is very similar to that suggested in earlier work by [4, 5, 7, 10]. The main catalytic cycle is initiated by the electrophilic reaction of toluene with Pd(TFA)\(_2\) to form a methyl aryl complex, Pd(TFA)(C\(_6\)H\(_4\)CH\(_3\)) and TFAH. A CO from the reaction mixture then binds to the complex and undergoes a migratory insertion to form Pd(TFA)\(_2\)(COC\(_6\)H\(_4\)CH\(_3\)). This species then reacts via reductive elimination to produce Pd(0) and a mixed anhydride. The mixed anhydride then either hydrolyzes to give TFAH and toluic acid, or exchanges a proton with TFAH to produce trifluoroacetic anhydride and the toluic acid. Only the former version is shown in Scheme 1. The reduced Pd catalyst is re-oxidized with NH\(_4\)VO\(_3\)/O\(_2\) via a sequence of steps, which are taken to be identical to those established for the oxidation of Rh(I) to Rh(III) during the oxidative carboxylation of toluene catalyzed by Rh(III) acetate complexes [11-13].

Scheme 1 suggests that the reaction of Pd(TFA)\(_2\) with toluene will become the rate-limiting step sequence provided that the rate of reoxidation of Pd(0) to Pd(II) is very rapid and that the rates of carboxylation and mixed anhydride formation are rapid and, hence, kinetically insignificant. To test whether the rate of Pd(0) oxidation could be made very rapid, experiments were carried out in which the amount of NH\(_4\)VO\(_3\) was varied while keeping the quantity of Pd present in the reactor constant at 4.8 \( \mu \)mol. In the absence of any NH\(_4\)VO\(_3\), ~10 turnovers of Pd were observed. This suggests that O\(_2\) alone can carry out a slow oxidation of Pd(0), but is insufficient to maintain the catalytic activity of Pd, since the deposition of Pd black on the walls of the reactor was observed under these conditions. The number of Pd turnovers increased linearly with the amount of NH\(_4\)VO\(_3\) charged to the
reactor up to 0.516 mmol of vanadium, at which point 1740 Pd turnovers were achieved in 4 h. No additional toluic acid was formed when the charge of NH₄VO₃ was increased above 0.516 mmol. The small number of turnovers observed without NH₄VO₃ indicates that a Pd(II) species are responsible for activating the C-H bond of toluene. The linear relationship between NH₄VO₃ concentration and Pd turnovers shows that Pd(II) is reduced during the reaction cycle, and that a sufficient V/Pd ratio is necessary to prevent re-oxidation from becoming the rate-limiting step.

Strong evidence that the oxidative carbonylation of arenes by Pd(II) proceeds via an electrophilic mechanism is the sensitivity of the apparent rate constant for this reaction on the composition of the substituent present on the benzene ring. Figure 1 shows a Hammett plot for the oxidative carbonylation of arenes by Pd(II) complexes in the presence of NH₄VO₃/O₂ (see Figure 1). The slope of this line (\(\rho = -1.53\)) indicates that the reaction proceeds through a mechanism that slightly favors an electron-donating substituent [24]. This result suggests that the oxidative carbonylation of toluene and other arenes occurs via coordination of the arene to the Pd(II) complex followed by activation of the C-H bond.

Further support for this interpretation comes from an examination of the effects of ligands composition on the activity of Pd(II) for the oxidative carbonylation of toluene. Figure 2 illustrates the effect of the pKₐ of the acid, from which the anionic ligands for Pd are derived, on the number of turnovers obtained after 4 h of reaction. Values of the pKₐ were taken from Ref. [25]. Only acids with a pKₐ near zero are effective in producing toluic acid, and optimal activity is observed for CF₃COOH. The order of activity observed in Figure 2 can be attributed to two opposing factors – the electron withdrawing nature of the ligands, which makes the metal center more electropositive and thus more capable of toluene coordination, and the ability of the ligand to abstract a proton. While more electron withdrawing ligands facilitate the coordination of toluene to the metal, they are less able to abstract a proton from the coordinated toluene to form the aryl-palladium complex. The optimal activity is observed for the ligand that best balances these opposing factors, which in the case of Pd is CF₃COOH. Figure 3 shows the effects of ligand composition on the distribution of para, meta and ortho toluic acid products. For all but one ligand (CCH₂COO⁻), the ortho isomer is more abundant than the para and meta isomers and the meta isomer is always the least abundant.

Under conditions of high V/Pd ratio in the reaction mixture, Pd(II) becomes the most abundant form of Pd and the rate of toluic acid formation is then limited by the coordination and activation of toluene. This step may be broken into two substeps, as depicted in Figure 4. The first is the coordination of toluene to Pd(TFA)₂, characterized by the free energy change \(\Delta G_{\text{coord}}^\circ\), whereas the second step is the activation of a C-H bond on coordinated toluene, characterized by the free energy barrier, \(\Delta G_{\text{act}}^\circ\). \(\Delta G_{\text{coord}}^\circ\) can be used to compute the equilibrium constant for toluene binding, \(K_{\text{coord}}\) (Eq. 1), while \(\Delta G_{\text{act}}^\circ\) can be used to calculate \(k_{\text{act}}\) (Eq. 2). In the limit that most of the Pd in solution is present as Pd(TFA)₂, the overall rate of toluic acid production, \(k_{\text{app}}\), is described by equation 3.
Equation 3 suggests that \( k_{app} \) can be described by a single parameter, the total change in free energy which is defined as \( \Delta G_{app} = \Delta G_{coord} + \Delta G_{act} \). This expression indicates that any changes in free energy for the oxidative carbonylation of toluene by Rh(III) complexes are expected to affect the rate of reaction through the strength of toluene coordination and/or the rate of C-H activation.

To further understand the effect of ligand composition on the coordination and activation of toluene by Pd(II) complexes, values of \( \Delta G_{app} \) were determined theoretically. Figure 5 shows the calculated values of \( \Delta G_{app} \), assuming that toluene coordination occurs in the para, meta, and ortho positions. The values of \( \Delta G_{app} \) for all three coordination positions decrease as the anionic ligand is changed from the comparatively weakly basic \( \text{CH}_3\text{COO}^- \) anions to the relatively more basic \( \text{CF}_3\text{CF}_2\text{COO}^- \) anions, and rise again for the very weakly basic \( \text{CH}_3\text{SO}_3^- \) anions. Figure 6 shows the computed values of \( k_{app} \) determined from Eqs. 1-3 for the oxidative carbonylation of toluene at the para, meta, and ortho positions. For short reactions times, the logarithm of \( k_{app} \) is proportional to the cumulative turnover number (TON), and thus the activity of a particular catalyst can be evaluated solely through \( k_{app} \). Pd(II) ligated with \( \text{CF}_3\text{CF}_2\text{COO}^- \) anions are predicted to be the complex with the highest activity. The activity of the Pd complexes is predicted to decrease for anions that are either more or less basic than \( \text{CF}_3\text{CF}_2\text{COO}^- \). This pattern is roughly the same as that seen experimentally, but with the peak predicted activity occurring for a slightly more basic ligand, \( \text{CF}_3\text{COO}^- \). These theoretical predictions do not match exactly with experiment due to the sensitivity of \( k_{app} \) to the exact value of \( \Delta G_{app} \), which contains an inherent error from the inexact nature of DFT calculations.

The results presented in Figure 3 show that the formation of \textit{para-} and \textit{ortho-} toluic acid is preferred over the formation of \textit{meta-} toluic acid independent of ligand composition; however, the selectivity differences among the three stereoisomers are not large. This pattern suggests that product stereoselectivity is driven primarily by the free energy for toluene coordination, \( \Delta G_{coord} \), since the \textit{para} and \textit{ortho} carbons of toluene are more negatively charged than the \textit{meta} carbon and not by effects of steric hinderance, as was observed for the case of toluene coordination with Rh(III) complexes. The lack of steric hinderance is apparent in the computed values of \( \Delta G_{coord} \) for coordination of toluene. When coordinated with Pd(II), toluene interacts through an \( h^2 \) bond. Figure 7 illustrates the computed values of \( \Delta G_{coord} \) for coordination to four of the six possible \( h^2 \) configurations. The \( h^2 \) configurations involving the primary carbon of the phenyl ring were ignored. The values presented show only a small difference between the various coordination sites, indicating a lack of steric hindrance. While small differences in the values of \( \Delta G_{coord} \) are observed for different forms of toluene coordination and different ligands, the accuracy of the calculations is insufficient to reproduce the selectivity patterns seen in Figure 3.

