UNIVERSITY OF KWAZULU-NATAL

THEORETICAL STUDY ON THE ESTERIFICATION OF METHANOL WITH ACETIC ACID AND ACID HALIDES

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MONSURAT MOTUNRAYO LAWAL
214584429

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A thesis submitted to the School of Pharmacy and Pharmacology, Faculty of Health Science, University of KwaZulu-Natal, Westville, for the degree of Master of Medical Science.

This is the thesis in which the chapters are written as a set of discrete research publications, with an overall introduction and final summary. Typically, these chapters will have been published in internationally recognized, peer-reviewed journals.

This is to certify that the content of this thesis is the original research work of Miss Monsurat Motunrayo Lawal.

As the candidate's supervisor, I have approved this thesis for submission.

Supervisor: Signed: ---------------------Name: **Prof. H. G. Kruger**   Date: 11/11/2015

Co-Supervisor: Signed: _Honarparvar_ Name: **Dr. B. Honarparvar**   Date: 11/11/2015

Co-Supervisor: Signed: ----------------Name: **Dr. G. E. M. Maguire**   Date: 11/11/2015

ABSTRACT

Esters are a unique class of organic compounds whose production and reactivity are examined in chemical industries and research laboratories throughout the world on a daily basis. An ongoing advancement in esterification reactions is applied in biofuel production from natural and waste organic sources. The roles of esters in daily and industrial activity are enormous, which includes: perfumery, glues, solvents in chemical reactions, dye production, cosmetics removal and functional groups in the production of pharmaceutical drugs.

Dating back to the 1890s, Fischer esterification remained a crucial process through which esters are formed by coupling carboxylic acid with alcohol in the presence of an acid. For the past three decades, focus on esterification in the presence of solid acids as well as eco-friendly catalysts have been developed to enhance this process between carboxylic acids and alcohols. Important derivatives of esters are acid anhydrides and acid halides. They produce esters when reacted with alcohol either in presence or absence of catalyst.

A number of mechanisms involved in ester formation have been proposed and kinetics obtained *via* experiments while little attention has been paid to exploiting mechanistic aspects at the molecular level. Herein, a thorough investigation on ester formation from acetic acid and acid halides (acetyl fluoride, chloride, bromide and iodide) reacting with methanol is done using density functional methods. In the first step, efforts were made to examine the feasibility of an uncatalyzed model for this reaction in gas and solvent (methanol only). Before this could be achieved, a comprehensive investigation was done to assign a suitable basis set in which defTZVP was upheld for being sufficient and efficient for all atoms involved in this project at the B3LYP and M06-2X levels of theory. A notable conclusion from the basis sets investigation is that a broad basis set is required to span all halogen atoms.

Esterification of these substrates to yield methyl acetate was modelled to have occurred in a concerted manner through three different cyclic transition states. The one-step 6-membered mechanism gives lower activation energies for XAc with X = Cl, Br and I. On the other hand, the two-step 6-membered concerted model gave the lowest activation barriers for XAc with X = OH and F. The calculated thermodynamic parameters gave free energy barriers of 35.4 and 21.9 kcal mol^{-1} for acetic acid and acetyl chloride reaction with methanol respectively. This observation is in excellent agreement with experimental values of about 34 and 20 kcal mol^{-1} from literature.

The esterification reaction of acetic acid and its halide analogues with methanol was also studied in the presence of an acid catalyst using the M06-2X hybrid density functional and the defTZVP basis set. The reaction was modelled as a one-step concerted 6-membered cyclic transition state. An activation of 19.77 kcal mol^{-1} which is in reasonable agreement with experimental value was obtained. The simple one step concerted 6-membered ring mechanism provides a suitable description of the acid-catalyzed esterification reaction. Esterification of acid halides (X = Cl, Br and I) with methanol in the presence of a hydrogen ion also produced values confirming their spontaneous reactivity while acetyl fluoride vary with a high solution phase free energy of 9 kcal mol^{-1}.

The outcome of this research has provided a rational molecular level understanding on the concerted mechanism of esterification *via* 6-membered ring transition states.

DECLARATION

I, Miss Monsurat Motunrayo Lawal, declare that;

1.   The research reported in this thesis, except where otherwise indicated, is my original research.

2.   This thesis has not been submitted for any degree or examination at any other university.

3.   This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

4.   This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

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5.   This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the References sections.

A detail contribution to publications that form part and/or include research presented in this thesis is stated (include publications submitted, accepted, in *press* and published)

Signed:

LIST OF PUBLICATIONS

Publication **1**: A Focus on Uncatalyzed Esterification of Acetic Acid and Acid Halides with Methanol, Cyclic Transition States and Thermochemistry Prediction - Monsurat M. Lawal, Md. Rauf Shah, Thavi Govender, Glenn E. M. Maguire, Bahareh Honarparvar and Hendrik G. Kruger. Monsurat M. Lawal contributed to the design of the project, carried out all the calculations and wrote the paper.

The paper was submitted to Journal of Molecular Modelling 2nd of November 2015.

Publication **2**: A Density Functional Theoretical Study on Acid-Catalyzed Esterification Reaction - Monsurat M. Lawal, Tricia Naicker, Thavi Govender, Glenn E. M. Maguire, Bahareh Honarparvar and Hendrik G. Kruger.

Monsurat M. Lawal contributed to the design of the project, carried out all the calculations and wrote the paper.

The paper was submitted to Journal of Molecular Modelling 10th of November 2015.

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LIST OF ACRONYMS

A	Pre-exponential or Arrhenius factor
AOs	Atomic orbitals
B3LYP	Becke 3 Lee-Yang-Parr
BrAc	Acetyl bromide
BSSE	Basis set superimposition error
c	Concentration
CAMD	Computer-aided molecular design
CBS	Complete basis set
CI	Configuration interaction
ClAc	Acetyl chloride
CPCM	Conductor-like polarizable continuum model
DCC	Dicycloedhexylcarbodiimide
DFT	Density functional theory
DMAP	4-(dimethyl amino) pyridine
E_A	Activation energy
FAc	Acetyl fluoride
$G^{\ddagger}$	Gibbs free energy of activation
GUI	Graphical user interface
H	Planck's
$H^{\ddagger}$	Enthalpy of activation
HF	Hartree-fock
HOAc	Acetic acid
IAc	Acetyl iodide
Int	Intermediate
IRC	Intrinsic reaction coordinate
IRC	Intrinsic Reaction Coordinate
k	Rate constant
k_B	Boltzmann constant

MeOAc	Methyl acetate
MeOH	Methanol
MM	Molecular mechanics
MMFF	Merk molecular force field
MP	Moller-plesset
NMR	Nuclear magnetic resonance
Pc	Precomplex
PCU	Penta-cyclo undecane
PDs	Pro-drugs
PES	Potential energy surface
QM	Quantum mechanics
QST	Quadratic Synchronous Transit
R	Gas constant
$S^{\ddagger}$	Entropy of activation
SAC	Solid acid catalyst
SCF	Self-consistent field
SCRF	Self-consistent reaction field
SMD	Solvation model based on density
$SnCl_2$	Tin(II) chloride
T	Temperature
TD-DFT	Time-dependent density functional theory
TS	Transition state
UFF	Universal force field
ZPE	Zero point energy

CHAPTER ONE
INTRODUCTION

Ever increasing scientific hypotheses lead to experimental activities that have the aim to achieve informative data, which ultimately either serve to improve existing theories in the world of science, or to create new theories. Most important, are the prospects in the use of various computer software packages to assist in solving chemical problems at the molecular level, based on theoretical chemistry methods.[1-3] In fact, it is interesting to note that computational chemistry research accounts for roughly a third of the super computer usage worldwide.[4]

Computational chemistry has become a prominent part of chemistry over the years with merits and Nobel prizes won by research scientists in this field. Notable are John A. Pople and Walter Kohn (1998) for developing computational methods in quantum chemistry and the development of density functional theory (DFT)[5] respectively. The 2013 edition was jointly awarded to Martin Karplus, Michael Levitt and Arieh Warshel[6] for developing multi-scale models for complex chemical systems.

1.1 Computational Chemistry

Following the first theoretical calculations in chemistry by Walter Heitler and Fritz London (1927), there has been dynamic and outstanding progress in the use of computational research. These include simulation of reactions, modelling molecules (micro and macro), drug design, and identification of correlations between chemical structures and properties, amongst several other applications, which had matured and serve to complement experimental results.[7, 8]

Computational chemistry covers a wide range of theoretical fields including, molecular mechanics and dynamics, minimizations of energy, quantum mechanics and conformational analysis. These approaches and other computer-based models are used to determine the behaviour of molecular systems,[4, 7] approximate energies of compounds, and the chances of obtaining different stereoisomers. Dating back to the 1940s, technological developments have led to the advancement of computer hardware and software to proffer solutions to wave equations (arising from the Schrödinger equation) for larger systems. Earlier literature on theoretical chemistry knowledge include contributions by Pauling,[9] (1935) and Eyring *et al.*[10](1944) about an introduction to

quantum mechanics and Coulson's (1952) textbook on Valence, which involves the basics required for all theoretical and computational chemists to date.

There is a germane link between theoretical and computational chemistry, in fact some scholars do mix these two fields up, but a quick summary of the former may be termed a mathematical description of chemistry,[11, 12] while the later can simply be referred to as the application of theoretical algorithms to solve numerous chemical problems.[13, 14] Advancement of sophisticated computer hardware and software as well as computer-aided molecular design (CAMD) has become a subject worthy of discussion not only to theoretical chemists but also to experimental chemists.[15] This is evident as numerous researchers embrace the use of computational methods to fully exploit their respective fields.[16-20]

Computational methods have been coupled with: spectroscopic, chromatographic, and other experimental methods to study drug action and inhibition; such as anti-cancer,[21-24] antibiotic,[25-27] antiretroviral,[8, 28] antimalarial,[29-31] and anti-tuberculosis[32] drugs. A review paper was published in our laboratory and appeared recently, which encourages scientists to integrate experimental observations with computational methods in the drug discovery process.[8] Many studies on the inhibition of pathogens, particularly anti-HIV, anti-tuberculosis and antiretroviral drugs have been adroitly addressed in our research unit.[8]

Protein structure determination with experimental methods *via* Nuclear Magnetic Resonance (NMR) spectroscopy and X-ray crystallography has proven to be unsuccessful with many proteins, particularly, the membrane proteins.[8, 33] However, the determination of 3D protein structures using NMR techniques is time consuming; furthermore, not all molecules readily forms crystal structures suitable for X-ray analysis. Prediction of 3D structure of some macro-molecules, such as protein from its amino acid sequence was a basic scientific problem in the past. This has been solved through comparative modelling.[8, 34, 35]

Computational chemists use advanced computer software that enables them to garner theoretical insight into chemical processes through an array of quantum mechanical (QM), semi empirical and molecular mechanics/dynamics methods. QM methods (which will be discussed herein) are very accurate but the most expensive calculations in terms of computational resources and time.[8, 36] However, these developments have not replaced the traditional wet chemistry experiments, but

have assisted broadly in investigating costly and rare experimental materials. Computational chemistry is also focused on the determination of molecular structure and its changes including the determination of their thermodynamic properties.[4, 8, 37]

Reaction mechanisms that have not been established by experimental kinetic data can be verified through a series of electronic structure calculations. These quantum mechanical calculations are invaluable tools which can be utilized to determine the feasibility of chemical reactions especially when more than one mechanism or reaction pathway seems to be possible.[7, 8, 37] Recent reviews on various computational approaches employed by chemists to solve problems are available in literature,[8, 38-44] most of which have focussed on industrial, medicinal and chemical applications amongst others. An abstract on the choice of theoretical and computational models for this study is presented herein.

1.1.1   Theoretical Models

Models used in describing systems through a particular set of approximations are referred to as theoretical models.[37, 45] Algorithms depending on approximations are then applied to atomic orbitals to calculate energies, compute frequencies and perform geometry optimizations of molecules.[37, 45, 46] Computational approaches employed in chemistry can be generalized as quantum and non-quantum mechanical methods. Quantum Mechanics (QM) methods, are also known as electronic structure theories, aimed at solving the Schrödinger equation (1926)[47] to study properties of molecules.[45] Semi-empirical, ab-initio and density functional theory methods are discussed next, as examples of theoretical models.

1.1.1.1   Semi-Empirical Methods

Semi-empirical are based on QM and not on classical physics[2] usually employed to study bigger systems like proteins and biomolecules, to obtain qualitative short-time results.[7, 8, 48] AM1, PM6, PM3, ZINDO, INDO are frequently used semi-empirical methods implemented in a number of programs,[7, 45] for modelling these larger systems.[14, 49] A number of experimental quantities are incorporated in semi-empirical methods and used during the calculation. The most severe approximation of semi-empirical methods is the neglect of certain classes of electron repulsion integrals. Due to this dramatic approximation, much larger systems varying from big to medium size molecules containing up to 3000 atoms, can be modelled in a realistic manner.[50] To give a

practical example, our group is working on HIV Protease with more than 3100 atoms. A PM3 optimization on 8 CPUs and with 1.5 GB of memory takes about 24 hours on a Linux cluster.

A noteworthy defect of these methods in investigating electronic structures is that, if the molecules to be studied are not sufficiently similar to the parameterized molecules in the database, incorrect or erratic results may be obtained.[7, 51] PM6 is an exciting method with broad applications[52] and it will be used to model some approximate transition structures in these studies. The latest review on quantum–chemical semi-empirical methods was published in 2014 by Thiel.[53]

1.1.1.2   *Ab initio* Methods

Ab initio methods are based mainly on the laws of quantum mechanics derived strictly from theoretical principles.[45, 54, 55] Although the methods grouped under this model have the same basic approach, but they vary in the mathematical algorithm approximations adopted.[2] Despite the requirements in terms of computational resources and duration, *ab initio* methods remain the most prevalent type of electronic structure method employed by computational and theoretical chemists. Compounds or systems containing up to 300 atoms can be studied with these theoretical models; the time required for such calculations depends on the computer hard- and software as well as the level of theory and basis set. These methods do not only provide accurately qualitative results, but also, highly quantitative estimation for a wide variety of systems.[54]

Hartree-Fock (HF), Moller-Plesset (MPn – including electron correlation) and Configuration Interaction (CI) are examples of *ab initio* methods. These methods systematically approach the correct "answer" as the level of theory and the size of the basis set are increased. This comes at considerable cost in terms of computer resources and time. In recent years, reviews on *ab initio* calculations have been directed to specific type of calculations or studies as this method is extensive.

1.1.1.3   Density Functional Theory (DFT) Methods

To design a more effective electronic structure method, Kohn, Sham and Hohenberg,[56, 57] proposed an alternate approach which uses density functional models. Energies are computed using electron densities instead of wave functions. DFT is also an extension of HF calculations.[12] With computational time reduction compared to MP methods, DFT method uses approximately the same computer resources as HF theory.[46] Time-Dependent Density Functional Theory (TD-DFT) is an extension of DFT which is widely used to simulate the optical properties of both inorganic and organic compounds. An update on this model was presented by Laurent and Jacquemin[58] in 2013.