It is useful to compare and contrast the findings of this study with those reported recently for the oxidative carbonylation of toluene by Rh(III) complexes.
containing ligands identical to those investigated here [13]. In that work it was demonstrated that the oxidative carboxylation of toluene catalyzed by Rh(III) complexes also proceeds by way of an electrophilic mechanism, in which the rate limiting step involves toluene coordination and C-H activation. A similar volcano plot of overall activity versus pK$_a$ was found; however, the highest activity in this case was for CCl$_2$COO$^-$ anions. Theoretical analysis of that system revealed a minimum in the computed $\Delta G_{app}$ vs pK$_a$ for CCl$_2$COO$^-$ anions, with a value of 26.9 kcal/mol. The experimentally observed $p/m$ ratios ranged between 1.75 and 3.75, with the higher values occurring for ligands with a conjugate acid pK$_a$ near zero. The production of o-toluic acid was minimal.

Under analogous reaction conditions, the activity of the Pd(II) complexes reported here is significantly higher than those for the Rh(III) complexes reported earlier [12]. The peak in TON (1740) for Pd(II) occurs for a more basic ligand, CF$_3$COO$^-$; and is more than three times that (560) for Rh(III) with the optimal ligand, CCl$_2$COO$^-$. The calculated values of $\Delta G_{app}$ determined for Pd(II) and Rh(III) complexes are consistent with both the higher activity of Pd(II) relative to Rh(III) and the shift in the basicity of the optimal ligand. For Pd(II), the lowest value of $\Delta G_{app}$ for para activation of toluene is 18.5 kcal/mol with CF$_3$CF$_2$COO$^-$ ligands. This value is nearly 10 kcal/mol lower than that for the minimum value of $\Delta G_{app}$ (26.9 kcal/mol) found for Rh(III) with CCl$_2$COO$^-$ ligands, consistent with experiment. Finally, the predicted selectivity for the Pd catalysts is low, given the relatively similar values of $\Delta G_{app}$ for para, meta, and ortho activation. This result is likely due to the lack of steric hindrance towards toluene binding in the present square planar Pd(II) complex. The analogous Rh(III) system is octahedral and has ligands positioned to interfere with the methyl group of toluene and drive selectivity towards the para position.

### 5.6 Conclusions

The results of this study indicate that Pd(II) in the presence of CO, O$_2$, TFAH, and NH$_4$VO$_3$ is effective at promoting the oxidative carboxylation of toluene to toluic acid. The reaction mechanism proceeds via coordination of toluene to the Pd(II) complex followed by activation of one of the C-H bonds on the benzene ring. This step is followed by the migratory insertion of CO into the Pd-C bond of the tolyl species and subsequent reductive elimination of a mixed anhydride of toluic acid and trifluoroacetic acid. The second of these two steps also results in the reduction of Pd(II) to Pd(0). The mixed anhydride then undergoes hydrolysis to produce toluic acid. The reoxidation of Pd(0) to Pd(II) occurs via a separate catalytic cycle, in which [VO$_2$(TFA)]$_2$ is the oxidant. The VO(TFA)$_2$ produced as a product of the oxidation process is then reoxidized by O$_2$ to reform [VO$_2$(TFA)]$_2$. For sufficiently high V/Pd ratios, most of the Pd is in the form of Pd(TFA)$_2$, and the rate of toluic acid formation becomes limited by the reversible coordination of toluene and the activation of a C-H bond on the benzene ring. The overall rate of toluic acid formation is very sensitive to the basicity of the anionic ligand and passes through an optimum as the pK$_a$ of the conjugate acid of the anionic ligand is varied from -1 to 5. This trend is
explained by a theoretical analysis of the effects of ligand composition on the equilibrium constant for toluene coordination and the rate coefficient for activation of a C-H bond on the benzene ring. Consistent with experimental observation, the predicted apparent first-order rate coefficient passes through a well-defined maximum versus conjugate acid pK_a's. Only minor numerical differences are seen in ΔG^o_coord for coordination of toluene in the para, meta, and ortho positions, in agreement with the experimentally observed lack of selectivity for any specific isomer of toluic acid. Finally, when compared against previous studies of the analogous Rh(III) system, the present computations predict a higher activity for Pd(II) complexes relative to Rh(III) complexes, and a shift in the peak activity away from CClF_3COO^- (the optimal ligand for Rh(III)) towards less basic ligands. The calculated curves for ΔG_app vs pK_a of the conjugate acids of the anionic ligand for activation in the para, meta, and ortho positions are more similar for Pd than for the Rh-based system in agreement with the observed low selectivity of Pd(II) complexes relative to the high selectivity to para-toluic acid seen for comparable Rh(III) complexes.
5.7 Figures

Figure 5.1 Hammett plot for Pd-catalyzed arene oxidative carbonylation in the presence of NH₄VO₃/O₂. Values of σ are taken from reference 23 and correspond to para substitution.

Figure 5.2 Pd catalyzed oxidative carbonylation of toluene to toluic acid versus pKa of designated acid. Reaction conditions: 37.5 mmol toluene (3.46 g); 13.0 mmol designated acid; 3.8 mmol corresponding anhydride; 5 μmol Pd(TFA)₂ (0.0016 g), 0.516 mmol NH₄VO₃ (0.0604 g); PₓCO = 0.345 MPa; PₓO₂ = 0.345 MPa; T = 353 K; t = 4 h.
Figure 5.3  Normalized distribution of para, meta, and ortho toluic acid products formed vs pKₐ of the ligand conjugate acids. Data reported is based on a standard 4 h batch reaction.

Figure 5.4  Reaction schematic for the rate-limiting step of toluene coordination and C-H bond activation at the Pd(CF₃COO)₂ catalyst. Para coordination of toluene is illustrated though both meta and ortho also occur.
Figure 5.5 Plot of calculated $\Delta G_{\text{app}}$ vs pK$_a$ of the conjugate acid of the catalyst ligand for \textit{para}, \textit{meta}, and \textit{ortho} activation.

Figure 5.6 Plot of calculated $k_{\text{app}}$ vs pK$_a$ of the conjugate acid of the catalyst ligand. The values plotted are for the cumulative rate of all 3 toluic acid isomers.
Figure 5.7 Computed values of $\Delta G^\circ_{\text{coord}}$ for toluene binding in various $\eta^2$ configurations, and model toluene structure to indicate positions of the different carbons.
5.8 Schemes

Scheme 5.1 Proposed mechanism for Pd-catalyzed toluene oxidative carbonylation.
5.9 References

Chapter 6

Incorporating Linear Synchronous Transit interpolation into the Growing String Method: algorithm and applications

6.1 Abstract

The Growing String Method is a powerful tool in the systematic study of chemical reactions with theoretical methods by allowing for the rapid identification of transition states connecting known reactant and product structures. However, the efficiency of this method is heavily influenced by the choice of interpolation scheme when adding new nodes to the string during optimization. In particular, the use of cartesian coordinates with cubic spline interpolation often produces guess structures which are far from the final reaction path, and require many optimization steps (and thus many QM calculations) to yield a reasonable final structure. In this paper, we present a new method for interpolating and reparameterizing nodes within the Growing String Method using the Linear Synchronous Transit method of Halgren and Lipscomb. When applied to the alanine dipeptide rearrangement and a simplified cationic alkyl ring condensation reaction, a significant speedup in terms of computational cost is achieved.

6.2 Introduction

One of the key contributions of theoretical chemistry to the systematic study of chemical reactions is the ability to accurately predict kinetic rate constants. These kinetic rate constants are typically calculated with Transition State Theory, which requires knowledge of the transition state structure. While locating stable minima on the Potential Energy Surface (PES) is considered relatively easy in
Theoretical chemistry, the automated location of first order transition states remains a challenge.

The principle method for obtaining exact first order transition states connecting known reactant and product configurations is to first generate a rough guess of the structure, and then refine this structure to the exact answer through surface walking [1-2]. The algorithms for surface walking are similar to the algorithms to locate PES minima. Because there are many more transition states than minima on a typical PES, this guess must be very close (within the basin of attraction) to the proper transition state in order to properly converge. Once the transition state has been refined, it must be confirmed by integrating the reaction path downhill to the reactant and product configurations [3-4].

Several algorithms for finding transition state guesses from known reactant and product configurations have been developed [5-31], including the Nudged Elastic Band Method (NEB) [5-8], the String Method (SM) [9-14] and the Growing String Method (GSM) [15-20]. In each of these “chain-of-states” methods [21], the minimum energy pathway is located by iteratively optimizing a discretized representation of the pathway. Each of the nodes in the chain-of-states is a full molecular structure at some intermediate stage of the transition between reactant and product. Optimization steps are taken by moving each image downhill on the PES, perpendicular to the direction of the reaction path. Additionally, the nodes in the chain are kept equally spaced through the optimization process, either through an additional spacing force, or by explicit reparameterization. This ensures that this node-based description of the pathway does not contain large gaps, where the PES may be left unsampled.

When using ab initio surfaces in each of these methods, the overall cost of generating a suitable guess of the transition state can be stated in terms of the overall number of QM nuclear gradient calculations performed. All other calculations needed to perform these methods can be considered negligible. Higher order derivatives of the QM energy, such as the nuclear hessian, would provide faster convergence, but are prohibitively expensive in ab initio calculations.

The most commonly encountered chain-of-states method is the Nudged Elastic Band method [5-6], which finds an approximate reaction path by optimizing a series of images connected to each other through a set of contrived hookian springs. The optimization step direction for each node, \( \hat{\nu}_{\text{NEB}}^i \), is comprised of two components, as shown in equation 1.

\[
\hat{\nu}_{\text{NEB}}^i = \frac{-g_i^\perp + f_i^\parallel}{\left| -g_i^\perp + f_i^\parallel \right|}
\]  

(1)

The first term is the perpendicular force, used to minimize the energy of each node and given by equation 2.
\[-{g_i}^\perp = -(I - \hat{t}_i\hat{t}_iT)g_i \tag{2}\]

The tangent direction, $\hat{t}_i$, is typically found by normal finite difference, but other schemes have been proposed for improved performance [7-8]. The second term, $f_i^\parallel$, expanded in equation 3, is a force along the reaction path which arises from the springs that connect each node in the chain to its neighbors. Here, $k$ is the spring constant, and $R$ denotes the coordinates of a molecular structure.

$$f_i^\parallel = \hat{t}_i\hat{t}_iT[(R_{i+1} - R_i) - (R_i - R_{i-1})]k \tag{3}$$

This component is added to ensure that the images remain equally spaced during the optimization process.

A slightly newer method, similar in concept to the Nudged Elastic Band, is the String Method [9-14]. The reaction path is again represented by a series of molecular images, but optimization is broken into two separate steps: evolution and reparameterization. In the evolution step, the molecular images are moved in the direction of the negative perpendicular gradient, similarly to the first term in equation 1. The tangent direction is determined by creating a cubic spline through each cartesian coordinate of the string of images. The reparameterization step is performed by re-interpolating the molecular images along this set of cubic splines to achieve the desired parameterization density. This avoids the need to decide an arbitrary spring constant, as in the NEB.

The Growing String Method [15-20] is a modification of the original String Method, which aims to reduce overall computational cost by “growing” the set of nodes from the reactant and product configurations inwards towards the transition state. In principle, this avoids performing gradient calculations on excessively rugged parts of the PES that are far from the final reaction pathway. Initially, the string consists of only the reactant and product configurations, with one node being added to each side during the first reparameterization. The string is then evolved and reparameterized in the normal fashion until the specified convergence criteria for node addition is achieved by the innermost nodes on the reactant and product sides. New nodes are added accordingly until the string is fully populated. The string then continues to optimize until convergence is reached. Several schemes have been developed to accelerate practical use by improving optimization, and using cost-saving dual basis techniques [16-18].

The Nudged Elastic Band and String Method both require initial pathways from which the optimizations are launched. This initial pathway has a tremendous impact on convergence and must be chosen carefully [12]. Cartesian interpolation may work for some simple reactions, however it is not always an appropriate choice. Reactions such as the HNC to HCN isomerization are poorly described by cartesian interpolation despite having only a handful of internal degrees of freedom. Such simple reactions, as well as more complex reactions with many atoms, require an interpolation scheme with chemical intuition built-in. The GSM does not require
a full initial guess pathway, but does require a methodology for reparameterizing and interpolating new nodes.

To alleviate this shortcoming of the GSM specifically (and more generally the SM and NEB) we propose using Linear Synchronous Transit (LST) interpolation [32-33] for node interpolation and reparameterization. LST is a method for interpolating between two fixed molecular geometries that seeks to preserve internuclear distances within the molecule as it morphed from one to the other. In doing so, the usual drawbacks of cartesian interpolation in which chemical bonds are overly compressed or stretched are avoided. A simple example of the contrast between LST and cartesian interpolation is demonstrated in Figure 1 with the HCN to HNC isomerization. In this paper, we demonstrate the advantages of LST interpolation in the GSM by direct comparison to cartesian interpolation.

6.3 Modified Implementation of the Growing String Method

6.3.1 Evolution Step

To demonstrate the use of LST versus cartesian interpolation within the GSM, a modified version of the algorithm was developed. The evolution step direction for node $i$, denoted as $\mathbf{v}_{GSM}^i$, is the same as the original GSM as shown in equation 4. The perpendicular gradient, $g_{i\perp}$, is defined in equation 2.

$$\mathbf{v}_{GSM}^i = -\frac{g_{i\perp}}{|g_{i\perp}|}$$

(4)

The length of the evolution step at each node is determined by using a scaling factor, $\gamma$, with the magnitude of the perpendicular gradient as shown in equation 5. This produces a damped steepest descent step, and has the effect of generating a large step when there is a large perpendicular gradient far from convergence, and a small step when the node is near convergence.

$$d_i = \frac{|g_{i\perp}|}{\gamma}$$

(5)

This differs from the original GSM [15], which seeks to minimize the string by taking several small trial steps in the downhill direction, fitting the observed energy profile to a quadratic function, and moving to the estimated minimum.

6.3.2 Reparameterization Step

After each evolution step, the string is reparameterized to achieve a uniform node density along the arclength of the reaction path. If nodes are numbered starting with the reactant node as $i = 1$ and the product node as $i = N$, where $N$ is the number of nodes in the fully populated string, the desired parameterization is
given by equation 6. $N_R$ and $N_p$ are the number of nodes on the reactant and product sides respectively, and $s_{tot}$ is the current total arclength from reactant to product.

$$s_i = s_{tot} \left( \frac{i-1}{N-1} \right) \quad i \leq N_R \quad \text{and} \quad N - N_p < i \leq N \quad (6)$$

The algorithm is started with two nodes on each side of the string – the fixed reactant and product structures and one variable node on each side. Once the magnitude of the perpendicular gradient for the innermost node for a side has fallen below the specified tolerance for node addition, a new node is added to a side by incrementing $N_R$ or $N_p$ during the reparameterization step. This has the effect of growing a new node on the appropriate side until the string is fully populated. Once the full string has been grown, convergence may be considered. The objective function for locating the intrinsic reaction coordinate (IRC) is the sum of the perpendicular gradient magnitudes for each node, as indicated by equation 7. If the endpoints are assumed to be stable minima on the PES, they may be neglected in the sum since they contribute nothing.

$$F = \sum_{i=2}^{N-1} \left| g_i^j \right| \quad (7)$$

6.4 Interpolation Method

If cartesian coordinates with cubic splines are used for reparameterization, the procedure is straightforward. A cubic spline is determined for each cartesian coordinate using the structures of the nodes and their positions along the string in terms of arclength, and the appropriate nodes are interpolated.

The use of Linear Synchronous Transit reparameterization is slightly more complicated. It is based on the use of LST interpolation between two fixed molecular images, as given by the resultant structure in the minimization of equation 8.

$$G = \sum_{a>b}^{\text{atoms}} \left( \frac{r_{ab}^i - r_{ab}^c}{r_{ab}^i} \right)^2 \quad + 10^{-6} \sum_{a=1}^{\text{atoms}} \sum_{j=x,y,z}^{\text{atoms}} (w_{a,j}^i - w_{a,j}^c)^2 \quad (8)$$

The $r$ variables denote internuclear distances, while the $w$ variables denote pure cartesian coordinates. The $i$ and $c$ superscripts denote “interpolated” versus “computed” values respectively. The interpolated values are determined by mixing the values of the fixed molecular structures, while the computed values are derived from the interpolated structure being optimized to minimize $G$. We are careful to
stress that the “computed” internuclear distances, $r_{ab}$, are derived from the coordinates provided by the cartesian “computed” structure, $w^c$. Thus, there is only one full set of cartesian coordinates being manipulated. The numerator of the first term of equation 8 serves to preserve internuclear distances from being overly stretched or compressed during interpolation while the denominator weights this effect in favor of shorter internuclear distances (i.e. bonding interactions). The second term of equation 8 provides a small force to align the interpolated molecule with the fixed end structures.