The hybrid method by Becke[59] and Lee et al.,[60] (B3LYP) is the most popular among the DFT models (especially for organic molecules). This model uses exact exchange and gradient corrected density functional approximations to calculate correlation energies from electron densities.[59-62] Although some criticism, such as its poor estimation of barrier heights and weak interactions has been noted,[63, 64] B3LYP has been embraced to give relatively good geometries of most organic and organometallic molecules.[4, 19, 20, 65-67] M06-2X[63, 64] is another hybrid functional which can be used to obtain accurate thermodynamic and kinetic data when studying reaction mechanisms. Hence, these two methods will be used in this thesis to investigate the mechanism of esterification reaction, since the major part of these studies focus on transition state geometries and energetics.

1.1.1.3.1   Basis Sets

Electronic wave functions are described mathematically with basis sets,[45] molecules are described by molecular orbitals, which are expressed in terms of atomic orbitals.[68] The larger the basis set, the better the computational output, since approximations of the orbitals are obtained by imposing less restriction on the location of electrons in space. Becke's three parameter hybrid exchange DFT functional together with Lee, Yang and Parr's correlation functionals (B3LYP)[59, 60] will be coupled with 6-31+G(d),[69, 70] LANL2DZ,[71-73] MidiX,[74, 75] DGDZVP,[76, 77] aug-ccpVTZ,[78-80] and def2-TZVP [81, 82] basis sets, to assign a suitable basis set for all atoms involved in this reaction. Comprehensive updates on basis sets were recently published in 2013 by Frank[83] and Grant.[84]

1.1.1.4   Molecular Mechanics (MM) Methods

Unlike the electronic structure methods, MM uses classical physics and not quantum mechanics. Hence, it is usually referred to as non-quantum mechanical methods. Approximations of atoms in

MM simulations are done by applying classical physics laws, such as the equation of motion, to predict structures and properties of a system or a molecule. The several MM methods are characterized by their particular *force field*.[45]

Very large systems can be modelled, including enzymes, proteins and other biological molecules. Examples of force field are the Universal Force Field (UFF),[85] AMBER[86] and Merk Molecular Force Field (MMFF).[87] Though a less expensive approximation method, MM methods cannot be applied to follow a course of reaction because electronic effects are neglected.[45] However, its (MM) combination with QM is now increasingly used in practical applications, such as the design of drug leads and catalysts as well as to predict drug metabolism and drug resistance.[8, 40, 88]

1.1.2   Geometry Optimization

This is a crucial step when investigating molecules, systems and reactions. Optimization of geometries of reactants is required in order to locate the lowest possible minimum on the potential energy surface (PES).[45] Modelling of transition structures also make use of optimization, these transition structures are then re-optimized to ensure they are saddle points on the PES connecting two different structures.[68] A survey of geometry optimization was reported by Schlegel[89] in 2011 which remains the most recent review covering this aspect.

1.1.3   Modelling Transition State (TS) Structure

A transition state structure is often indicated in a square bracket with double-dagger superscript, representing an energy maximum on passing from reactants to products of a given reaction.[90] The three methods generally used for locating transition state geometries are:

1.1.3.1 Intelligent guess of critical transition state coordinates – partial geometry constraints

This method involves the fixing of some critical bonds and angles of the molecule (particularly in reaction coordinates) to obtain structures with geometries closer to the TS. Experience with transition state bond lengths is crucial; alternatively, such knowledge can be obtained from literature. A partial optimization, which locates an approximate starting point close enough to the saddle point is performed. Usually the unconstrained TS optimization is followed by a frequency calculation in order to inspect the normal mode associated with the "one and one only" imaginary

value.[45, 91]   The imaginary normal mode in the TS should reflect the expected transition from reactant(s) to product(s).

1.1.3.2 Finding a suitable transition state starting geometry utilizing a relaxed scan calculation

Another more automated method involves a relaxed scan calculation (Figure **1**). This is used when the researcher lacks knowledge or experience with a certain new transition state. Any critical coordinates in the transition is either moved closer to the expected transition state, or moved further apart. This could be two atoms (bond formation), or an angle.
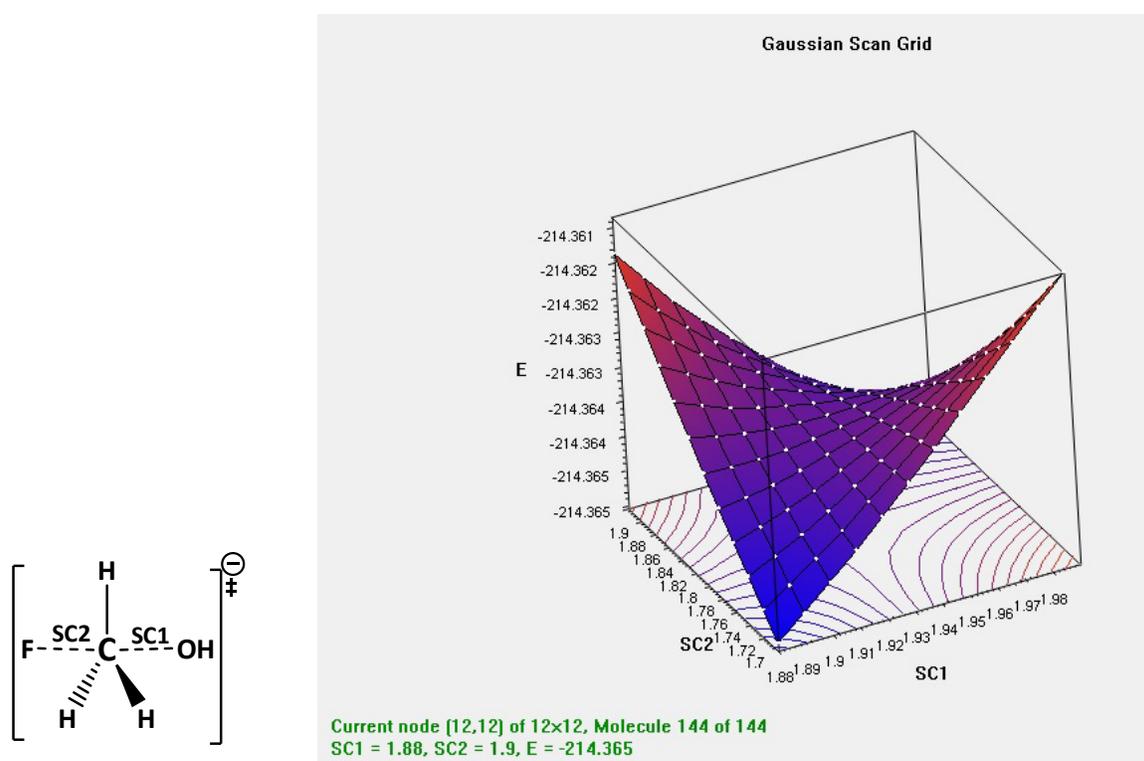
Figure **1**: A relaxed scan calculation for the S_N2 attack of fluorine on methanol. Reproduced from literature.[8]

Approximate starting structures for an unconstrained TS optimization are then extracted from the 3D scan results.

1.1.3.3 Saddle point calculations

There are alternate ways of locating TSs, using the Quadratic Synchronous Transit[92] (QST2 and QST3) methods. In the former, one submits the reactant and product geometries, the program interpolates between the two structures to find a starting point for a TS calculation. It is necessary for the atom numbering to be consistent between both structures. QST3 requires (an accurate) estimate for the transition state geometry as well.[45]

1.1.4 Intrinsic Reaction Coordinate (IRC) Calculation

In order to follow the reaction path to ensure the TS structure obtained with any of the aforementioned methods connects the intended reactant(s) and product(s) explicitly,[45] IRC[93] calculations are usually carried out. In practice, this is performed for a new transition state, or cases where the movement of atoms associated with the negative eigenvalue (from a frequency calculation) provide an ambiguous picture.

1.1.5 Solvation Studies

Solvation effects will be calculated by using the self-consistent reaction field (SCRF)[94] keyword. This keyword is used to specify the dielectric constant for the different solvents with the Conductor-like Polarizable Continuum Model (CPCM)[95] and the Solvation Model based on Density (SMD) solvation model.[96] These methods have been used effectively in studying a pentacyclo undecane (PCU) cage lactam in our unit.[4, 65]

1.1.6 Computational Program

1.1.6.1 The GaussView Program

GaussView[97] is a pre- and post-processor Graphical User Interface (GUI) program for Gaussian. All molecules will be modeled, manipulated and viewed through this suite.

1.1.6.2 The Gaussian 09 Program

Gaussian 09 Rev D.01[98] is the latest version of the Gaussian program which started with Gaussian 70, 92, 94, 98 and 03[99] versions. Due to high computer resource demand of many accurate computational methods, electronic structure calculations are often carried out *via* shared processors. The mechanism of esterification is investigated using Gaussian 09 Rev D.01[98] that is

installed on clusters at the Centre for High Performance Computing in Cape Town (www.chpc.ac.za).

1.2 Esterification Reactions

The importance of organic esters as suitable chemical has long been established.

$$R_1COOH + R_2OH \xrightleftharpoons[\Delta]{H^+} R_1COOR_2 + H_2O$$

$$\text{Carboxylic acid} \quad \text{Alcohol} \quad\quad \text{Ester} \quad \text{Water}$$

Scheme **I**: Esterification reaction of carboxylic acid and alcohol.

Esters find extensive industrial applications in the production of flavourants, and as emulsifiers in cosmetics and food firms.[100, 101] They are also used in making plasticizers (from polyesters), producing surfactants like detergents, and in the manufacture of pharmaceuticals.[100, 102] Methyl acetate (MeOAc) has a mild ester-like smell and it is liquid at room temperature. Its miscibility with several organic solvents confers a wide range of uses on this ester.[102, 103] MeOAc has been used to replace ketones and ethyl esters. It is a relatively low boiling point solvent, which is applied in environmentally friendly reactions.[104, 105]

Esterification reactions, which have profound significance to industries,[100, 106-108] are reactions leading to the formation of esters, protection of carboxylic acids and hydroxyl functional groups.[100, 109] A recent advancement in esterification reactions is its application in biofuel production,[110-113] from natural and waste organic sources. Biodiesel is obtained through esterification of crude feedstock oils,[114, 115] alcohols,[116, 117] stale cooking oils[118-120] and reduced animal fats,[112] which have a substantial amount of free fatty acids in the form of carboxylic acids. It is also noteworthy that formation of fats and oils are results of esterification reactions. Fats are of major importance in all living systems for the synthesis of hormones, storage of energy and safeguarding of vital parts of the body. They initiate biochemical responses that support; growth, reproduction, the immune system and many aspects of basic metabolic activities. They assist other biologically important molecules, such as proteins, in their activities.

The application of esterification in medicinal chemistry is also overwhelming. Some biologically less active pro-drugs (PDs) and nutrients have been esterified[121-126] to increase their reactivity.

Several available synthetic routes for the production of organic esters have been highlighted,[127] and reviewed in 2012.[128] A thorough insight on esterification of cyclic, aromatic and long-chained carboxylic acid were carried out by Ganapati and Pranav,[129] Bhaskar *et al.*,[130] Charles and Ram,[131] as well as Chan *et al.*,[107] with the former and latter groups using solid acid catalyst (SAC) and tin(II) chloride ($SnCl_2$), respectively. The use of acid catalyst to drive the equilibrium of esterification to the product can be traced back to the earliest esterification model (Fischer-Speier, 1895),[132] with the use of inorganic acids such as sulfuric and hydrochloric acids.[133-135] However, heterogeneous catalysts have become popular in place of this homogeneous method due to less product contamination and reusability of catalysts.[129, 136, 137]

Esterification can occur either as a forward or backward reaction, these two pathways have been investigated kinetically for the formation of MeOAc.[102, 106, 136, 138] Mandake *et al.* reported activation energies of 4.81 and 3.00 kcal mol^{-1} for the uncatalyzed forward and backward reaction, respectively,[136] values of 9.00 and 4.42 kcal mol^{-1} were obtained with the catalyzed model. A lower value (1.98 kcal mol^{-1}) was observed by Jagadeesh Babu *et al.* for the catalyzed backward reaction with an entropy value of 24.70 kcal mol^{-1} K^{-1} and 7.17 kcal mol^{-1} for the enthalpy value.[102] This explains why normal esterification reactions seldom reach more than 70% yield.[90] In order to obtain better yields , several strategies have been developed, this includes excess alcohol refluxing in the presence of acid catalyst,[90, 127, 134, 138] with intermittent removal of water *via* a Dean-Stark apparatus to push the equilibrium towards ester formation.[90] Some studies have shown that using microchannel reactors,[139] batch reactors[106, 135, 138] and reactive distillation[140-142] also increase the yield of MeOAc. Higher yields of esters have also been reported using dicyclohexylcarbodiimide (DCC) as a coupling agent in the presence of acid catalyst.[127, 143] DCC (or other carbodiimides) also removes water and shifts the equilibrium towards the product.

Other substrates through which esters can be obtained are acyl halides, especially the acyl chlorides. Esterification of acyl chlorides with alcohols to obtain esters was studied in 2000.[101] However, due to the exergonic character of this reaction, investigations have generally been restricted to conditions which slow down the rate of reaction to allow the reaction course to be followed with the available methods at that time.[101, 103] In 2000, Willms *et al.*,,[101, 103, 144] dedicated much study to the alcoholysis of acetyl chloride with aliphatic alcohols using a calorimetric method.