Equation 8 fails to adequately show that the “interpolated” values must be computed by choosing a mixing ratio, $f$, of the two fixed structures. This is shown in equation 9, where the superscripts 1 and 2 denote the fixed endpoint structures.

$$
\begin{align*}
    r_{ab}^i & = r_{ab}^1 + f (r_{ab}^2 - r_{ab}^1) \\
    w_{a,j}^i & = w_{a,j}^1 + f (w_{a,j}^2 - w_{a,j}^1)
\end{align*}
$$

From these equation it becomes obvious that $G$ is really $G = G(f)$, and the choice of $f$ (between 0 and 1) will determine how close the interpolated image is to the fixed endpoints. A value of $f = 0$ will produce an interpolated structure identical to structure 1, while $f = 1$ will reproduce structure 2. If all values of $f$ between 0 and 1 are sampled, and the LST equation minimized at each value, it yields a continuous description of the deformation from structure 1 to structure 2, with an integrated arclength of $s_{LST}$. There exists a monotonically increasing, but nonlinear mapping between $f$ and $s_{LST}$ such that it is impossible to know a priori which value of $f$ to use to return a desired value of $s_{LST}$. To avoid this problem, a high-density series of LST interpolations must be performed between each neighboring set of nodes in the evolving string.

The general strategy for using LST interpolation for reparameterization in the GSM is shown in Figure 2. First, a high-density set of LST interpolations is performed between each neighboring pair of nodes. From this, the normalized arclength position of each interpolated node along the growing string is computed. Finally, the nodes which yield the appropriate node spacing, as given by equation 6, are selected from the high-density string and taken as the reparameterized string. From this same high density LST interpolated string, the tangent vector at each selected node is computed and stored.

6.5 Computational Details

The examples detailed below demonstrate the use of cartesian and LST interpolation in our modified implementation of the Growing String Method interfaced with Q-Chem 3.2 [34]. For each example, a string of 11 nodes was grown from the reactant and product structures, and optimized until a specified objective function was achieved. At the beginning of the GSM execution, the reactant and product structures were aligned to be in maximum coincidence in non-mass-
weighted cartesian coordinates [35]. This step is essential to ensure that the rotational and translational degrees of freedom between the two structures do not significantly affect the interpolation. It also ensures that the computed arclength between nodes does not include appreciable non-internal motion.

The scaling factor used to generate the step length of each node during the evolution step was $\gamma = 5.0$ hartrees/Å². Reparameterization was performed after each evolution step, with new nodes added to the string (during the reparameterization steps) if the magnitude of the perpendicular gradient at a frontier node fell below 0.1 hartrees/Å. For reparameterization and node addition with LST, 200 images were included in each high-density interpolation string running from reactant to product. The structures of this high-density string were optimized with Newton-Rasphon minimization of equation 8 to a tolerance of $|\nabla G| < 0.001$ when computed in units of Å.

After the string was fully optimized, the nodes of the string were used as the starting point of a surface walking transition state optimization calculation in Q-Chem. This algorithm, which operates in delocalized internal coordinates, seeks to maximize the energy along the eigenvector of the lowest hessian eigenmode, and minimize the energy along all other eigenmodes. To aid in this calculations, an exact hessian was calculated at the outset of the search, and updated via the Powell/Murtagh-Sargent scheme [36-37].

Once a first-order saddle point was isolated from these optimizations, a high-quality IRC was integrated downhill from the transition state, via the Schlegel-Gonzalez IRC following algorithm [4] in non-massweighted cartesian coordinates, to ensure that the transition state connected the reactant and product structures initially fed to the Growing String Method. It is possible that multiple transition states may be found if each node is used to launch a calculation. For elementary reaction steps, only the highest energy node for an adequately converged string should result in a meaningful transition state. For non-elementary reaction steps, legitimate transition states may be found for each elementary reaction. Both of these possibilities are explored in the test cases presented below.

### 6.6 Alanine Dipeptide Rearrangement

A common test problem for the benchmarking of IRC and transition state finding algorithms is the rearrangement of alanine dipeptide from the C$_5$ isomer to the C$_{7\text{AX}}$ isomer. The minimum energy pathway involves the concerted rotation of the two dihedral angles, $\phi$ and $\psi$, shown in Figure 3. The relevant values of the dihedral angles for the reactant, TS and product in the gas phase at the B3LYP/6-31G level of theory given in the work of Perczel et al. [38] are shown in Table 1. This is the same level of theory used in the present example.

Figure 4 shows the value of the objective function $F$ (from equation 7) as a function of iteration. These curves can each be broken into two regions: growth and refinement. The initial growth phase, during which new nodes are still being added to the string, results in the spikes seen initially in Figure 4. Since the number of nodes in each iteration is not constant in this phase, the number of QM gradients
necessary for each iteration also varies. The subsequent refinement phase begins once the string has been fully-grown and is marked by the monotonically decreasing value of $F$ during which the string settles into the reaction pathway. For alanine dipeptide rearrangement with cartesian interpolation, the growth phase is completed after the 33rd iteration, corresponding to 133 QM gradient calculations. With LST interpolation, growth is completed after the 11th iteration and 55 QM gradient calculations. The growth phase is much faster with LST due to the superior quality of the new interpolated nodes. This demonstrated in Figure 6 which shows the energy as a function of iteration for the first node added to the reactant side of the string. The LST interpolated node begins at a much lower energy and achieves the threshold for the next node addition more quickly.

Table 2 lists the number of QM gradient calculations necessary to fully grow the string and achieve the desired level of convergence. For a convergence criteria of 0.3 hartrees/Å, LST interpolation reduces the number of QM gradients required by 49% percent, effectively doubling the speed of the GSM. The string energy profiles for each interpolation method at a convergence of 0.3 hartrees/Å shown in Figure 6 indicate that the overall quality of the string with cartesian and LST interpolation is approximately the same. For a more tightly converged reaction coordinate at $F=0.2$ hartrees/Å, the speedup is similar at 41%. For each of the four strings resulting from LST and cartesian interpolation methods in the GSM at these two convergence criteria, the highest energy node yields the proper transition state using the standard Q-Chem surface-walking algorithm detailed in the computational details section.

### 6.7 Ring Condensation Reaction

The second benchmarking case is the cationic ring condensation of 2-(but-3-enyl)oxiranium to 4-hydroxycyclohexan-1-ylium. This reaction is inspired by the much more complicated (and enzymatically catalyzed) reaction of 2,3-oxidosqualene to produce lanosterol during cholesterol synthesis [39]. Even though this reaction is simplified, it possesses four transition states on the path from linear reactant to final product at the gas-phase HF/STO-3g level of theory. Each of these Transitions, and the stable intermediates are depicted in Figure 7. TS1, TS2, and TS4 are each internal rotations of the molecule with small barriers between 2.0 and 3.0 kcal/mol. The remaining transition state, TS3, involves the rearrangement of bond orders and possesses a much higher barrier of 23.2 kcal/mol.

Figure 8 shows the convergence rate of the GSM with both cartesian and LST interpolation for this reaction. With cartesian interpolation the growth phase is completed after 36 iterations, which corresponds to 186 QM gradient calculations. With LST interpolation, the growth phase requires only 16 iterations, corresponding to 84 QM gradient calculations. As denoted in Table 3, a 27% reduction in the number of gradients is observed for convergence to 0.4 hartrees/Å, and a 37% reduction is observed for convergence to 0.3 hartrees/Å. Figure 9 shows the exact energy profile for this reaction, as well as the energy profiles for both GSM executions once the objective function reached 0.3 hartrees/Å.
In each of the four cases noted in Table 3, launching TS optimization calculations in Q-Chem [34] from the converged strings’ nodes resulted in several first order transition states. In all cases TS1, TS2, and TS3 from Figure 7 were successfully recovered. However, TS4 (which involves a subtle hydroxyl group rotation) was only observed for the more tightly converged (F=0.3 hartrees/Å) LST interpolated string.

6.8 Conclusions

The Growing String Method is a powerful tool in the study of chemical reactions from an ab initio perspective, because it allows for the rapid identification of transition states, from which approximate kinetic rates constants may be computed with Transition State Theory. However, the interpolation method by which the string is reparameterized and new nodes are added during the growth phase has a large impact on the rate of convergence, and thus the quality of results. In particular, choosing an interpolation scheme which compresses or expands chemical bonds arbitrarily can necessitate a large number of QM calculations in order to properly find the intrinsic reaction coordinate and transition state.

Our results indicate that using the Linear Synchronous Transit method developed initially by Halgren and Lipscomb [32] can be a powerful addition to the traditional string method. This interpolation method is an improvement over cartesian interpolation because it preserves bond lengths, and performs rotational rearrangements seamlessly. The guessed pathways are thus closer to the final result, and require less computational effort to optimize.

When applied to the isomerization of alanine dipeptide, the GSM with LST interpolation requires roughly half of the computational effort as the GSM with cartesian interpolation. In the condensation of 2-(but-3-enyl)oxiranium to 4-hydroxycyclohexan-1-ylium, computational cost is reduced by roughly one third when LST interpolation is used. In this latter reaction, which contains multiple transition states between the reactant and product, the LST version of the GSM proves superior by properly identifying every transition states (major and minor) where the cartesian version misses at least one.
### 6.9 Tables

<table>
<thead>
<tr>
<th></th>
<th>$\phi$</th>
<th>$\psi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_5$</td>
<td>-161.5</td>
<td>167.1</td>
</tr>
<tr>
<td>TS</td>
<td>113.7</td>
<td>-141.9</td>
</tr>
<tr>
<td>$C_\text{7AX}$</td>
<td>72.5</td>
<td>-59.5</td>
</tr>
</tbody>
</table>

Table 6.1 Dihedral angles (in degrees) of the alanine dipeptide isomerization

<table>
<thead>
<tr>
<th>Conv. Criteria</th>
<th>Method</th>
<th>QM gradients</th>
<th>Speedup</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 hartrees/Å</td>
<td>Cartesian</td>
<td>268</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>LST</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>0.2 hartrees/Å</td>
<td>Cartesian</td>
<td>367</td>
<td>41%</td>
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<tr>
<td></td>
<td>LST</td>
<td>217</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.2 Computational Cost in QM gradients for the alanine dipeptide rearrangement, with speedup for LST versus Cartesian interpolation.

<table>
<thead>
<tr>
<th>Conv. Criteria</th>
<th>Method</th>
<th>QM gradients</th>
<th>Speedup</th>
<th>TS1</th>
<th>TS2</th>
<th>TS3</th>
<th>TS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 hartrees/Å</td>
<td>Cartesian</td>
<td>411</td>
<td>27%</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>LST</td>
<td>300</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>0.3 hartrees/Å</td>
<td>Cartesian</td>
<td>645</td>
<td>37%</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>LST</td>
<td>408</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

Table 6.3 Computational costs, speedups and success in identifying various TS structures for the cationic ring condensation reaction
6.10 Figures

Figure 6.1 Contrast of cartesian and LST interpolation between reactant and product configurations of the HCN to HNC reaction. Note that the cartesian interpolated pathway is far from the IRC, while the LST interpolated pathway is rather close. In addition, the LST methods’ tendency to preserve internuclear distances is clearly shown.

Figure 6.2 Cartoon of the strategy for using LST interpolation within the GSM. The spaces between the previous iterations nodes are filled with a discrete set of LST interpolated images. The set of interpolated images which returns the appropriate parameterization density is then returned for the next iteration.
Figure 6.3 The reactant, transition state and product configurations for the alanine-dipeptide rearrangement reaction.

Figure 6.4 Objective function, $F$, vs iteration for the alanine dipeptide rearrangement reaction. The spikes in the initial portion of each curve indicates the addition of new nodes during the growth phase.
Figure 6.5 Comparison of the intermediate energy profiles for the LST and cartesian GSM, and the exact IRC energy profile for the alanine dipeptide rearrangement. The GSM energy profiles are snapshots taken when the objective function, $F$, reached 0.3 hartrees/Å.

Figure 6.6 Energy of the first interior node from the reactant side versus iteration for the alanine dipeptide rearrangement. Note that the LST interpolated node begins at a much lower energy than the cartesian interpolated node, and achieves the threshold for node addition much sooner.
Figure 6.7 Reactant, product, stable intermediates, and transition states on the pathway between the linear and ring structures.

Figure 6.8 Objective function, $F$, versus iteration for the cationic ring condensation reaction. The spikes in the initial portion of each curve indicates the addition of nodes during the growth phase.
Figure 6.9 Comparison of the intermediate energy profiles for the LST and cartesian GSM, and the exact IRC energy profile for the ring condensation reaction. The GSM energy profiles are snapshots taken when the objective function, $F$, reached 0.3 hartrees/Å.
6.11 References

Chapter 7

The Freezing String Method: algorithm and applications

7.1 Abstract

The ability to efficiently locate transition states is critically important to the widespread adoption of theoretical chemistry techniques for their ability to accurately predict kinetic constants. Existing surface walking techniques to locate such transition states often require an extremely good initial guess that is often beyond human intuition to estimate. To alleviate this problem, automated techniques to locate transition state guesses have been created that take the known reactant and product endpoint structures as inputs. In this work, we present a simple method to build an approximate reaction path through a combination of interpolation and optimization. Starting from the known reactant and product structures, new nodes are interpolated inwards towards the transition state, partially optimized orthogonally to the reaction path, and then frozen before a new pair of nodes is added. The algorithm is stopped once the string ends connect. For the practical user, this method provides a quick and convenient way to generate transition state structure guesses. Tests show that this “Freezing String” method is an efficient way to identify complex transition states with significant cost savings over existing methods, particularly when high quality interpolation is employed.

7.2 Introduction

The ability to efficiently locate first order saddle points on \textit{ab initio} potential energy surfaces is critical to the widespread adoption of theoretical techniques for chemical research. Stable minima on these potential energy surfaces are relatively easy to locate, but finding the transition states (TS) that connect minima remains
challenging. Locating the TS's, however, is required to determine chemical mechanisms and elementary rate coefficients.

To find an exact transition state, one must typically employ a surface-walking algorithm that will refine a guess of the transition state to the exact answer [1-2]. These operate in a similar way to the algorithms for locating stable minima, and typically employ a quasi-Newton-Raphson technique. These algorithms are crucial to isolating structures that possess a zero gradient and only a single imaginary vibrational frequency, but require a guess structure that is very close to the transition state in order to succeed. Otherwise, the wrong TS, or no TS at all will be found. Because of this difficulty, TS location is often a severe problem for complicated chemical systems.

To alleviate this problem, a number of double ended transition state search algorithms have been developed [3-37]. While some of these are capable of locating the exact transition state by themselves, they are most commonly used to generate transition state guesses which are refined in the type of surface walking algorithms described above. Such double-ended algorithms typically fall into two general categories: interpolating algorithms and path optimization algorithms. The interpolating algorithms such as Linear and Quadratic Synchronous Transit [38-39] attempt to find the transition state by deducing an approximate reaction pathway in a single pass, and then using a surface-walking algorithm to refine some midpoint of this pathway to the exact transition state. The advantages of these methods are their simplicity and lack of computational expense. However, these methods offer no recourse when they fail to locate a TS.

The reaction path optimization algorithms, such as the Nudged Elastic Band (NEB) method [8-11], String Method (SM) [12-17], and Growing String Method (GSM) [18-22] describe the reaction pathway as a series of molecular images (the “string”), and iteratively optimize the string until it rests along the reaction path. Once the reaction path is located, it is easy to identify if the maximum energy node and use surface walking techniques to isolate the exact saddle point.

The String Method [12-17] optimizes a string of molecular images into the reaction pathway by breaking optimization into two steps: evolution and reparameterization. In the evolution step, the nuclear gradients are calculated using ab initio techniques. The tangent (reaction path) direction through each image in the string is computed via cubic splines. From this information, an optimization step is taken in the direction of the negative perpendicular gradient. This acts to settle the string into the reaction path. To keep the nodes evenly spaced during optimization, a reparameterization step is subsequently performed. Using the same cubic spline technique needed to find the tangents, the molecular images are shifted along the current guess of the pathway to achieve uniform node density in terms of arclength. The string method requires an initial string that spans the space between reactant and product. If interpolation is used to generate these guess structures, the initial iterations may require many gradient calculations to properly optimize the nodes.

Unlike the SM (and NEB), which begins with a fully populated chain of images, the GSM [18-22] begins with only two variable nodes close to the input reactant and product structures. New nodes are added to either side of the “growing” string
towards the transition state during reparameterization only when the frontier nodes have achieved a satisfactory level of convergence. This is measured in terms of the perpendicular gradient at the frontier node. Dynamically adding new nodes avoids unnecessary QM calculations at the beginning of the run, when the central portion of the reaction path is poorly described.