The simplified route for the reaction of acyl halides with alcohol requires no acid catalyst and it is represented in Scheme **II**.

$$R_1COX \quad + \quad R_2OH \quad \underset{Base}{\rightleftharpoons} \quad R_1COOR_2 \quad + \quad HX$$

Acyl Halide   Alcohol   Ester   Hydrogen Halide
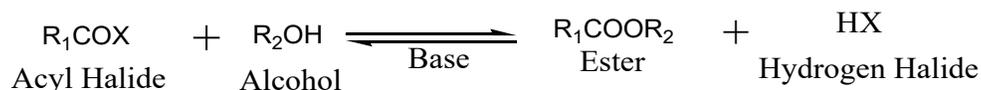
Scheme **II**: Esterification of acetyl halide with methanol. [X=F, Cl, Br, I], adopted from standard textbooks.[90, 127, 145]

Although, esterification of acetic acid with methanol was thoroughly studied in recent years,[102, 106, 135, 136, 141, 146] little effort has been made to shine light on the molecular level understanding of MeOAc formation, especially with acyl halides. This problem is complicated by the number of probable mechanisms concerned in esterification, as indeed might be expected from the theory of general acid and base catalysis.[147] However, computational studies have reported a cyclic four-membered transition state (TS) on esterifying mono carboxyl-substituted armchair and zigzag single-walled nanotubes with methanol.[148] Cyclic transition states have been realized to be energetically favourable as reported by Kruger and co-workers[19, 20, 65, 109] In their earlier studies (2002 and 2004), a highly feasible six-membered ring transition state was observed (Scheme **III**) during acetylation of anhydride with methanol.
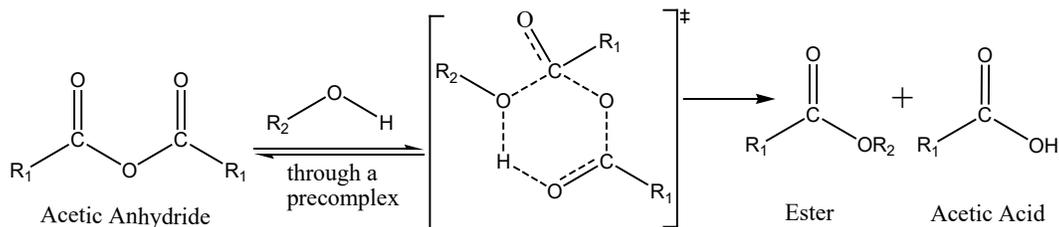
Scheme **III**: Formation of ester from acetic anhydride, redrawn from literature.[20, 109]

Precomplexes, which are organizing structures necessary to facilitate the formation of the cyclic six membered TS molecules, have been reported in a number of results by Kruger *et al.*[19, 20, 109, 149] These six-membered ring transition states reported by Kruger and his group were similar to a related system first reported by Yamabe and Ishikawa on investigating the hydrolysis of acetic

anhydride by water.[150] To this effect, it can be affirmed that the formation of cyclic TSs are well established when following reaction paths, as observed in literature.[4, 20, 65, 67, 109, 149, 151-153]

A cyclic six-membered transition state was also reported in the base (DMAP) catalyzed esterification of alcohol with acetic anhydride.[154] Depending on the concentration of methanol, the thermo-kinetic investigations for the formation of MeOAc from acetyl chloride and acetic acid have obeyed the kinetic law in Eq. **1**.[90] This indicates a second-order reaction, where r and k_1 are the rate and rate constants, respectively.

$$r = k1\,[XAc][ROH] - - - - - - - - - - - - - - - - - - \mathbf{1} \quad [X=OH, F, Cl, Br, I]$$

Therefore, mixed kinetic equations for this bimolecular-type reaction have been derived by several authors[103, 106, 136, 155-158] based on the catalysts and solvent models employed The involvement of two mechanisms has been observed in many of these equations on increasing the concentration of MeOH slightly but not in excess[102, 159, 160] to increase the yield of MeOAc. This study will employ this principle to account for the formation of MeOAc, by increasing the molecules of methanol from one to two (explicit) and three *via* implicit solvation model.

1.3 Aims and Objectives

The aims of this study are:

- ✓ To provide a molecular level understanding of the mechanism of uncatalyzed esterification of methanol with acetic acid and acetyl halides (F, Cl, Br, and I) in both gas and solution phase.
- ✓ To explore the possible pathways involved when esterifying these reactants through concerted cyclic transition structures
- ✓ To examine a suitable catalyzed model which can be applied to both acetic acid and its halide derivatives with reasonable activation barriers.

Density Functional Theory methods will be used extensively to determine all possible cyclic (and acyclic) transition states involved during this reaction in gas (vacuum) and solvent (using methanol) media. In both cases, the study will strive to correlate observed experimental results

with the calculated ones. Thermodynamic and kinetic data, such as the energies of starting material, precomplexes, intermediates and transition states, are impossible to obtain by experimental techniques. Computational model offers a unique opportunity to enhance our understanding on these basic parameters.

1.4 Thesis Outline

This study proceeds as follows

Chapter **2** focuses on a DFT mechanistic investigation of the uncatalyzed esterification of methanol with acetic acid and acetyl halides,

Chapter **3** describes the catalyzed mechanisms of esterification reaction of methanol with acetic acid and acetyl halides,

Chapter **4** gives a summary of the dissertation.

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CHAPTER TWO

A Focus on Uncatalyzed Esterification of Acetic Acid and Acid Halides with Methanol: Cyclic Transition States and Thermochemistry Prediction

Monsurat M. Lawal,[a] Md. Rauf Shah,[a] Thavi Govender,[a] Glenn E. M. Maguire,[a,b] Bahareh Honarparvar,[a] and Hendrik G. Kruger[†a]

[a]Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa.

[b]School of Chemistry and Physics, University of KwaZulu-Natal, Durban 4041, South Africa

[†]**Corresponding author**: kruger@ukzn.ac.za (Hendrik G. Kruger), Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa.

Abstract: In recent years, investigations into the kinetics and mechanism of acid-catalyzed esterification reactions have gained renewed attention. This is due to the wide range of applications of esters (*particularly carboxylic esters*) from daily to industrial usage. A complete mechanistic insight at the molecular level is absent. Herein, we describe the uncatalyzed esterification of acetic acid and its halide derivatives (XAc, where X= OH, F, Cl, Br, I) with methanol (MeOH) to give insight into the understanding of the mechanism(s) involved. This investigation was performed using Density Functional Theory (DFT) with the B3LYP and M06-2X functionals in gas phase and methanol. A number of basis sets (6-31+G(d), aug-cc-pVTZ, LANL2DZ, def2-TZVP, MidiX, and DGDZVP) were probed to ascertain accurate option, based on basis set superimposition error (BSSE) corrections. BSSE results suggested that def2-TZVP is an adequate choice for all the considered halogen atoms. Esterification through cyclic 4- or 6-membered transition state structures in one or two-step concerted mechanisms were investigated. The computed kinetics and thermodynamic parameters for the most feasible mechanistic routes are in reasonable agreement with experimental data. The present study suggests that the one-step 6-membered mechanism gives lower Gibbs activation energies for XAc; X = Cl, Br and I. On the other hand, the two-step 6-membered concerted model gave the best results for XAc; X = OH and F.

1. Introduction

Esterification reactions are performed on a daily basis in thousands of research laboratories and also have widespread industrial applications.[1-8] The rudimentary esterification reaction is presented in Scheme **1**. Generally, the widely studied procedure for ester synthesis is the direct esterification of carboxylic acids with alcohols usually catalyzed by acid. Modern textbooks[6, 9-11] teach slight variations of a stepwise mechanism (Scheme **1**) for this reversible reaction. The carbonyl oxygen of **1** is first protonated by an acid to form the transition state **2**.[8, 12] This protonation process aids nucleophilic attack of methanol **3** on the reduced acetic acid to form a tetrahedral intermediate **4**.[8, 12, 13] Theoretical mechanistic studies from our group suggested that the corresponding tetrahedral intermediate, is not a minimum on the reaction profile (*i.e.* it reverts back to reagents).[14, 15] The reaction proceeds through intermediates **5** and **7** to yield ester **8**. A similar stepwise mechanism is accepted for the esterification reaction involving acetyl chloride (ClAc)[6, 10, 11] and other acid halides.[16]
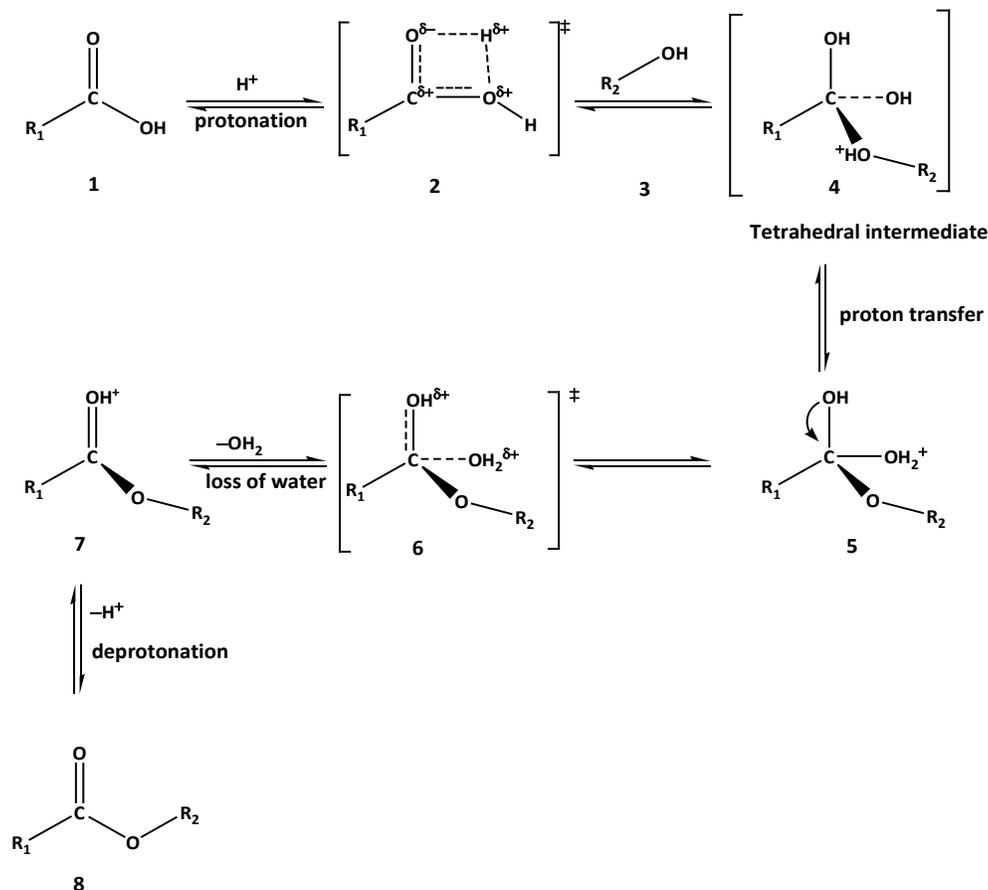
Scheme **1**: Linear stepwise mechanism for acid catalyzed esterification of acetic acid with methanol, adopted from literature.[8, 12, 17, 18]

Formation of methyl acetate (MeOAc) from acetic acid (HOAc) and methanol (MeOH) has been kinetically mediated by homogeneous[10, 13, 19-22] or heterogeneous catalysts[5, 22-24] and references cited herein, with more research being performed on the latter due to increased reusability[25], high selectivity[2] and less product contamination.[22, 25, 26] The synthesis and kinetics *via* microwave, membrane, batch and microchannel reactors,[27-30] have been studied.

Few experimental studies on the uncatalyzed reaction of HOAc with MeOH are found in literature.[5, 20, 31, 32] An earlier report (Rolfe and Hinshelwood, 1934) gave an experimental figures to estimate the Gibbs free energy of activation ($\Delta G^{\ddagger}$) of approximately 34 kcal mol^{-1} at 373 K for the uncatalyzed esterification reaction of HOAc with MeOH; they have tagged the reaction as "slow" due to a lnk (k is rate constant) value of about -27.[31] Rönnback *et al.*(1997)[20] reported that the same uncatalyzed reaction at 313 K failed to reach equilibrium by the 49th day. Thus, indicating the "slow" nature of the reaction without catalyst. Meanwhile, Mandake *et al.* (2013)[32] reported a

lower experimental activation energy (E_A) of 4.8 kcal mol^{-1} for the reaction of these substrates which seems difficult to rationalize.

However, a recent study[33] on uncatalyzed esterification of HOAc with ethanol (at temperatures 373 to 523K) observed an E_A of 11 kcal mol^{-1}. The gas or vapor phase mechanism was found to be thermodynamically favorable,[25, 34] even at 1:1 equimolar ratios of both reactants (carboxylic acids and alcohol), esterification can proceed successfully.[33]

The *in situ* generation of acid chlorides from carboxylic acids and subsequent reaction with alcohol to produce esters is the second most common method for the synthesis of esters.[10, 11, 35] Experimental $\Delta G^{\ddagger}$ values of between 16 and 20 kcal mol^{-1} for ester formation from of ClAc and MeOH in different solvents was reported.[36, 37] Experimental entropy contributions for the esterification of HOAc and XAc with alcohols of between -30 to -60 cal/(mol.K) were reported.[1, 33, 36, 38] Experimental lnk for the reaction of ClAc with methanol was -5.0.[37]

Although, microscopic aspects of the uncatalyzed mechanism and kinetics of esterification of MeOAc were attempted,[20, 31, 32] little effort was made on understanding the reaction mechanism at molecular level, especially from acid halides. This question is complicated by the number of possible mechanisms concerned in esterification, as indeed is expected from the theory of general acid and base catalysis.[31, 39, 40]

Computational studies have reported a cyclic four-membered transition state (TS) model on esterifying mono carboxyl-substituted armchair and zigzag single-walled nanotubes with methanol.[41] In both cases, it was assumed that the reaction passes through a four-membered ring transition state having an energy barrier (E_A) of 42.2 and 46.1 kcal mol^{-1} (without entropy and catalyst) respectively using DFT calculations [B3LYP with the 6-31G(d) basis set]. Cyclic transition states have been found to be energetically plausible as reported by our group during acetylation of anhydride with methanol.[14, 42] The 6-membered ring transition states reported are similar to a related system first reported by Yamabe and Ishikawa on investigating the hydrolysis of acetic anhydride by water.[43] These transition states seem similar to pseudo-pericyclic transition structures reported before by Birney and his group.[44-46] Experimental and theoretical investigations on dimers of acetic acid,[47] hydrolysis of alkyl acetate,[1, 48-51] alcoholysis of acyl halides[35, 37, 40, 52] and methanolysis of acetic acid using explicit solvation model,[53] have also supported cyclic TS formation. The moieties in these cyclic TS models vary in conformation with respect to the nature of the substrates (4-, 6-, and 8-membered inclusive). To this effect, it can be

affirmed that the formation of cyclic TSs are well established and favorable due to the concerted arrangement of these TSs over the reactants in the reaction complex.[33, 54]

Further, a cyclic six-membered transition state was also reported in the base (DMAP) catalyzed esterification of alcohol with acetic anhydride.[55] This theoretical study by Xu *et al.* also confirmed the need for a base to facilitate the nucleophilic attack on the anhydride carbonyl group. Precomplexes (Pcs), which are organizing structures necessary to facilitate the formation of the cyclic 6-membered TS molecules, have been reported in a number of theoretical studies.[14, 15, 42] A pre-reaction complex (4-membered) was also observed in the reaction of acyl chloride and acyl iodide with methanol at 1:1 molar ratio.[35]

When a simpler non-catalytic model is investigated using acetic acid or acid halide, it is essential for the proton of the incoming (nucleophilic) alcohol to be transferred to the hydroxyl group of acetic acid[37] or to the halogen atom of acid halide. Depending on the concentration of methanol, the thermo-kinetic investigations for the formation of MeOAc from acetyl chloride and acetic acid follows the kinetic law shown in Eq. **1**.[11] This indicates a second-order reaction where r and k_1 are the rate of reaction and rate constants, respectively.

$$r = k1\,[XAc][ROH] - - - - - - - - - - - 1 \quad [\text{X=OH, F, Cl, Br, I}]$$

In general, the two possible mechanisms usually studied for esterification of carboxylic acids can be summarized as: (1) The carboxylic acid molecule is initially adsorbed or protonated by H^+ ions before it is esterified with alcohol which was observed to be the rate-limiting step[13] and (2) the H^+ ions and alcohol molecules therefore form complexes, while esters are produced through molecular interaction of the complex with carboxylic acid molecules.[53]

Ester formation from acid halides seldom requires acid catalysts. In practice, the reaction is normally performed in the presence of a base to initiate the nucleophilic attack on the carbonyl carbon of the acid, and to scavenge the hydrogen halide by-products of the reaction.[11, 17]

Our study attempted to determine if a single computational model can account for the uncatalyzed esterification of XAc (X = OH, F, Cl, Br and I) with MeOH in gas phase. We decided to investigate three potential cyclic models: (a) concerted 4-membered ring, (b) one step and (c) two-step or 6-membered ring transition state structures mechanism. A literature study revealed that finding a suitable single basis set for this reactions is not trivial. Analysis of basis set superimposition error

(BSSE) was performed to determine a suitable basis set for the respective computational models. Further, this research was advanced to study the reaction in solvent (methanol) for the most plausible reaction mechanism(s) *only*. The study strives to draw a correlation between reported experimental values and data from this theoretical model.