Unfortunately, iterative methods such as the SM and GSM require a large number of QM calculations for the string to obtain a reasonable estimate of the reaction path and transition state. The optimization steps include a large number of QM calculations on the outer portions of the string – nodes that are close to the reactant and product structures and far from the desired transition state. In this paper, we propose an alternative to existing string methods that aims to minimize the number of QM calculations needed to obtain meaningful approximations to TS structures. This is achieved by freezing newly grown nodes after a fixed number of iterations. In this way, expensive QM calculations are not wasted on settling the string of nodes into the reaction path where they do not describe the transition state anyway.

7.3 Theoretical Methods

7.3.1 Freezing String Method Algorithm

The Freezing String Method (FSM) operates by iteratively growing pairs of molecular structures along the reaction path from the starting reactant and product structures inwards towards the desired transition state. A flowchart of the algorithm is shown in Figure 1. Each iteration involves an interpolation step to generate a pair of new nodes along an approximate reaction path, followed by a series of perpendicular optimization steps to move these nodes closer to the exact reaction path. After each pair of nodes is interpolated and optimized, they are frozen in place for the remainder of the string generation. This ensures that an excessive number of QM gradient calculations are not performed on nodes that are far from the desired transition state. A simple cartoon of the FSM algorithm’s operation on the 2D Muller-Brown potential energy surface is presented in Figure 2. This figure is not to scale, and is only intended to guide the readers understanding of the algorithm. Exact results of the FSM algorithm when applied to the same 2D surface are given below.

The interpolation step is performed by adding nodes at a user-defined distance, $s$, from the string’s innermost pair of nodes. In the first iteration, the innermost nodes are just the user-input reactant and product structures, while later iterations use the nodes from the previous iteration as the basis for interpolation. The interpolation distance is an input to the calculation, and remains constant throughout the run. In principle, these interpolations can be performed with many different coordinate systems, however we only report on two kinds of interpolation here – simple cartesian interpolation, and the more sophisticated (and chemically realistic) Linear Synchronous Transit (LST) interpolation [38-39].

Straight-line cartesian interpolation will in many cases produce structures which contain inappropriately stretched or compressed bonds. For illustrative
purposes, an example of this is the rotation of spectator methyl group hydrogen atoms around the carbon. Cartesian interpolate will tend to compress the C-H bond length, resulting in a high-energy structure. LST interpolation avoids this type of error by interpolating in the redundant space of internuclear bond distances. The details of LST interpolation are presented in the original paper [38].

The practical application of LST interpolation to the FSM requires a structure at a specified distance from the previous pair of nodes. Because LST cannot interpolate directly to a predefined distance \textit{a priori}, an alternative method is used. Similarly to the scheme for the implementation of LST in the GSM, a high-density string of interpolated images is created between the innermost nodes (see Chapter 6). From this high-density string, the distance of each interpolated structure from the innermost nodes of the FSM string is computed. Then, those structures in the high density string which best match the user-input interpolation distance are chosen and used as the new FSM nodes.

The optimization of the newly interpolated nodes is performed with a conjugate gradient scheme for a specified number of steps, \( N_{\text{steps}} \). The direction of the first step, \( \hat{v} \), is along the negative perpendicular gradient, \( g^\perp \), of the interpolated geometry as shown in equation 1.

\[
\hat{v} = - \frac{(I - \hat{t}^T \cdot) g^\perp}{| (I - \hat{t}^T \cdot) g |} = - \frac{g^\perp}{| g^\perp |} \tag{1}
\]

The tangent direction, \( \hat{t} \), is determined during the interpolation step. It is taken as the direction along the interpolation connecting the innermost nodes. The distance of the first optimization step (denoted \( \Delta x_1 \)) is computed by dividing the magnitude of the perpendicular gradient by a scaling factor \( \gamma \). This step size, combined with the direction in equation 1, is shown in equation 2.

\[
\Delta x_1 = - \frac{(I - \hat{t}^T \cdot) g_1}{\gamma} \tag{2}
\]

The remaining \( N_{\text{steps}} - 1 \) steps (denoted \( \Delta x_j \)) are performed with conjugate gradients. This has the effect of augmenting equation 2 with a second term given in equation 3.

\[
\Delta x_j = - \frac{(I - \hat{t}^T \cdot) g_j}{\gamma} + \alpha_j \Delta x_{j-1} \quad \alpha_j = \begin{cases} 
\frac{|g^\perp_j|^2}{|g^\perp_{j-1}|^2} & \text{if } g_j > g_{j-1} \\
1 & \text{if } g_j < g_{j-1} 
\end{cases} \tag{3}
\]
A number of constraints are placed on each optimization step to ensure smooth convergence. No cartesian coordinate is allowed to move more than 0.05 Å during a given step from equation 2. Additionally, stepping of each node is stopped before $N_{\text{steps}}$ steps if the distance between the new pair of nodes exceeds a specified distance. This distance is equal the initial distance between the new nodes, $d_o$, plus $\frac{1}{2}$ of the interpolation step size $s$, and ensures that string makes forward progress towards joining ends.

The algorithm is iterated until the string is fully populated. This is determined by examining the distance between the innermost (newest) nodes in the string after these nodes have been optimized. If the distance between these nodes is less than the interpolation distance $s$, the algorithm is ended. If this distance is between one and two times the interpolation distance, only one node is added halfway between the two previous nodes and optimized, after which the algorithm ends. Once the algorithm is complete, one or more nodes in the final string can be used to launch a search for the exact transition state connecting the input reactant and product structures. Typically, this is simply the highest energy node of the FSM string. However, it is occasionally necessary to examine the output string in more detail to determine which node is most appropriate for finding the exact transition state. This situation will be discussed in the example reactions presented later.

The properties of FSM reaction paths can be qualitatively described by plotting the strings in two dimensions. The Muller-Brown (MB) [40] potential energy surface is an example of a reaction path that is not easily described by direct interpolation: drawing a straight line between the intermediates results in a path far from the lowest energy path. Because of its relatively complicated nature, this two dimensional surface represents a good trial case for any method that automatically generates reaction paths.

The MB surface is shown in Figures 3 and 4 along with 2D FSM strings. In Figure 3, several strings are grown with an increasing number of perpendicular steps (from 1 to 15) allowed for each string. The interpolation step size $s$ is fixed for strings in Figure 3. With a small number of perpendicular steps, the string could not follow the minimum energy path. With a larger number of perpendicular steps, the string moves closer to the minimum energy path at the cost of additional gradient calculations. Complementary insights can be gathered from Figure 4, which shows the convergence of the strings with decreasing inward step size. As the inward step size decreases, the node density increases and the string settles more closely to the minimum energy reaction path (although it does not necessarily reach the exact minimum energy path), again at a cost of additional gradient calculations. At the limit of a large number of perpendicular gradients and a small interpolation step size (large number of nodes), the FSM generates a good representation of the reaction path, and therefore an accurate guess at the transition state. Combining the results of Figures 3 and 4 suggests the most efficient operation of FSM: a balance of moderate interpolation step size and a small number of perpendicular steps. The results that follow utilize FSM in molecular cases with these principles in mind to create reaction paths with a minimum number of QM computations.
7.3.2 II. Growing String Method Algorithm

For comparison to existing double-ended transition state search algorithms, a modified version of the Growing String Method was employed (see Chapter 6). The algorithm operates by growing nodes inwards from the reactant and product structures, while iteratively optimizing all nodes in the string towards the reaction path. This is accomplished by breaking the optimization into two steps: reparameterization and evolution. In the reparameterization step, the existing nodes of the string are re-distributed along the current guess of the reaction path via interpolation to ensure that they remain equally spaced. Additionally, new nodes are added to the “growing” string during reparameterization only if the innermost node on a given side is sufficiently converged, up to a maximum of $N_{GSM}$ nodes. In the evolution step, each node (denoted by the subscript $i$) in the string takes an optimization step according to equation 4.

$$\Delta x_i = -\gamma \frac{(I - \hat{f}_i \hat{f}_i^T)g_i}{\gamma}$$  \hspace{1cm} (4)

This is the same as the step described in equation 2 except that the scaling factor, $\gamma$, must be somewhat larger in order to keep the string from developing kinks. Unlike equation 2, the tangent direction of the GSM at each node is updated during each step by evaluating a series of cubic splines through the existing nodes, or with the use of LST. Convergence of the GSM is measured in terms of the sum of the perpendicular gradients at each node, as denoted in equation 5.

$$F = \sum_{i=1}^{N_{GSM}} |g_i^\perp|$$  \hspace{1cm} (5)

The cost of using the GSM algorithm described above is typically expensive because each node is updated during every iteration, even though many of them are far from the desired transition state. Additionally, more conservative steps are needed to ensure proper behavior during optimization, which slows the ability of the algorithm to find the proper reaction path.