Improved knowledge of the mechanism of the most feasible esterification mechanism will potentially enable researchers to use kinetic control for the regioselective protection of multifunctional structures.[14, 15, 42, 53] It will also move the field forward to find appropriate catalyzed theoretical reaction mechanisms.

2. Computational Details

2.1 Choosing a Suitable Basis Set(s) Combination

All calculations were performed within the Gaussian 09[56] program package. Density Functional Theory (DFT) method using B3LYP[57, 58] hybrid exchange correlation functional was coupled with 6-31+G(d),[59-61], LANL2DZ,[62-64] MidiX,[65, 66] DGDZVP,[67, 68] aug-cc-pVTZ[69-72] and def2-TZVP[73, 74] basis sets, to assign a suitable basis set (or mixture of basis sets) for all atoms involved in this reaction. Boys and Bernardi counterpoise correction (CP)[75] approach was used to obtaining the BSSE corrections for a TS representative (TS-6.2.4-X, see Figure **2**) for each reaction. Detailed discussion on our findings for this aspect is provided in supporting information while a summary is presented herein.

Based on the results for all basis sets studied, it appears that all other combinations of basis sets provide lower energies except aug-cc-pVTZ (supporting information, Table **S1**). From the BSSE corrections, it is quite obvious that aug-cc-pVTZ basis set actually converges smoothly towards the complete basis set (CBS) limit.[76, 77] This basis set and its combination with def2-TZVP has the lowest BSSE correction ranging from 0.47 to 1.91 kcal mol^{-1}. According to these results, aug-cc-pVTZ/def2-TZVP is the best choice for this study. However, higher computational demand while using aug-cc-pVTZ/def2-TZVP made us choose def2-TZVP only for this investigation. Some defects highlighted[78, 79] on barrier height and thermochemistry predictions with B3LYP made us perform a comparison on B3LYP, X3LYP[80] and M06-2X[78, 79, 81] functionals with def2-TZVP basis set, before upholding the latter for accuracy reasons [see the supporting information (Table S2)].

2.2 Esterification Reactions of Methanol with Acetic Acid and Acetyl Halides

DFT calculations was carried out with full optimization of the geometries of reactants, TS structures and products using def2-TZVP basis set at B3LYP and M06-2X level of theory. Vibrational frequencies[82] were computed for these unconstrained compounds to group them as precomplexes, minima, transition state (TS) structures (with one-negative eigenvalue) and intermediates on the potential energy surface (PES). Cartesian coordinates of the representative optimised TS structures (including imaginary frequency values) reported herein are presented in supporting information.

Intrinsic reaction coordinate (IRC)[83, 84] were computed to ensure the TSs are indeed first-order saddle points connecting the expected reactants and products on the reaction pathways. Relative energies, enthalpies, entropies and Gibbs energies at 298.15 K were computed via the ideal gas approximation as applied in Gaussian 09 suite. Arrhenius factor A, and the rate constant of each reaction were calculated using the modified Eyring equation (Equations **2** and **3**) as described in,[85] where k_B, h, and R, are Boltzmann, Planck, and gas constants, $\Delta G^\ddagger$ and $\Delta S^\ddagger$ are free energy and entropy of activation, respectively.

$$k = \frac{k_B T}{hc^0} \, exp\left(-\frac{\Delta G^\ddagger}{RT}\right) - - - - - - - - - -2$$

$$A = \frac{k_B T}{hc^0} \, exp\left(\frac{\Delta S^\ddagger}{R}\right) - - - - - - - - - - -3$$

1M standard concentration[85] was used to calculate the rate constants k, which were converted to lnk and frequency factor A as lnA from Equations **2** and **3**. Energies are reported (Tables **1**, **2** and **3**) in gas phase at 298.15 K using B3LYP and M06-2X hybrid density functionals, the relative total or activation energy (in kcal mol^{-1}) takes into account the zero point energy (ZPE) plus self-consistent field (SCF) energy.[86] The raw thermodynamic data are available in the supporting information (Tables S3, S5, and S7 respectively).

To achieve reasonable agreement between computational thermochemical properties and experimental values, solvent effects is crucial. The interactions of solute and solvent are essential in modeling the energy, structure and the system in its entirety. A number of methods have been established[53, 87-89] to obtaining free energy in solution phase. Using the approach of Silva et al[106] for neutral hydrolysis of esters, solution phase free energy and lnk were obtained using Equations **2** and **5**. ΔG^0_{sol} is the observable solution phase free activation energy at 1M concentration of

solute and pure solvent which was obtained from Eq. **5**, while Eq. **4** is a pre-step to estimate Eq. **5**.[90]

$$\Delta G^*_{sol} = \Delta G^*_g + \Delta\Delta G^*_{solv} \text{ --- --- --- --- --- 4}$$

$$\Delta G^0_{sol} = \Delta G^*_{sol} - nRTln[MeOH] \text{ --- --- --- --- 5}$$

Solvation free energy ($\Delta\Delta G^*_{solv}$) was calculated by subtracting the gas phase energy (SCF) from the single point solvation calculation using Solvent Model based on Density (SMD)[89] while ΔG^*_g is the gas phase free energy value obtained from frequency calculation. An entropy penalty is paid for by subtracting its correction (nRTln[MeOH] = 1.9 kcal mol^{-1}) to compress the solution concentration to 1M.[88, 90] For reactions involving main group atoms, conductor-like polarizable continuum model (CPCM)[50, 91-94] has been observed to produce higher free activation barrier in methanol[53] and references cited therein. However, we decided to investigate if this observation is also true for the reaction involving acid halides. Given in Table **4** is a summary of the best models for each reaction while we presented the thermodynamics and kinetics of the reaction in solution in Table **5**.

GaussView[95] was used as the pre- and post-processor visual interface for this study.

3. Results and Discussion

Studies have shown that alcohols go through diastereomic transition states to form esters[10, 14, 42]. These were considered in the computational model of the uncatalyzed esterification of MeOH with acetic acid and acetyl halides (XAc) [X = OH, F, Cl, Br and I]. Three uncatalyzed reaction mechanisms presented in Fig. **1** were investigated.

Figure **1**: Overview of reaction pathways for potential cyclic transition structures

Two one-step reactions, one in which 4-membered ring transition states are involved and a second in which 6–membered ring transition states are involved. The third mechanism involves a two-step reaction where both transition states are 6-membered rings.

(a) One step concerted cyclic 4-membered

TS.4.1-X   TS.4.2-X

TS-6.1.1-X   TS-6.1.2-X   TS-6.1.3-X   TS-6.1.4-X

(b) One step concerted cyclic 6-membered

TS-6.2.1-X   TS-6.2.2-X   TS-6.2.3-X   TS-6.2.4-X

(ci) Two step concerted cyclic 6-membered: First step

TS-6.3.1-X   TS-6.3.2-X

(cii) Two step concerted cyclic 6-membered: Second step
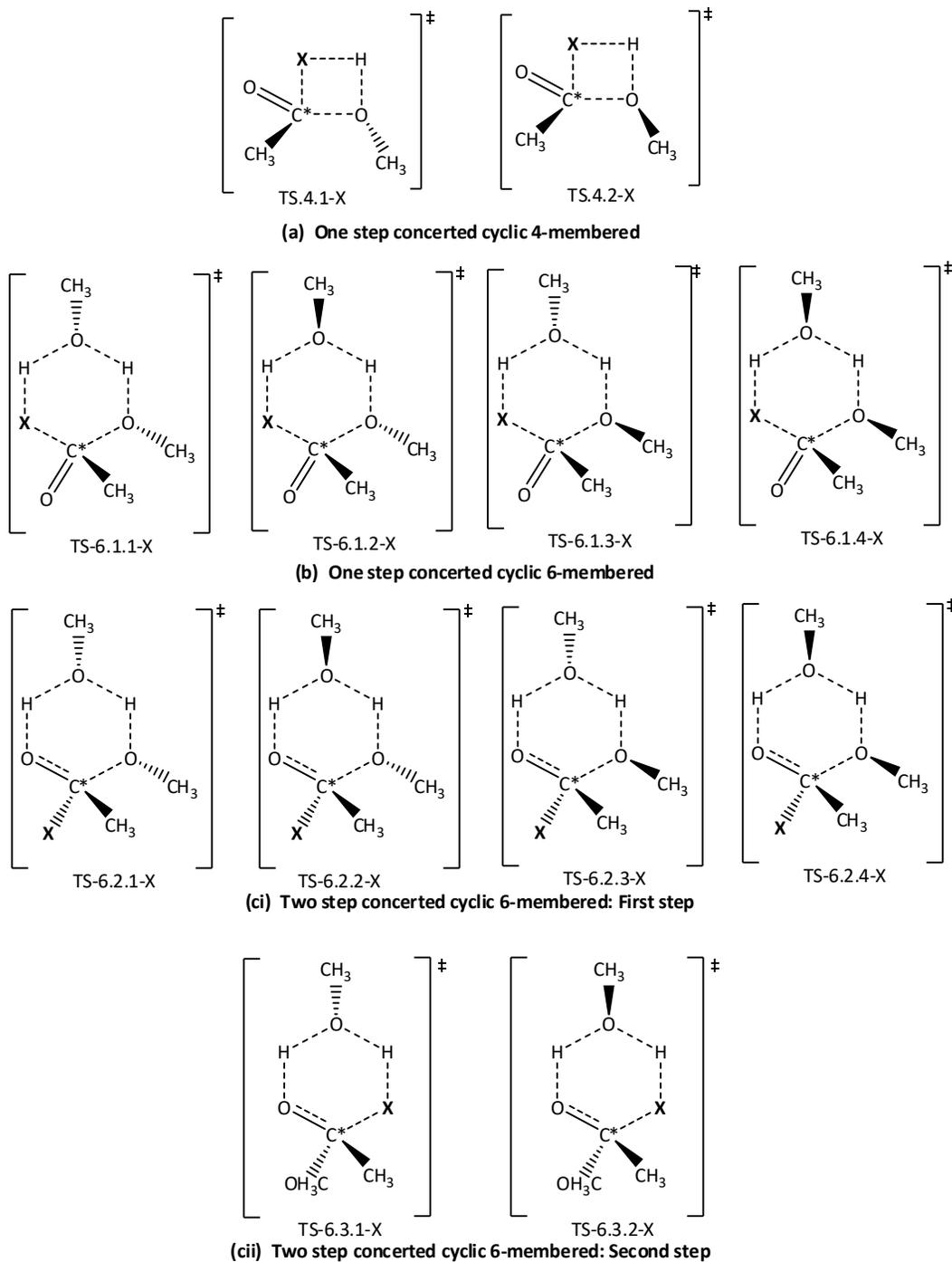
Figure **2**: Cyclic transition state structures considered (with reference to Figures **1**).

All the possible cyclic transition states are presented in Fig. **2**. It is important to note that the cyclic transition states are chiral in nature.[14, 15, 42] In all cases, organizing precomplexes that aids the structural details of the corresponding TS structure was sought.

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3.1 Esterification of Acids with Methanol: One Step Concerted Four-Membered Ring Mechanism

The uncatalyzed esterification reaction of acetic acid and acetyl halides with methanol in a 1:1 molecular ratio was first investigated as a concerted mechanism through a 4-membered cyclic TS leading to product (Figures **1** and **2a**). A second methanol molecule was included to maintain a consistency in the system size for all the possible mechanisms. A number of observations can be made from the results in Fig. **3**. The stability of the precomplexes correlates to the strength of the hydrogen bonds involved, *i.e.* OH hydrogen bonds are stronger than HX[96-98] with X = halogens. The activation energies of the transition states correlate to the order of the ability of X as the leaving group.[96, 98, 99] Lastly, one can conclude that the reaction is exergonic for the overall process leading to product in all cases.
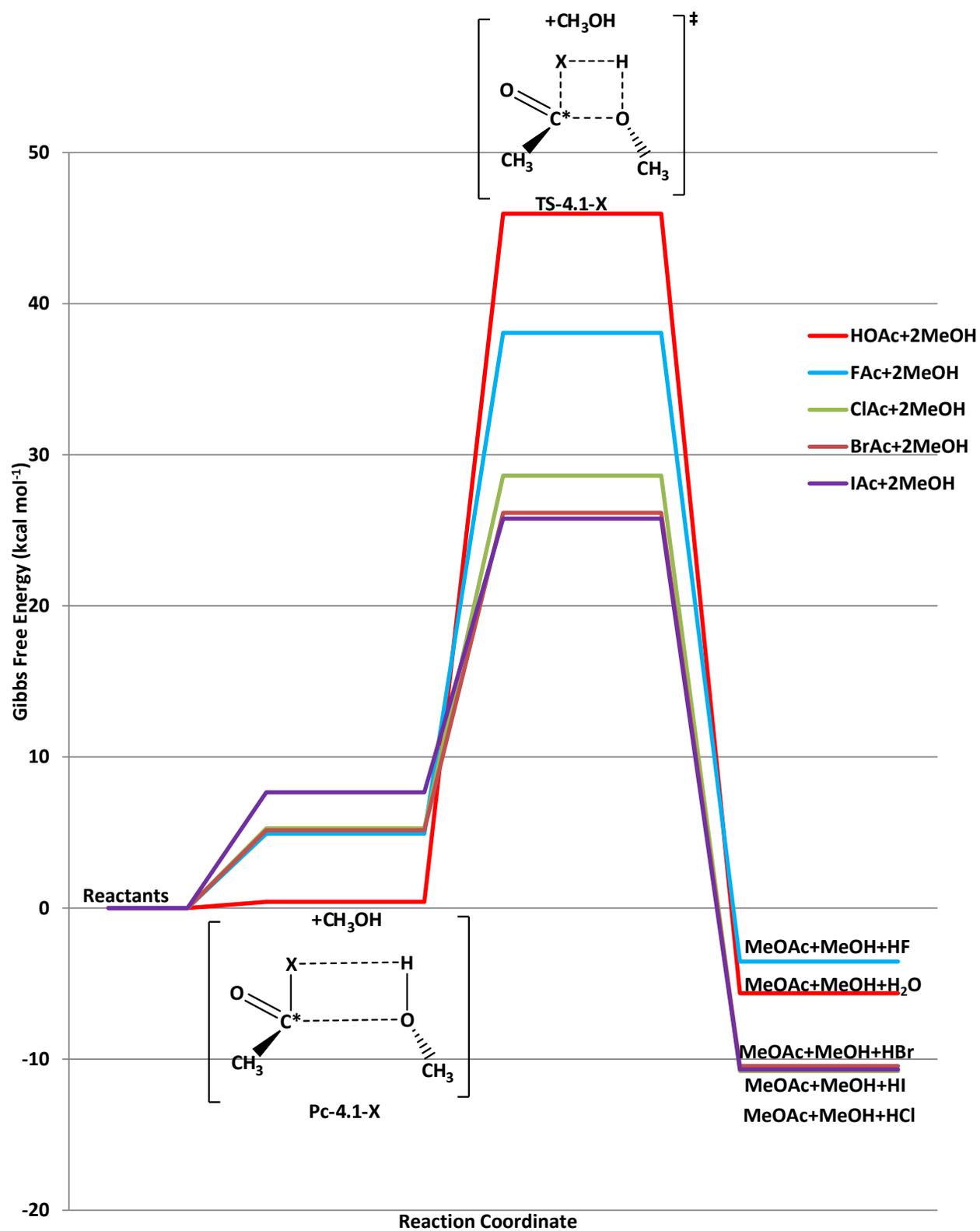
Figure **3**: Free energy profile for *trans*- (lowest energy) one step 4-membered esterification ring mechanism with B3LYP/def2-TZVP.

The reaction mechanisms involve interaction of ordered pre-reaction species that ease the structural features of 4-membered ring transition state. The precomplexes formed between a molecule of acid and methanol (Pc-4.1-X), were greatly favored due to hydrogen bond stabilization. However, it suffers an entropy penalty as expected, to the extent that the relative Gibbs energies of the Pcs become positive (Table **1**, entries 2 and 3). Considering entropic contribution for the Pcs, a trending order (HOAc<FAc<BrAc ~ ClAc <IAc) was observed (Table **1**, entry 3). The difference in $\Delta G^{\ddagger}$ for TS-4.1-X and TS-4.2-X, can be explained in terms of steric effects due to the corresponding methyl groups (see Fig. **2a**) in either *trans-* (lower energy) or *cis-* positions (higher energy).[11, 37]

Table **1**: Relative energies for the concerted four-membered ring esterification mechanism with DFT/def2-TZVP

Structure	HOAc + 2 MeOH	FAc + 2 MeOH	ClAc + 2 MeOH	BrAc + 2 MeOH	IAc + 2 MeOH
	B3LYP				
Reactants	0.00	0.00	0.00	0.00	0.00
Precomplex[a,b]	-7.31	-2.53	-2.54	-2.79	-1.83
Precomplex[b,c]	0.42	4.93	5.27	5.16	7.66
E_A(TS-4.1-X)[a]	34.32	26.78	17.33	14.80	14.42
$\Delta G^{\ddagger}$(TS-4.1-X)[c]	45.95	38.07	28.61	26.15	25.78
E_A(TS-4.2-X)[a]	38.19	31.54	21.82	19.18	19.02
$\Delta G^{\ddagger}$(TS-4.2-X)[c]	49.63	42.88	33.03	30.40	30.33
Products[a]	-8.00	-6.52	-13.50	-13.11	-13.33
Products[c]	-5.64	-3.53	-10.78	-10.45	-10.68
	M06-2X				
E_A(TS-4.1-X)[a]	33.09	27.13	15.42	11.19	9.83
$\Delta G^{\ddagger}$(TS-4.1-X)[c]	44.87	38.26	27.07	22.68	21.40

Energies are calculated in gas phase at 298.15K. E_A and $\Delta G^{\ddagger}$ are in kcal mol^{-1}.
[a] Total or activation energies (E_{SCF} +ZPE) relative to the sum of energies of separated reactants (Acid+2MeOH).
[b] Precomplex associated with the lowest energy TS (TS-4.1-X).
[c] Gibbs energies reported relative to the sum of Gibbs energies of separated reactants (Acid+2MeOH).

B3LYP activation energies (E_A) of 34.32 and 38.19 kcal mol^{-1} for the acetic acid reaction (Table **1**, entry 1) are in good agreement with values of 38.7 and 39.3 kcal mol^{-1} calculated [B3LYP/6-31G(d)] by Basiuk[41] for the esterification of COOH fragments of single-walled carbon nanotubes

with MeOH (4-membered TS).   The corresponding M06-2X values are considerably lower. Shagun and Voronkov[35] reported an E_A of 19 kcal mol^{-1} for the IAc and MeOH reaction (4-membered ring TS) using B3LYP/LANL2DZ. The lower energy values of 9.8 kcal mol^{-1} in our model can be attributed to the dispersion effects of M06-2X. An average calculated $\Delta S^{\ddagger}$ value of about -41 cal/(mol.K)$^{-1}$ was found (supporting information, Table S4).

Measured interatomic distances within the cyclic structure for Pcs and TSs are available in the supporting information (Table S9).

3.2 Esterification of Acids with Methanol: Concerted One Step Six-Membered Ring TS

In this reaction, one acid and two methanol molecules reacts to form a 6-membered ring TS leading to product (Figures **1**, **2b** and **4**). Here, a hydrogen from the hydroxyl entity of methanol facilitates the translocation of the acid's leaving atom (X) by the Grotthuss-type mechanism.[100]   This mechanism is also similar to an auto-ionization model reported for hydrolysis[90, 101] and self-catalyzed aminolysis of esters.[102]   Halogen and hydroxyl substituents (X2) of the carbonyl carbon (*C1) cleave off the acid to react with the proton (H3) of MeOH to yield a hydrogen halide or water (Fig. **4**). The methoxide (RO4) simultaneously abstracts the hydrogen (H5) of the second methanol within the ring to form a neutral MeOH while the nucleophilic methoxide (RO6) attacks the reduced acid to yield the ester (Fig. **4**). We present the calculated energies and reaction profile for lowest energy diastereomer (TS-6.1.1-X) in Fig. **4** and Table **2**.
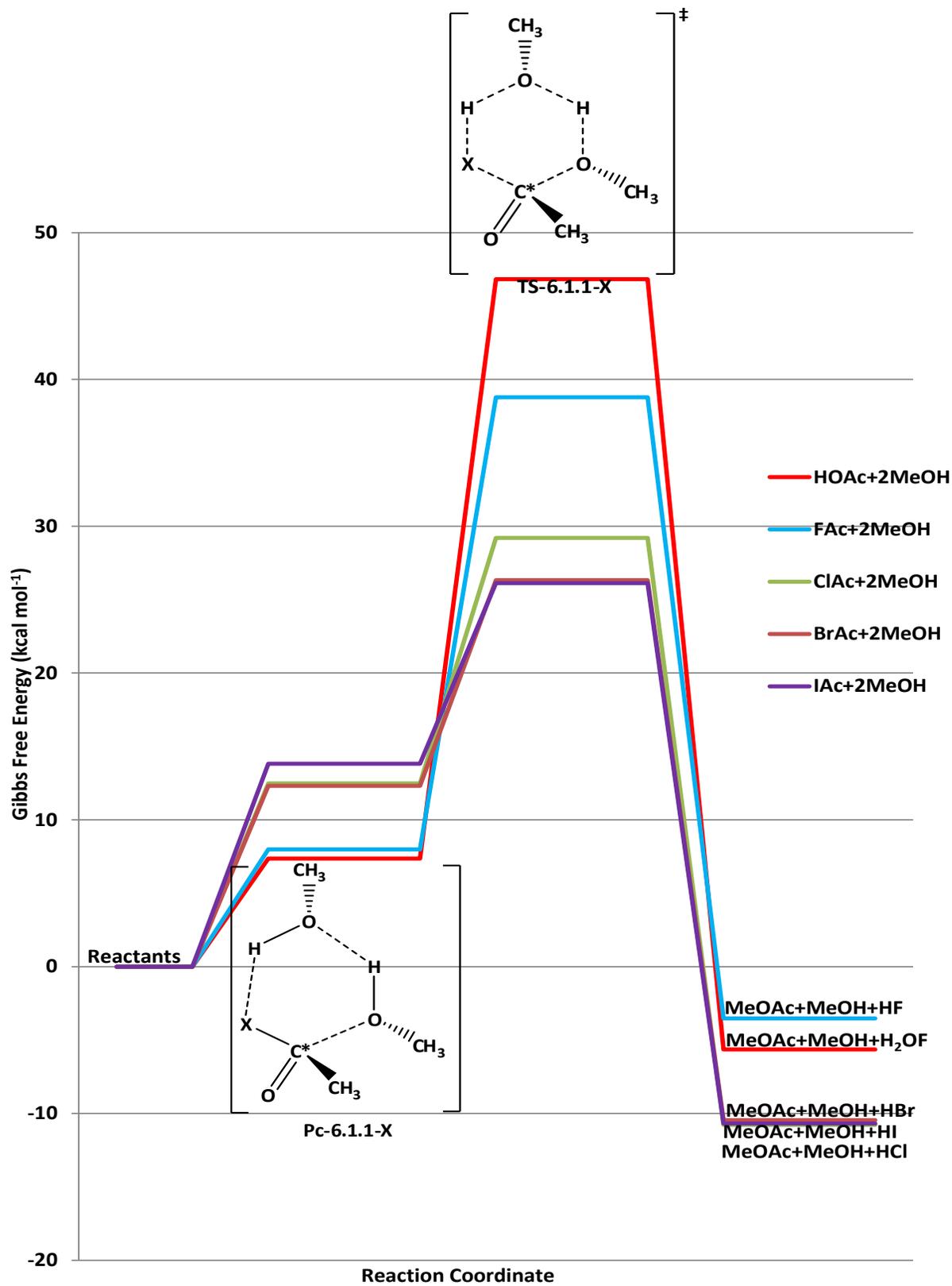
Figure **4**: Free energy profile for one step 6-membered ring esterification mechanism with B3LYP/def2-TZVP.

The following observations can be made from Fig. **4**. As was the case with the 4-membered ring mechanism, the stability of the Pcs correlates to the strength of the hydrogen bonds[76, 96-98] involved, *i.e.* HO---H hydrogen bonds are strongest and that for acetyl iodide is the weakest. Although, the acetyl bromide case was only marginally favored over acetyl iodide for TS-6.1.2-X, the differences for the other three diastereomers are more pronounced with decreasing order down the group (Table **2**). The $\Delta G^{\ddagger}$ of the transition states correlate with the order of the ability of X to leave (Fig. **4** and Table **2**).

Table **2**: Relative calculated energies for the one step cyclic six-membered esterification mechanism with DFT/def2-TZVP

Structure	HOAc + 2 MeOH	FAc + 2 MeOH	ClAc + 2 MeOH	BrAc + 2 MeOH	IAc + 2 MeOH
			B3LYP		
Reactants	0.00	0.00	0.00	0.00	0.00
Precomplex[a,b]	-11.35	-8.69	-7.04	-7.48	-6.42
Precomplex[b,c]	7.37	7.99	12.48	12.32	13.82
E_A(TS-6.1.1-X)[a]	24.41	16.53	7.16	4.37	4.07
$\Delta G^{\ddagger}$(TS-6.1.1-X)[c]	46.83	38.79	29.21	26.33	26.13
E_A(TS-6.1.2-X)[a]	23.40	16.42	9.03	4.62	4.83
E_A(TS-6.1.3-X)[a]	28.30	18.69	8.89	6.12	5.74
E_A(TS-6.1.4-X)[a]	27.65	21.15	11.15	8.17	7.63
Products[a]	-8.00	-6.52	-13.50	-13.11	-13.33
Products[c]	-5.64	-3.53	-10.78	-10.45	-10.68
			M06-2X		
E_A(TS-6.1.1-X)[a]	17.86	12.28	0.65	-3.08	-4.53
$\Delta G^{\ddagger}$(TS-6.1.1-X)[c]	40.54	35.00	22.42	18.32	17.00

Energies are calculated in gas phase at 298.15K, E_A, $\Delta G^{\ddagger}$ and E_A (kcal mol^{-1}). Other calculated thermochemistry values are reported in supporting information.
[a] Total or activation energies (E_{SCF} +ZPE) reported relative to the sum of energies of separated reactants (Acid+2MeOH).
[b] Precomplex associated with the lowest energy TS (TS-6.1.1-X).
[c] Gibbs energies reported relative to the sum of Gibbs energies of separated reactants (Acid+2MeOH).

Formation of 6-membered Pcs, which enables the cyclic structural conformation of the cyclic TSs were highly feasible as observed in our previous studies.[14, 15, 42] Free energy changes (ΔG) for Pc-

6.1.1-X become exergonic with respect to starting materials, ranging between 7.37 and 13.82 kcal mol^{-1} (Table **2**). This is the result of bringing three molecules together in an ordered orientation.[33]

Acetic acid has a higher activation energy compared to acetyl halides, which is inherently due to the weaker pKa nature of this molecule. A relative E_A energy of 7.16 kcal mol^{-1} [B3LYP/def2-TZVP] obtained for TS-6.1.1-Cl is comparable with an earlier study, 6.4 kcal mol^{-1}, at MP2/[6-31+G(d,p)] level for the 6-membered anhydride analogue.[14] This indicates that the abilities of chlorine and acetate groups to leave are similar.[11]

These six-membered rings TSs (TS-6.1.1-X to TS-6.1.4-X) leading to products displayed increased entropy penalties down the group with values ranging from -75 to -83 cal (mol.K)$^{-1}$. A large positive entropy change reflects the disorder in the free reactants to form products, which in turn makes ΔG more negative and favors the association of the TS to products.[11, 33] The complete relative energy profile and other thermochemistry data for this 6-membered concerted mechanism (the 4 possibilities) involving all the studied acids are available in the supporting information (Table S6). Detailed interatomic distances of all Pcs and their corresponding TSs for each reaction are also provided with the supporting information (Table S9).

3.3 Esterification of Acids with Methanol: Two-Step Concerted Six-Membered Ring TS

The esterification of acetic acid and acetyl halides with methanol was also modeled passing through two TSs as described in Figures **1**, **2c** and **5**. In the first TS (TS-6.2.2-X), the carbonyl oxygen (O2) is protonated (H3) in an autocatalytic way [CH$_3$---O4---H3 receives a proton (H5) and also delivers a proton (H3), Fig. **5**, TS-6.2.2-X] to yield the tetrahedral intermediate (Int-6.2.2-X, Fig. **5**).