Unlike the FSM, the algorithm may be converged to an arbitrary level of convergence, which brings the string closer to the exact reaction path. At the same time, the highest energy node of the string, which acts as the estimate of the transition state, moves closer to the exact answer. In practical use however, the highest energy node of the first fully-grown string is typically a sufficient guess of the transition state to successfully find the exact solution. A full outline of the difference between the novel FSM algorithm and the comparative GSM algorithm is presented in Table 1.
7.4 Computational Details

The examples documented below demonstrate the use of the Freezing String Method with ab initio methods by employing an interface with Q-Chem [41]. The ab initio method and basis set for each calculation varies by reaction. The levels of theory chosen are somewhat arbitrary, as the FSM is applicable with any approach for computing molecular energies and gradients. The only restriction on this choice is the applicability of the level of theory for the reaction being investigated, which must be independently rationalized by the user.

At the start of each FSM algorithm run, the input reactant and product structures were aligned to maximum coincidence in non-mass weighted cartesian coordinates [42]. This step ensures that the structures are not rotated or translated during the interpolation step. The new node interpolation distances employed in the examples documented below were taken as fractions of the initial distance between the reactant and product structures (at maximum coincidence). Spacings of 1/10th and 1/20th of the initial interpolation distance \( d_o \) were used, and are referred to as the large and small spacing FSM respectively. With cartesian interpolation, the initial interpolation distance is simply the straight line distance between the reactant and product structure, and is trivial to compute. With LST interpolation, a high-density string of LST images must be interpolated between the reactant and product, and the overall arclength is computed by numerical integration. Since the initial cartesian interpolation distance is the shortest possible distance between the reactant and product structures, the LST FSM step sizes are slightly larger in the examples presented. Additionally, optimization steps were performed with a scale factor of \( \gamma = 1.75 \) hartrees/Å² for a maximum of \( N_{\text{steps}} = 3 \).

Once the FSM algorithm had completed the string, the determined guess structures were used to launch local surface-walking transition state optimizations with default parameters in Q-Chem. Each calculation was initiated with an exact initial hessian, which was subsequently updated with the default Powell/Murtagh-Sargent scheme [43-44]. After a viable transition state was located, its identity was confirmed by integrating the IRC downhill from this transition state to the input reactant and product structures, with the Schlegel-Gonzalez algorithm in non-mass weighted coordinates [4].

The comparative GSM computations presented below were performed with 11 nodes (including the two fixed end nodes) in the fully-grown string. Additionally, optimization steps of each node were taken with a scale factor of \( \gamma = 5.0 \) hartrees/Å². A larger scale factor is needed for the GSM (relative to the FSM) due to the need to keep the string reasonably well aligned (i.e. no large kinks) for the reparameterization step. New nodes were added during the reparameterization step when the magnitude of the perpendicular gradient of the innermost node on a side fell below 0.1 hartrees/Å.
7.5 Example Applications

7.5.1 cis,cis-2,4-hexadiene to trans-3,4-dimethylcyclobutene

The first example reaction is the conversion of cis,cis-2,4-hexadiene to trans-3,4-dimethylcyclobutene. They key minima and transition states for this reaction are shown in Figure 5. This test case was performed with Hartree-Fock wavefunctions, and the STO-3G basis set. The FSM calculations were performed with 3 perpendicular steps. Figure 6 shows the energy versus normalized reaction coordinate for both the large and small spacing FSM runs and the first fully formed GSM string. This is shown for both cartesian and LST interpolation, along with the exact IRC energy profile for comparison. From these plots, it is clear that the quality of the FSM energy profile is comparable to the more computationally expensive GSM energy profile. In all cases the strings shown have not completely settle into the reaction path, resulting in a shift of the peak energy from the far right (as shown with the exact IRC) towards the center.

Table 2 shows the number of QM gradient calculations needed to complete the FSM with large and small steps, and to create the first fully grown GSM string with both cartesian and LST interpolation. The FSM algorithm with large steps required 38 QM gradient calculations for both cartesian and LST interpolation, while the FSM with small steps required 78 QM gradient calculations for both interpolation methods.

By comparison, the 11-node GSM required 212 QM gradients to simply grow a completed string with cartesian interpolation, and 194 gradients with LST interpolation. Further convergence of this string requires even more QM gradients, and provides an increasingly accurate description of the desired transition state. Tighter convergence of the GSM was not necessary as the first fully-grown string is able to recover the proper transition state. The relative computational cost of the FSM with large steps relative to the 11-node GSM is only 18% with cartesian interpolation, and 20% with LST interpolation. It is not clear from this reaction whether there is an advantage to LST interpolation in the FSM, as the results are comparable in cost and quality.

For each string computed with the FSM and GSM, the high-energy transition state shown in the exact IRC profile of Figure 6 was successfully recovered by launching transition state search calculations from the highest energy nodes of each completed string. When this transition state (TS2 of Figure 5) was confirmed with an IRC integration calculation the product shown in Figure 5 was recovered on one side, however the reactant was not recovered. Instead, the intermediate of Figure 5 was recovered and the reaction was surmised to consist of two elementary steps. This can be seen in the exact IRC profile of Figure 6 (and in the diagram of the reaction in Figure 5), in which a very small bond rotation barrier is present before the high-energy transition state. This low-energy transition state is shown as TS1 in Figure 5. Isolation of this rotational transition state is possible by running the FSM again with the original reactant and the recovered intermediate as the new string endpoints, however these results are not presented.
7.5.2 Alanine dipeptide rearrangement

The alanine dipeptide C$_5$ to C$_{7AX}$ isomerization is a reaction often used to benchmark *ab initio* transition state finding methods. It involves the concerted rotation of two dihedral angles, $\phi$ and $\psi$, through a single transition state. Figure 7 shows the reactant, transition state and product structures for this reaction. This example was performed with the B3LYP density functional and 6-31G basis set, with which the barrier for this rearrangement is $\Delta E^\ddagger = 7.5$ kcal/mol while $\Delta E_{\text{rxn}} = 0.8$ kcal/mol. These values are very close to those reported by Perczel et al. with the similar 6-31+G(d) basis set and same density functional [45].

Figure 8 shows the energy profiles of the exact IRC, the large and small spacing FSM, and the first fully-grown string of the GSM. Both cartesian and LST interpolation are shown, and the results are dramatically different. With cartesian interpolation, the rotating ligands become compressed and are unable to properly relax into the reaction pathway. This results in the double peak profile seen in the first frame of Figure 8. There is also a noticeable difference between the quality of the two FSM spacings with cartesian coordinates. Similar to the 2D MB example shown in the algorithm details section, the smaller spacing FSM obtains a better guess of the energy profile, but comes at higher computational cost.

The double peak energy profile demonstrates a possible problem with using straight-line cartesian interpolation. If the interpolation distance is large, or the number of optimization steps is small, the nodes may not be able to properly settle into the reaction path. Even with the deficiencies indicated by the cartesian FSM energy profiles, the middle nodes of these strings are able to properly capture the exact transition state when used to launch surface-walking searches in Q-Chem. Normally, one would take the maximum energy node of the FSM string as the transition state search guess, but here, this is impractical. For the large spacing FSM string with cartesian interpolation, the middle two nodes were successfully used to isolate the exact transition state. For the corresponding small spacing FSM, the node with the central local maximum in energy was successfully used. Additionally, the highest-energy node of the first fully-grown GSM string was able to capture the transition state.

With LST interpolation in the FSM, the string energy profiles are much better behaved than with cartesian interpolation. This is due to the superior ability of FSM to interpolate new nodes that are near to the reaction path. In fact, the LST interpolation FSM with both large and small spacing gives a better approximate energy profile than the first fully-grown string of the GSM with LST interpolation, as shown in the second frame of Figure 8. With both of the LST FSM strings, as well as the first fully formed GSM string, the highest energy nodes were successfully used to resolve the exact transition state through surface walking.