A specific trend was not observed with respect to the relative energies of all four potential TS conformations (Fig. **2ci**, TS-6.2.1-X to TS-6.2.4-X) in all five reactions (see Table S8). This implies that, the leaving group (X) for ester formation does not form an integral part of the first cyclic TS structures (TS-6.2.1-X to TS-6.2.4-X). In general, TS-6.2.1-X and TS-6-2.2-X gave the lowest energies. We therefore chose to present TS-6.2.2-X as a model in Fig. **5** and Table **3** for this two-step mechanism. The second TS (TS-6.3.2-X) involve re-distribution of hydrogen atoms within the cyclic TS. This results in bond formation and breaking processes in which the hydrogen (H3) bonded to the carbonyl oxygen leaves to form methanol with RO4, and H5 is transferred to the leaving group X7 (Figures **2c** and **5**). This process where a second methanol molecule splits

off the TS complex appears to be similar to Gilkerson's conclusion on the reaction of ethanol with *p*-nitrobenzoyl chloride.[103] It was established that acid chloride follows a first order reaction while a second order process was noticed with respect to methanol.
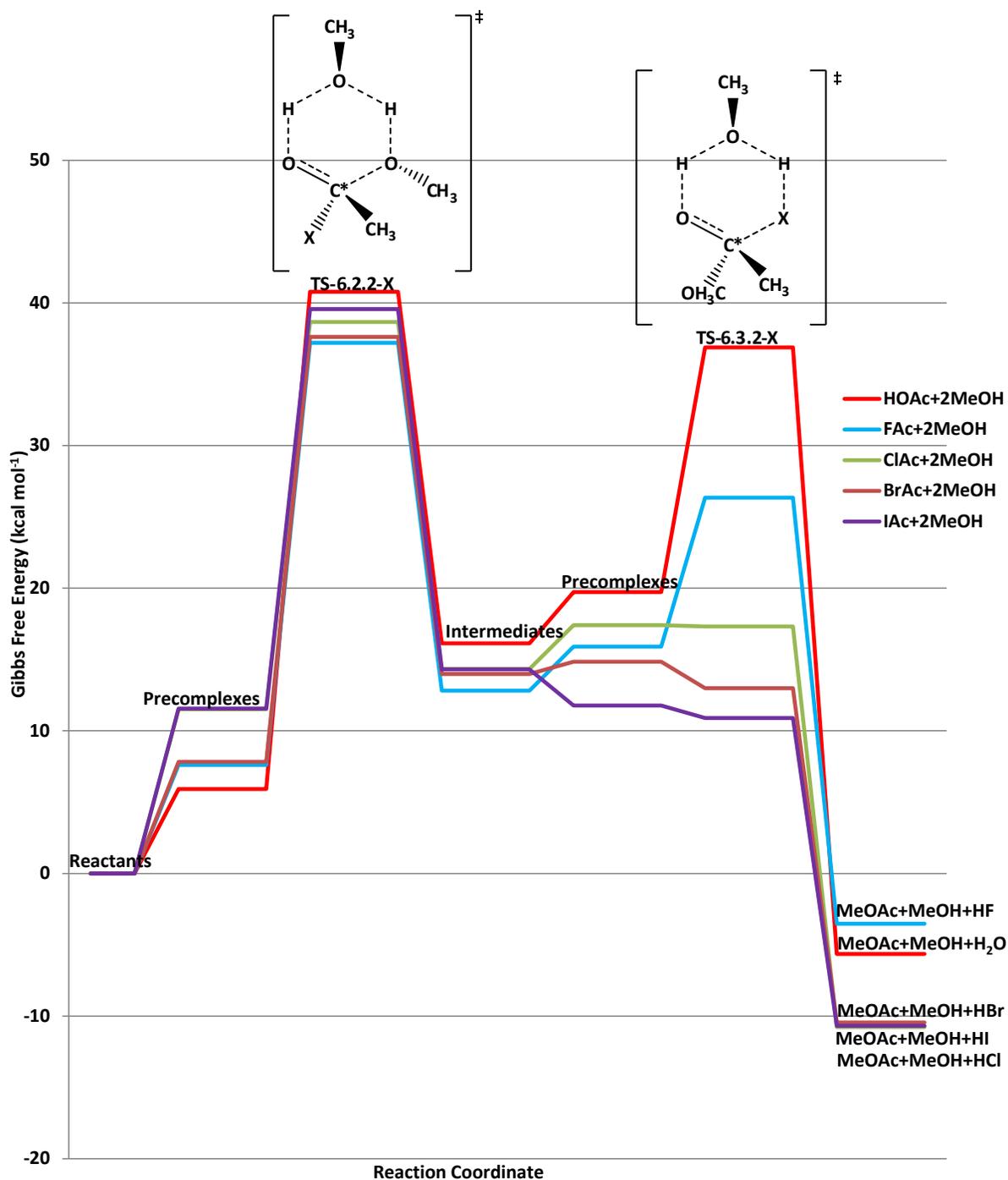
Figure **5**: Free energy profile for the two-step concerted 6-membered ring esterification mechanism with B3LYP/def2-TZVP.

From Fig. **5**, the initiation of this gas phase mechanism also involves the complexation of reactants in a cyclic precomplex leading to the corresponding transition state. The relative energies of 6-membered ring Pcs correlate to the order: IAc>ClAc>BrAc>FAc>HOAc. The relative energies

of the transition states (TS-6.2.2-X) which is the rate determining step follow the order: HOAc>IAc>ClAc>BrAc>FAc. This intermediate-forming transition states (TS-6.2.2-X) involve the substrate (the acid), a nucleophile (first methanol), and a proton- or hydrogen-bond acceptor (second methanol). Intermediate structures (Int-6.2.2-X) are exergonic minima on the potential energy surface (PES); they also follow a decreasing trend similar to that of TS-6.2.2-X.

The energies of the second precomplexes (Pc-6.3.2-X) and transition states (TS-6.3.2-X) correlate to the leaving ability of X,[96, 98] IAc>BrAc>ClAc>FAc>HOAc. The first transition state (TS-6.2.2-X) is rate limiting and the overall reaction leading to exergonic products in all cases. Table **3** shows the calculated relative energies with respect to starting materials obtained for each acid. As was the case before, when entropy contributions were included, the Gibbs energies of the first pre-reaction complexes (Pc-6.2.2-X), becomes positive. The first TSs, (TS-6.2.1-X to TS-6.2.4-X) exhibit theoretical entropy changes ranging between -80.74 to -85.77 cal (mol K)$^{-1}$ (supporting information, Table S8). These are attributed to an associative mechanism.[33]

The Gibbs energies of activation ($\Delta G^{\ddagger}$) for the first transition states (TS-6.2.2-X) range approximately between 37 and 41 kcal mol^{-1}, with the order HOAc>IAc>ClAc>BrAc>FAc. Since the halogens (X) involved in esterification do not take part in the transition (TS-6.2.2-X), an opposite trend (order) compared to the one-step 6-memebered model was observed.

Table **3**: Relative calculated energies for the two-step concerted six-membered ring esterification mechanism with DFT/def2-TZVP

Structure	HOAc + 2 MeOH	FAc + 2 MeOH	ClAc + 2 MeOH	BrAc + 2 MeOH	IAc + 2 MeOH
			B3LYP		
Reactants	0.00	0.00	0.00	0.00	0.00
Precomplex[a,b]	-11.57	-9.86	-8.57	-9.15	-8.30
Precomplex[b,c]	5.92	7.61	11.51	7.82	11.56
E_A(TS-6.2.1-X)[a]	18.07	14.43	16.88	13.95	19.72
E_A(TS-6.2.2-X)[a]	17.89	14.31	15.84	14.90	16.00
$\Delta G^{\ddagger}$ (TS-6.2.2-X)[c]	40.78	37.21	38.66	37.62	39.57
E_A(TS-6.2.3-X)[a]	16.94	15.58	17.06	16.23	16.52
E_A(TS-6.2.4-X)[a]	16.11	17.58	19.63	19.21	19.35
Int-6.2.2-X[a]	4.32	0.94	2.26	1.86	2.13
Int-6.2.2-X[c]	16.13	12.82	14.33	13.98	14.31
Precomplex[a,d]	-1.79	-5.20	-5.37	-8.05	-10.71
Precomplex[c,d]	19.73	15.91	17.41	14.85	11.77
E_A(TS-6.3.2-X)[a]	14.03	3.65	-5.27	-10.52	-12.41
$\Delta G^{\ddagger}$ (TS-6.3.2-X)[c]	36.88	26.35	17.31	12.98	10.90
Products[a]	-8.00	-6.52	-13.50	-13.11	-13.33
Products[c]	-5.64	-3.53	-10.78	-10.45	-10.68
			M06-2X		
E_A(TS-6.2.2-X)[d]	10.48	6.94	5.87	4.77	5.64
$\Delta G^{\ddagger}$ (TS-6.2.2-X)[e]	32.68	30.09	28.51	27.00	29.05

Energies are calculated in gas phase at 298.15K relative to the sum of separated reactants, E_A, $\Delta G^{\ddagger}$ and E_A (kcal mol^{-1}).
[a] Total or activation energies (E_{SCF} +ZPE) reported relative to the sum of energies of separated reactants (Acid+2MeOH).
[b] Precomplex associated with the lowest energy TS (TS-6.2.2-X).
[c] Gibbs energies reported relative to the sum of Gibbs energies of separated reactants (Acid+2MeOH).
[d] Precomplex associated with TS-6.3.2-X.

Also, the lowest energy barrier estimated from the FAc reaction indicates that the smaller the leaving group (X) on the esterifying acid, the faster the reaction proceeds in the first phase. The intermediates have ΔG values of between 13 and 16 kcal mol^{-1}, which are more favorable than the value 19.6 kcal mol^{-1} [X3LYP/6-31+G(d)] reported by Silva *et al*[53] for the acid catalyzed esterification of HOAc in MeOH.

The calculated E_A for the second transition states (TS-6.3.2-X) varied between 14.03 (HOAc) and -12.41 (IAc) kcal mol^{-1}, with the expected order HOAc>FAc>ClAc>BrAc>IAc. Inclusion of entropy also results in exergonic $\Delta G^{\ddagger}$ similar to E_A. The overall reactions remain exergonic for all cases. As was the case before, the corresponding results at the M06-2X level of theory are also much lower in energies.

In addition to the calculated energies presented herein, the overall process including all possibilities (30 Pcs and TS structures) are provided in the supporting information (Table S8). Interatomic distances within the ring for TS structures involved in this mechanism and their corresponding Pcs are also provided in the supporting information (Table S9).

So far, we have explained the mechanisms of the different cyclic transition states involved in esterifying a molecule of acetic acid and its halide analogues with one or two methanol molecules. From the foregoing results, it is quite obvious that due to expected ring strain, the one step 4-membered mechanism with values from 21 and 45 kcal mol^{-1} at M06-2X level of theory is less feasible (compared to the 6-memebered rings values from 17 to 40.5 kcal mol^{-1}). Comparison of the two 6-membered mechanisms at both levels of theory reveals competition between the two models in terms of the rate-determining step. The one-step 6-membered mechanism (see Fig. **2b** and Table **2**) exhibits lower $\Delta G^{\ddagger}$ for the larger halides (ClAc, BrAc and IAc), while the two-step mechanism reveals lower $\Delta G^{\ddagger}$ for HOAc and FAc (Fig. **2c**, Table **3**). In other words, it appears that two different mechanisms are involved for the esterification reaction studied.

In the remaining part of the paper, the M06-2X/def2-TZVP theoretical results of the two-step 6-membered ring mechanism for HOAc and FAc and one step 6-membered ring TS for ClAc, BrAc and IAc (Tables **4** and **5**) will be compared with available experimental results from literature.

3.4 Comparison of the Theoretical Results (methanol as solvent) with Experimental Values from Literature

The thermodynamic and kinetic values of the most feasible pathways were computed at 298.15 K in gas phase and methanol. Rate constant k, which is the measure of the change in concentration of the reactants or products per unit time was obtained from Eq. **2** and reported as lnk (Tables **4** and **5**). The total number of collisions per second (pre-exponential factor A) usually derived from an Arrhenius plot, was calculated using Eq. **3** and converted to the natural logarithm lnA.

Shown in Table **4** are the gas phase thermochemistry properties of the reactions. Experimental entropy contributions for the esterification of carboxylic acids and acyl halides with alcohols have values of between -30 and -60 cal.(mol.K)[-11, 33, 36, 38] compared to the calculated entropy contributions of about -74 to -83 cal.(mol.K)[-1]. Generally, the large negative entropy values observed in this study resulted in lower pre-exponential factors[33, 104] and higher Gibbs energy of activation as well as a slower reaction rate as reflected in the results.

Table **4**: Thermodynamic and kinetic values for esterification of acids with methanol in gas phase involving cyclic transition structures using M06-2X/def2-TZVP

Structure	(XAc + 2 MeOH, X = OH and F, Figure **2c**)					
	E_A	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	lnk	lnA
TS-6.2.2-OH	10.48	9.39	-78.12	32.68	-25.70	-9.86
TS-6.3.2-OH	5.84	4.19	-83.03	28.94	-19.40	-12.33
TS-6.2.2-F	6.94	5.29	-83.17	30.09	-21.33	-12.40
TS-6.3.2-F	-2.38	-3.83	-82.07	20.64	-5.38	-11.84
(XAc + 2 MeOH, X = Cl, Br and I, Figure **2b**)						
TS-6.1.1-Cl	0.65	-0.12	-75.63	22.42	-8.39	-8.60
TS-6.1.1-Br	-3.08	-3.64	-73.63	18.32	-1.46	-7.60
TS-6.1.1-I	-4.53	-5.07	-74.03	17.00	0.76	-7.80

Energies are calculated in gas phase at 298.15 K relative to the sum of separated reactants, $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$ (kcal mol^{-1}), $\Delta S^{\ddagger}$ [cal (mol.K)[-1]]
E_A = Total energy (E_{SCF}+ZPE) of transition state $E^{\ddagger}_{TS}$ – sum of energy (E_{SCF}+ZPE) of separated reactants (Acid+2MeOH)
$\Delta H^{\ddagger}$ = Enthalpy of transition state $H^{\ddagger}_{TS}$ – sum of enthalpy of separated reactants (Acid+2MeOH).
$\Delta S^{\ddagger}$ = Entropy of transition state $S^{\ddagger}_{TS}$ – entropy of separated reactants (Acid+2MeOH).
$\Delta G^{\ddagger}$ = Gibbs energy of transition state $G^{\ddagger}_{TS}$ – Gibbs energy of separated reactants (Acid+2MeOH).

The calculated $\Delta G^{\ddagger}$ for HOAc reaction with MeOH increases from 32.7 (gas) to 35.5 kcal mol^{-1} (in solvent), accounting for about 2.8 kcal mol^{-1} increase in solution (Tables **4** and **5**). The value is in good agreement with an experimentally deduced value of ~34 kcal mol^{-1} with the associated lnk value of -27,[31] the latter is also comparable to -30.7 calculated in our model (Table **5**, TS-6.2.2-OH). The solvent induced barrier for TS-6.3.2-OH is 9.4 kcal mol^{-1} and the observable solution phase free energy(ΔG^d_{sol}) becomes 36.4 kcal mol^{-1} (Table **5**).

In this study, it was also observed that CPCM produced higher free energies in methanol. However, it is interesting to note that we obtained a lower lower ΔG^{*a}_{CPCM} (20.4 kcal mol^{-1}) for the BrAc reaction compared to the ΔG^d_{sol} calculated value 21.85 kcal mol^{-1} (Table **5**).

Esterification of ClAc with two molecules of MeOH (TS-6.1.1-Cl) was most favourable in a one-step concerted model with values of between 22.4 and 21.93 kcal mol^{-1} in gas and methanol, respectively. Solvent contribution displayed a lowering effect on the energy barrier of these substrates compared to other reactions. ΔG_{sol}^d of 21.93 kcal mol^{-1} (Table **5**) is comparable with experimental values of 16 – 20 kcal mol^{-1}.[36, 37] Thus, the corresponding lnk value of -7.56 is closer to the experimental lnk value -5.0 for the alcoholysis of acetyl chloride.[37]

Table **5**: Free energies and kinetics for esterification of acids with methanol in solution involving cyclic transition structures using M06-2X/def2-TZVP

Structure	(XAc + 2 MeOH, X = OH and F, Figure **2c**)					
	ΔG_g^{*a}	ΔG_{CPCM}^{*a}	$\Delta\Delta G_{solv}^{*b}$	ΔG_{sol}^{*c}	ΔG_{sol}^d	lnk
TS-6.2.2-OH	32.68	39.51	4.69	37.36	35.46	-30.40
TS-6.3.2-OH	28.94	36.05	9.40	38.34	36.44	-32.06
Products	-7.80	-5.12	2.91	-4.89	-6.79	
TS-6.2.2-F	30.09	34.30	3.03	33.12	31.22	-23.24
TS-6.3.2-F	20.64	23.42	3.55	24.19	22.29	-8.16
Products	-6.96	-7.27	-1.44	-8.40	-10.30	
(XAc + 2 MeOH, X = Cl, Br and I, Figure **2b**)						
TS-6.1.1-Cl	22.42	23.78	1.41	23.83	21.93	-7.56
Products	-13.53	-12.51	1.19	-12.34	-14.24	
TS-6.1.1-Br	18.32	20.04	5.44	23.75	21.85	-7.43
Products	-13.29	-11.92	2.27	-11.01	-12.91	
TS-6.1.1-I	17.00	19.14	3.82	20.82	18.92	-2.48
Products	-13.30	-11.60	1.56	-11.74	-13.64	

Energies are calculated in methanol at 298.15 K relative to the sum of separated reactants.
[a] Standard state 1 mol L^{-1} for all species
[b] Solvation free energy in SMD/M06-2X/def2-TZVP
[c] Standard state at 1 mol L^{-1} for all species
[d] Standard state at 1 mol L^{-1}for solute and pure solvent for methanol.

A possible reason for these small variations (between the experimental and our theoretical results) is that formation of HCl in the reaction may protonate the carbonyl oxygen atom, serving as a catalyst during a physical experiment. This potential acid catalytic effect was not considered in our computational model, and can perhaps explain these differences. Experimental data for the esterification of these compounds (FAc, BrAc and IAc) with methanol is lacking in literature.

4. Conclusion

The uncatalyzed esterification of acetic acid and its halide derivatives have been studied using B3LYP and M06-2X functionals in a concerted model going through cyclic transition states. A thorough basis set and combination of basis sets comparison were first made. Aug-cc-pVTZ basis set produced results that actually converge towards the complete basis set limit, we preferred to use def2-TZVP that also describes iodine. For this study, the most practical computational method that describes all the atoms involved is M06-2X/def2-TZVP. The comparative basis set study revealed that the basis sets of Dunning (aug-cc-pVTZ) and Peterson (aug-cc-pVTZ-pp) should be modified if possible at all, to also include all four halogens in a single basis set.

The one-step 6-membered mechanism gives lower activation energies for XAc with X = Cl, Br and I. On the other hand, the two-step 6-membered concerted model gave the best results for XAc with X = OH and F. The values obtained were in reasonable agreement with available experimental results.

Although few studies have addressed esterification theoretically, our investigation is the first to present the uncatalyzed mechanism involving acetic acid and its halide derivatives. The study has addressed three possible cyclic models in terms of kinetic and thermodynamic values in gas phase and solution. The models allowed the investigation for the less studied acid halides, in which results for acetyl chloride is in reasonable agreement with experimental data. A calculated free energy barrier of 35.4 kcal mol^{-1} was obtained for the acetic acid reaction with two methanol molecules, which is in excellent agreement with an experimental value of about 34 kcal mol^{-1} from literature.

It is expected that a catalyzed mechanism (for acetic acid) will exhibit lower theoretical activation energies. A detailed study in this regard where the catalyzed theoretical results is currently attempted in our laboratory.

Acknowledgements

Supporting Information

Additional discussion and details on the choice of basis sets are presented. Thermodynamic and kinetic data of each model (all the 60 transition states studied plus the bond length distances) are

given. Cartesian coordinates of the optimized TSs discussed and data obtained for the different hybrid functionals are also presented here.

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CHAPTER THREE

A Density Functional Theoretical Study on Acid-Catalyzed Esterification Reaction

Monsurat M. Lawal,[a] Tricia Naicker,[a] Thavi Govender,[a] Glenn E. M. Maguire,[a,b] Bahareh Honarparvar,[a] and Hendrik G. Kruger[a,*]

[a]Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa.

[b]School of Chemistry and Physics, University of KwaZulu-Natal, Durban 4041, South Africa.

Corresponding author: kruger@ukzn.ac.za (Hendrik G. Kruger), Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa.

Abstract:

Over the years, many experimental studies have been dedicated to the mechanism of ester formation from carboxylic acids, however investigation of mechanisms with theoretical tools has been largely neglegted. Recently, Pliego and his group reported a free energy barrier of 22.4 kcal mol^{-1} for the reaction of acid-catalyzed stepwise esterification of acetic acid in methanol at the X3LYP/6-31+G(d) level of theory. The energy barrier is about 3.4 kcal mol^{-1} higher than the experimental value of 19 kcal mol^{-1} referenced by these authors. Using a triple zeta basis set (def2-TZVP), we have observed a much lower free energy barrier of 19.7 kcal mol^{-1} with M06-2X functional in a one-step concerted mechanism through a cyclic transition state. Thus, a reasonable agreement with experimental values was achieved. This study was advanced to predicting the acid-catalyzed free energy barrier of some acid halide reactions in methanol. Conductor-like Polarizable Continuum Model, Solvation Model based on Density and the hybrid cluster-continuum models were applied. The free activation barriers obtained are in good agreement with available experimental data.

Keywords: Acid halides (XAc); Methanol (MeOH); Acetic acid (HOAc); Density Functional Theory (DFT); Concerted mechanism; Cyclic transition state (TS).

1. Introduction

Esters remain important intermediates in the chemical industry due to their widespread pharmaceutical applications and biodiesel production. Dating back to the 1890s, the Fischer esterification[1] has remained a crucial process through which esters are formed *via* dehydrative coupling of carboxylic acid (RCOOH) with alcohol (ROH) in the presence of inorganic liquid acid.[2-4] For the past three decades, focus on esterification using solid acids to promote the process between carboxylic acid and alcohol has become popular. Alcoholysis of acid anhydrides [(RCO)$_2$O] and acyl chlorides (RCOCl) are also used to obtain esters, with the latter more commonly studied.[5] Application of (RCO)$_2$O and RCOCl in regioselective protection of compounds with multifunctional groups are also well established.[6-9]

Studies on kinetics and mechanisms of methyl acetate (MeOAc) formation from acetic acid (HOAc) using homogeneous and heterogeneous acid catalysts are abundant.[2] A thorough literature study on the experimental and theoretical aspects of this reaction was recently presented by us.[10]

A number of experimental studies have reported free energy of activation for the acid-catalyzed esterification of methanol (MeOH) with HOAc ranging between 10 and 18 kcal mol^{-1}[3, 11-20] in different reaction media/solvents. Energy of activation as low as 8.7 kcal mol^{-1} was also revealed in literature[21, 22] using acidic cation-exchange resins. Using MeOH as solvent, an activation free energy of 19 kcal mol^{-1} was reported.[23] The rate constant value (lnk) of -2.6 was deduced from this result.

Pliego and his group recently described the acid-catalyzed mechanism for HOAc in a stepwise model with a free energy barrier of 22.4 kcal mol^{-1} in solution.[24] Meanwhile, Rönnback et al.[3] had described the overall reaction steps (a total of 7 transition states and 3 intermediates) for esterification of HOAc with MeOH in acidic solution as:

$$CH_3COOH + CH_3OH \overset{H_3O^+}{\Longleftrightarrow} CH_3COOCH_3 + H_2O \; ----------------- \textbf{1}$$

In our recent work, we proposed three possibilities of 4 (one-step only) and 6-membered ring TS (including one-step and two-step concerted mechanism) models for the uncatalyzed esterification reaction.[10] Amongst the proposed TS models, it was observed that a one-step concerted pathway had lowest energy barrier for acetyl chloride, bromide and iodide while a two-step concerted model was preferred for HOAc and its fluoride analogue.[10] In this study, we focussed on a common reaction mechanism for all the acids based on Eq.1. This was proposed to occur in a concerted mechanism involving two molecules of MeOH and protonated XAc passing through a one-step 6-

membered cyclic transition state (TS). Fig. **1** shows the reaction profile for this mechanism for all the acids XAc (where X = OH, F, Cl, Br and I).

Figure **1**: Concerted transition state studied for acid-catalyzed esterification of acid with two methanol molecules.

Bunto and Fendler[25] reported an increased reactivity of FAc in the presence of a catalytic amount of acid (H⁺). ClAc, BrAc and IAc were subjected to this mechanism as well to examine the effect of protonation on these acids compared to the uncatalyzed model. Here, we aimed at assessing the

suitability of their hydrolysis approach[25] to our proposed TS model. Efforts were also made to provide valid comparison of the calculated values herein (for the concerted mechanism invoving HOAc) and the stepwise mechanism reported by Silva et al.[24]

2. Computational Details: Thermochemistry and Kinetics Calculations

To achieve more realistic results with computational modelling of reactions, solvent effects are of great importance. Solute–solvent interactions are required to modify the structure, energy and total behaviour of systems. A number of methods have been established[24, 26-28] to obtaining free energy in solution phase, importantly is the hybrid cluster-continuum method[26] used in estimating solvation free energy of ionic species. The rate constant (k, converted to lnk) for the TSs were calculated using Eq. **4**. Where k_B, h, and R, are Boltzmann, Planck, and gas constants, respectively. ΔG^*_{sol}, ΔG^*_g and $\Delta\Delta G^*_{solv}$ are the calculated solution phase free energy, gas phase free energy and bulk solvent contribution, respectively at 1M standard state for all species (Eq. **2**) while ΔG^0_{sol} is the observable solution phase free activation energy at 1M (1mol L^{-1}) concentration of solute and pure solvent (MeOH) as stated in Eq. **3**.[27]

$$\Delta G^*_{sol} = \Delta G^*_g + \Delta\Delta G^*_{solv} -2$$

$$\Delta G^0_{sol} = \Delta G^*_{sol} + nRTln[MeOH] -3$$

$$k = \frac{k_B T}{h} \, exp\left(-\frac{\Delta G^{0\,\ddagger}_{sol}}{RT}\right) -4$$

The entropy penalty (around 1.9 kcal mol^{-1}) has been paid for through the addition of its correction to compress the concentration in solution to 1M.[27]

All calculations were performed using Gaussian 09 program.[29] The Minnesota hybrid density functional (M06-2X)[30, 31] was coupled with the def2-TZVP[32, 33] basis set. Density functional theory (DFT) calculations proceeded with full geometry optimization of reactants and products, and TS structures along with frequency calculations for each reaction in gas and in solvent MeOH using solvation model based on density (SMD)[28] and conductor-like polarization continuum model (CPCM)[34-38] solvation models.

Vibrational frequencies[39] at the same level and basis set were computed for the various unconstrained species to characterize them as local minima and transition state (TS) structures (one-negative eigenvalue) on the potential energy surface (PES). The cartesian coordinates for all the respective transition states in gas phase are provided with the supporting information. Intrinsic

reaction coordinates (IRC)[40, 41] were computed to verify the transition structures are truly the highest saddle points connecting the expected reactants and products on the reaction pathways. GaussView[42] was used as pre- and post-processor visual interface for this study.

3. Results and Discussion

The thermodynamics and kinetics for these reactions are presented in Table **1**. Esterification of HOAc with MeOH in the presence of acid yielded a gas phase free energy of activation of -3.9 kcal mol^{-1}. The obvious reason for this negative energy barrier is the fact that theoretical gas phase energy barrier is usually lower than in solution.[27] Solvation with CPCM gave 12.8 kcal mol^{-1}.

Table **1**: Thermodynamics and kinetics results for the esterification of acids with methanol using CH$_3$C(OH)$^+$X (X = OH, F, Cl, Br, I) + 2 CH$_3$OH as reference reactants (refer to Fig. **1**) at M06-2X/def2-TZVP level

	HO	F	Cl	Br	I
ΔG_{CPCM}	12.77	3.63	1.21	-8.31	-4.67
ΔG^{*a}	-3.91	-14.31	-14.34	-24.85	-18.36
$\Delta\Delta G^*_{solv}{}^b$	21.77	21.33	9.67	15.59	15.52
$\Delta G^*_{sol}{}^b$	17.87	7.02	-4.67	-9.27	-2.84
$\Delta G^0_{sol}{}^d$	19.77	8.92	-2.77	-7.37	-0.94
lnk	-3.91	14.40	34.13	41.89	31.04
ΔG^0_{sol}(Products)^d	-0.72	-19.60	-25.72	-27.50	-21.14

Values in kcal mol^{-1} at 298.15 K and reported relative to sum of separated reactants in methanol
^{a} Standard state 1 mol L^{-1} for all species in gas phase
^{b} Solvation free energy in SMD/M06-2X/def2-TZVP; [$\Delta\Delta G^{*\ddagger}_{solv}$ = ΔSCRF$_{SMD}$ SCF$_{gas}$]
^{c} Standard state at 1 mol L^{-1} for all species; [$\Delta G^*_{sol} = \Delta G^*_g + \Delta\Delta G^*_{solv}$]
^{d} Standard state at 1 mol L^{-1} for solute and pure solvent for methanol; $\Delta G^0_{sol} = \Delta G^*_{sol} + nRT \ln[MeOH]$

The bulk solvent contribution ($\Delta\Delta G^*_{solv}{}^b$) which takes into account the difference in gas phase total energy and single point energy from SMD was 21.8 kcal mol^{-1}. At 1M standard state for solute and pure solvent, the free energy barrier becomes 19.77 kcal mol^{-1} with an approximate lnk of -3.9 (Table **1**). This value is in good agreement with an experimental value of 19 kcal mol^{-1} and an estimated lnk value of -2.6 from literature.[23] The corresponding theoretical activation energy ($\Delta G^0_{sol}{}^d$) for the uncatalyzed mechanism (TS-6.1.1-OH)[10] was 41 kcal mol^{-1}. In other words, acid catalysis accounts for a very large decrease (up to 22 kcal mol^{-1}) in solution.