Table 2 presents the number of QM gradient calculations needed to complete the FSM with large and small spacing, and to create the first full string of the GSM with both cartesian and LST interpolation. The large step FSM algorithm required 38 and 42 QM gradient calculations with cartesian and LST interpolation respectively. The small step FSM execution requires 74 and 76 gradients respectively. By comparison, the GSM requires 142 QM gradients to simply grow an
11-node string with cartesian interpolation, and 64 gradients with LST interpolation.

The computational cost of the FSM with large spacing is only 27% of the cost of an 11-node GSM run with cartesian interpolation. While the overall quality of the cartesian FSM string is poor, it is considerably cheaper than growing the cartesian GSM string, and is suitable for locating the exact transition state. The FSM with LST interpolation and large spacing requires 65.6% the number of QM gradient calculations necessary when compared to the analogous GSM calculation.

7.5.3 Metallacycle formation in a Ni-exchanged zeolite

A third example of the cost-effectiveness of FSM involves the formation of a C-C bond in a Ni zeolite. This reaction, shown in Figure 9, occurs in a zeolite with 52 tetrahedral (ie Si and Al) atoms, which is a relatively large and totals approximately 200 atoms. A QM/MM model [46] is used for this reaction with the B97-D density functional and the 6-31G* basis set. In this simulation, the zeolite lattice atoms are frozen in their crystallographic positions and forces on these atoms are set to zero. This allows FSM and GSM to operate in conjunction with Q-Chem without any further modification.

The C-C formation reaction proceeds through coupling of two ethylene molecules that are absorbed on square planar Ni. This Ni(II) species is thought to selectively dimerize ethylene without producing longer chain oligomers, and represents a test case where no prior mechanism of the reaction was available. With the B97-D density functional and 6-31G* basis set, the barrier for C-C bond formation is $\Delta E^+ = 24.9$ kcal/mol and $\Delta E_{\text{rxn}} = 19.2$ kcal/mol. FSM and GSM perform well on this reaction, and all joined strings produce TS guesses that converge through surface walking algorithms to the TS. FSM requires 52 and 102 gradients for large and small forward step sizes, respectively, while GSM requires 112 gradients to join the string. Because FSM produced reasonable TS guesses in less iterations than any level of GSM convergence, FSM is significantly faster than GSM for this example. Table 2 lists the total number of gradients required for the FSM and GSM methods.

With the combination of FSM allowing for rapid determination of this TS and QM/MM for inexpensive zeolite simulations, the overall computation time is surprisingly low. The total wall time for FSM and TS search on 8 CPU cores was less than 24 hours, 7 of which were required for the frequency computation to initiate the TS search.

7.6 Conclusions

While envisioning chemically reasonable intermediates is a relatively simple first task for any reaction simulation, transition state structures are almost always significantly more difficult to find. Therefore, rapid transition state location algorithms have the potential to revolutionize the study of chemical reactions by removing one of the main difficulties in simulating reaction paths. The Freezing String Method is able to locate transition state structures with minimal user input
and low computational cost. The above examples show that complicated reactions can be investigated with lower overall effort than even the efficient Growing String Method. Speed increases of 50% or more over Growing String Method appear to be typical. In certain cases, the use of LST interpolation in place of straight-line cartesian interpolation improves the quality of the final strings dramatically. This is due to LST’s ability to add new nodes closer to the final reaction path. With high-quality interpolation, larger interpolation distances may be used. In the samples shown, interpolation distances of $1/10^{th}$ of the initial interpolation distance between reactant and product are found to satisfactory.

The Freezing String Method is actively being used by our research groups to locate transition states for a variety of chemical problems, and has been successful for many cases beyond those shown in this article. Because this method only requires the reactant and product geometries as input and can be implemented for any electronic structure code, it is generally useful for the identification of complex transition states in many systems.
### 7.7 Tables

<table>
<thead>
<tr>
<th>Aspect</th>
<th>FSM</th>
<th>GSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tangent direction</td>
<td>Cartesian or LST interpolation direction based on innermost nodes</td>
<td>Cartesian coordinates with cubic splines or LST interpolation over all nodes</td>
</tr>
<tr>
<td>Node growth</td>
<td>After 3 perpendicular optimization steps in frontier nodes</td>
<td>When frontier node on a side is sufficiently converged</td>
</tr>
<tr>
<td>Perpendicular optimization stype</td>
<td>Scaled conjugate gradient</td>
<td>Scaled steepest descent</td>
</tr>
<tr>
<td>Which nodes optimized</td>
<td>Innermost nodes only</td>
<td>All nodes along string</td>
</tr>
<tr>
<td>Redistribution of nodes along string</td>
<td>None</td>
<td>Performed every iteration using the appropriate interpolation scheme</td>
</tr>
</tbody>
</table>

Table 7.1 Qualitative Comparison of FSM and GSM methods
Table 7.2. Comparison of the number of QM gradient calculations necessary to complete the FSM for large and small step sizes, as well as to converge the corresponding GSM calculations for all three example applications. The FSM was performed with interpolation spacings of 1/10th and 1/20th the initial distance from reactant to product for the large and small step FSM runs respectively, a scaling factor of $\gamma = 1.75$ hartrees/Å$^2$, and 3 optimization steps. The GSM was performed with 11 nodes and a scaling factor of $\gamma = 5.0$ hartrees/Å$^2$.

<table>
<thead>
<tr>
<th></th>
<th>Hexadiene ring formation</th>
<th>Alanine dipeptide rearrangement</th>
<th>Ethene C-C formation</th>
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<tr>
<td></td>
<td>Cartesian</td>
<td>LST</td>
<td>Cartesian</td>
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<tr>
<td>FSM w/ large step size</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>FSM w/ small step size</td>
<td>78</td>
<td>78</td>
<td>74</td>
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<tr>
<td>GSM - growth phase only</td>
<td>212</td>
<td>194</td>
<td>142</td>
</tr>
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</table>

**Relative cost**

<table>
<thead>
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<th>Alanine dipeptide rearrangement</th>
<th>Ethene C-C formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSM Large Step vs. GSM growth phase</td>
<td>17.9%</td>
<td>19.6%</td>
<td>26.8%</td>
</tr>
</tbody>
</table>
7.8 Figures

![Algorithm flowchart for the Freezing String Method with parameter definitions.](image)

Figure 7.1 Algorithm flowchart for the Freezing String Method with parameter definitions.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$s$</td>
<td>Distance from previous node on same side of string</td>
</tr>
<tr>
<td>$\hat{i}$</td>
<td>Tangent direction of the interpolated pathway</td>
</tr>
<tr>
<td>$d$</td>
<td>Current distance between newly added nodes</td>
</tr>
<tr>
<td>$d_o$</td>
<td>Initial distance between newly added nodes</td>
</tr>
<tr>
<td>$N_{steps}$</td>
<td>Maximum number of optimization steps per node</td>
</tr>
</tbody>
</table>

![Cartoon depiction of the FSM algorithm operation on the MB potential energy surface.](image)

Figure 7.2 Cartoon depiction of the FSM algorithm operation on the MB potential energy surface.
Figure 7.3 An illustration of the practical operation of FSM: strings on the MB 2D potential energy surface with increasing number of perpendicular steps taken (1 to 15 perpendicular gradients). As the number of gradients increases, the string approaches the minimum energy path.

Figure 7.4 An illustration of the operation of FSM in practice: FSM strings on the MB 2D potential energy surface with decreasing inward step size on the string (number of perpendicular gradients is held constant at 3). As the number of nodes increases, the string appears to approach the minimum energy pathway.
Figure 7.5  Structures of the minima and transition states for the reaction cis,cis-2,4-hexadiene to trans-3,4-dimethylcyclobutene. All energies shown are relative to the reactant structure.

Figure 7.6  Energy versus reaction coordinate for the exact IRC, FSM runs with coarse and fine spacing, and the first fully formed GSM string for the conversion of cis,cis-2,4-hexadiene to trans-3,4-dimethylcyclobutene. The first frame corresponds to cartesian interpolation FSM and GSM, while the second frame corresponds to LST interpolation. The arrows indicate the location of the two transition states present.
Figure 7.7 Reactant, transition state, and product structures for the alanine dipeptide rearrangement. The angles $\phi$ and $\psi$ denote the important dihedral angle rotations of this reaction pathway.

Figure 7.8 Energy profiles of the final FSM strings, the first fully grown GSM string, and the exact IRC. The top frame corresponds to FSM and GSM performed with cartesian interpolation, while the second frame corresponds to LST interpolation.
Figure 7.9 Reactant, TS, and product for ethylene dimerization in the Ni zeolite.
7.9 References