A reported theoretical free activation energy of 22.4 kcal mol^{-1} in a stepwise mechanism using hybrid cluster continuum model was observed by Silva et al.[24] They used the following overall mechanism to calculate the relative energy differences:

$$CH_3COOH + CH_3OH_2^+ + 2\,CH_3OH \underset{\Delta}{\Leftrightarrow} CH_3C(OH)OCH_3^+ + 2\,CH_3OH + H_2O ------ 5$$
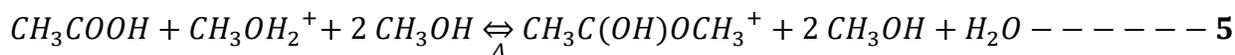
While reproducing their rate-limiting TS (TSb-3 in Table **2** A - C, Fig. **2**), we obtained similar energies and bond distances; the small discrepancies can be attributed to the choice of calculation parameters. Column B presents the reproduced TSb-3 with the same level of theory [X3LYP/6-31+G(d)] and reference substrates. When our level of theory (M06-2X/def2-TZVP) was applied to this same TS, values in column C were obtained. Column D represents the values obtained from our TS-6-OH when the reactant species are:

$$CH_3C(OH)OH^+ + 2\,CH_3OH \underset{\Delta}{\Leftrightarrow} CH_3C(OH)OCH_3^+ + CH_3OH + H_2O ---------- 6$$
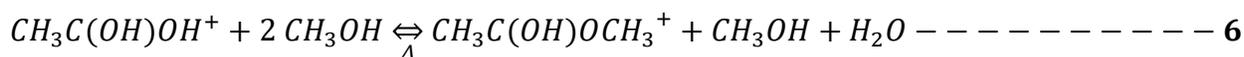
Table **2**: Thermodynamic properties for the reaction and activation of acid-catalyzed esterification of acetic acid in methanol (Eqs. **5** and **6**)

	A (Silva)[24]	B[a]	C[b]	D[c]
ΔG_{CPCM}	24.84	22.61	20.82	12.77
ΔG^{*d}	20.40	20.17	23.44	-3.91
$\Delta\Delta G^*_{solv}{}^e$	0.11	0.71	1.20	21.77
$\Delta G^*_{sol}{}^f$	20.51	20.88	24.64	17.87
$\Delta G^0_{sol}{}^g$	22.40	22.78	26.54	19.77

Values in kcal mol^{-1} at 298.15 K
[a] Energies of TSb-3 from Silva et al. work[24] with [X3LYP/6-31+G(d)]
[b] Energies of TS3-b with M06-2X/def2-TZVP
[c] Energies of TS-6-OH with M06-2X/def2-TZVP (From Table **1**)
[d] Standard state 1 mol L^{-1} for all species in gas phase
[e] Solvation free energy in SMD/M06-2X/def2-TZVP [$\Delta\Delta G^{*\ddagger}_{solv} = \Delta SCRF_{SMD}\ CPCM - SCF_{gas}$]
[f] Standard state at 1 mol L^{-1} for all species [$\Delta G^*_{sol} = \Delta G^*_g + \Delta\Delta G^*_{solv}$]
[g] Standard state at 1 mol L^{-1}for solute and pure solvent for methanol $\Delta G^0_{sol} = \Delta G^*_{sol} + nRT \ln[MeOH]$

When the cyclic rate determining step by Pliego and co-workers[24] was compared with the possible diastereomeric options studied by us earlier, it was found to match the geometry of TS-6.1.3-OH,[10] which is less feasible (than TS-6-OH) due to steric hindrance. The IRCs for both TS3-b (Table **2**,

columns A – C) and TS-6-OH (Table **2**, column D) gave the expected reactants and products. Bond length distance of 1.39 Å (Fig. **2**, M06-2X/def2-TZVP) between the carbonyl carbon and methanol for TS-6-OH is in good agreement with a distance of 1.42 Å [X3LYP/6-31+G(d)] reported by these authors.[24]
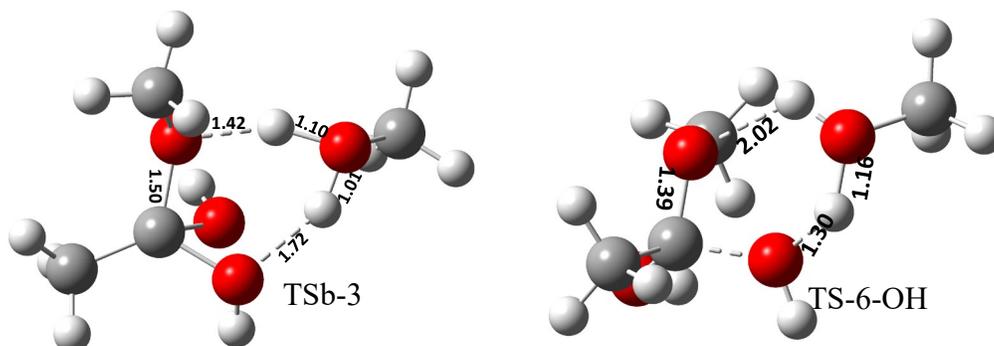
Figure **2**: TSb-3 reproduced from literature[24] using X3LYP/6-31+G(d) and our observed TS-6-OH model at M06-2X/def2-TZVP level of theory.

FAc esterification with two MeOH molecules mediated by hydrogen ion produced a gas phase free activation energy of -14.3 kcal mol^{-1} while solvation free activation energy of 21.82 kcal mol^{-1} (CPCM) was obtained. The observable solution phase free energy ($\Delta G^0_{sol}{}^d$) becomes 8.9 through the bulk solvent contribution which is 21.3 kcal mol^{-1} ((Table **1**). For the corresponding uncatalyzed TS (TS-6.1.1-F),[10] a solution phase free energy of 32.05 kcal mol^{-1} was estimated, thus, protonation accounts for a 23 kcal mol^{-1} reduction in the energy barrier.

Although the reaction of ClAc, BrAc and IAc proceeds without acid catalyst mediation, it is clear from experimental conditions[3] and the general reaction mechanism that acid is generated during the reaction. Protonation of the carbonyl oxygen of this acid lead to a reduction of the activation barrier to values between -7.4 and -0.9 kcal mol^{-1} compared to values ranging from 19 to 22 kcal mol^{-1} for the uncatalyzed model.[10] The negative solution phase free energy obtained buttressed the non-requirement of acid catalyst in this reaction. The overall pathway leading to product remains exergonic in all cases.

4.   Conclusion

The esterification reactions of acetic acid and its halide analogues with methanol was studied in the presence of an acid catalyst using M06-2X hybrid density functional and def-2TZVP basis set.

The reaction was modelled as a one-step concerted 6-membered cyclic transition state. An activation of 19.77 kcal mol^{-1} which is in reasonable agreement with experimental value was obtained. The simple one step concerted 6-membered ring mechanism provides a suitable description of the acid-catalyzed esterification reaction. Esterification of acid halides (X = Cl, Br and I) with methanol in the presence of hydrogen ions suggest spontaneous reactivity, while acetyl fluoride vary in this respect with a solution phase free energy of 9 kcal mol^{-1}. The simple and standard mathematical method for the computation of these energies in solution compared well with the hybrid continuum model.

Supporting Information

Cartesian coordinates of the optimized TSs (gas phase only) discussed herein are provided.

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CHAPTER FOUR
CONCLUSION

The uncatalyzed esterification of acetic acid and its halide derivatives was studied in a concerted model *via* cyclic transition structures using B3LYP and M06-2X density functionals. A detailed basis set analysis was performed in which def2-TZVP was upheld for its adequacy to all atoms involved in this study. An important conclusion from this basis set investigation is that a higher quality basis set is required to be modified to span through all atoms.

For the uncatalyzed mechanism, the one-step 6-membered mechanism gave lower activation energies for XAc with X = Cl, Br and I, while a two-step 6-membered concerted model offered the best results for XAc with X = OH and F. The values obtained were in reasonable agreement with available experimental results. The present research is the first account to present the uncatalyzed mechanism involving acetic acid and its halide derivatives. The models allowed the investigation for the less studied acid halides. A calculated free energy barrier of 35.4 kcal mol^{-1} was obtained for the uncatalyzed acetic acid reaction with two methanol molecules in solution which is in excellent agreement with an experimental value of about 34 kcal mol^{-1} from literature.

Esterification reaction of acetic acid and its halide analogues with methanol was also studied in the presence of an acid catalyst. Here, a single model was designed for all the reactions involving a 6-membered ring transition state. The catalyzed reaction resulted in a theoretical solution phase free energy barrier of 19.77 and 9 kcal mol^{-1} for acetic acid and acetyl fluoride, respectively. This calculated free energy barrier for acetic acid is in good agreement with a reported experimental value of 19 kcal mol^{-1}.

APPENDIX A

Supporting Information for Chapter Two

A Focus on Uncatalyzed Esterification of Acetic Acid and Acid Halides with Methanol: Cyclic Transition States and Thermochemistry Prediction

Monsurat M. Lawal,[a] Md. Rauf Shah,[a] Thavi Govender,[a] Glenn E. M. Maguire,[a,b] Bahareh Honarparvar,[a] and Hendrik G. Kruger[†a]

[a]Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa.

[b]School of Chemistry and Physics, University of KwaZulu-Natal, Durban 4041, South Africa

[†]**Corresponding author**: kruger@ukzn.ac.za (Hendrik G. Kruger), Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban 4041, South Africa.

SECTION 1

Choosing a Suitable Combination of Basis Sets

A single basis set that accurately describes all the halide derivatives (XAc= FAc, ClAc, BrAc and IAc) seems not to exist.[1] Therefore, insight on varying basis sets is required to obtain the best description of the computational model. Basis sets 6-31+G(d),[2-4] def2-TZVP,[5, 6] and aug-cc-pVTZ,[7, 8] were studied for all atoms and in parallel with LANL2DZ,[9-11] def2-TZVP,[5, 6] MidiX[12, 13] and DGDZVP[14, 15] to describe the halides, as outlined in Table S**1**. For this purpose, we chose a variable among the diastereomic TSs involving 6-membered entities transition state (TS-6.2.4-X) that proved to be most sensitive for a comprehensive basis set test. This transition state is very hindered sterically and some of its methyl groups easily interconvert by flipping over into the plane of the paper.

First, when 6-31+G(d) and aug-cc-pVTZ (for all atoms) are compared for F, Cl and Br, it is clear that 6-31+G(d) underestimates the activation energy for the acetyl bromide the, while aug-cc-

pVTZ and its combination with def2-TZVP produced higher values for the FAc reaction. Also, the ClAc reaction gave the highest relative energy compared to BrAc and FAc with aug-cc-pVTZ/def2-TZVP) (Table S**1**).

Dunning's aug-cc-pVTZ[7, 8, 16, 17] is considered superior over this *double zeta* basis set from Pople,[18-20] but unfortunately it does not describe iodine atoms. Based on the results for all other basis sets studied, it appears that all other combinations of basis sets provide lower energies (than aug-cc-pVTZ) for all acids involved.

From the BSSE corrections, it is very obvious that the aug-cc-pVTZ basis set are close to the basis set (CBS) limit.[20, 21] This basis set and its combination with def2-TZVP has the lowest BSSE correction ranging from 0.47 to 1.91 kcal mol^{-1}. According to these results, aug-cc-pVTZ/def2-TZVP is the best choice for this study. However, higher computational demand while using aug-cc-pVTZ/def2-TZVP made us choose def2-TZVP only for this investigation. This contracted Gaussian basis set is one of the "def2" bases series that was modified (in 2005) to allow the approximations for scalar relativistic effects in larger atoms.[5, 6, 18] It was therefore used in the rest of the study with B3LYP and M06-2X levels of theory. Although def2-TZVP is parameterized for all four halogens, it was shown in this study that it slightly underestimates the BSSE value ($\approx$1.61 kcal mol^{-1}) for all the halide reactions, when compared with the aug-cc-pVTZ results.
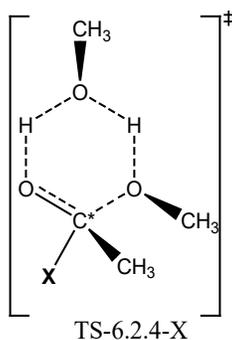
TS-6.2.4-X

Reference structure for Table S**1** (X = F, Br, Cl and I)

Table S1: The relative energies and BSSE corrections for TS-6.2.4-X using different basis sets

B3LYP	ΔE relative to starting materials[a]/kcal mol^{-1}			
Basis set	TS-6.2.4-F	TS-6.2.4-Cl	TS-6.2.4-Br	TS-6.2.4-I
6-31+G(d)	16.19 (4.78)	17.79 (2.72)	13.72 (6.80)	n.a.
aug-cc-pVTZ	19.19 (0.57)	21.11 (0.47)	20.79 (0.49)	n.a.
def2-TZVP	17.58 (1.84)	19.63 (1.86)	19.21 (1.90)	19.35 (1.91)
6-31+G(d)/LANL2DZ[b]	17.13 (3.22)	17.43 (3.39)	17.94 (3.25)	18.87 (3.05)
6-31+G(d)/def2-TZVP[b]	18.09 (2.60)	20.18 (2.64)	19.81 (2.65)	20.05 (2.60)
6-31+G(d)/MidiX[b]	13.30 (7.49)	12.85 (10.68)	17.23 (6.46)	18.08 (6.06)
6-31+G(d)/DGDZVP[b]	17.89 (2.67)	19.64 (2.75)	19.20 (2.73)	18.85 (2.93)
aug-cc-pVTZ/LANL2DZ[b]	18.52	19.77	20.26	20.94
aug-cc-pVTZ/def2-TZVP[b]	19.23 (0.55)	21.16 (0.59)	21.78 (0.63)	21.05 (0.51)
aug-cc-pVTZ/MidiX[b]	16.91	12.64	14.20	14.01
aug-cc-pVTZ/DGDZVP[b]	18.85	20.86	20.20	19.86

BSSE corrections in parentheses
[a] Total energy (including zero-point energy) relative to the sum of energies of separated reactants (XAc+2MeOH).
[b] Mixed basis sets with the first basis set for C, H, O and the second for the halogens.
[n.a.] Not applicable for the I only.

Some defects highlighted[22, 23] on barrier height and thermochemistry predictions with B3LYP made us perform a comparison between B3LYP, X3LYP[24] and M06-2X[22, 23, 25] functionals with def2-TZVP basis set, before upholding the latter for accuracy reasons (Table S2). Although, Peterson's modified version of Dunning's basis set (aug-cc-pVTZ-pp)[26] can describe bromine and iodine, these results suggest that aug-cc-pVTZ and aug-cc-pVTZ-pp basis sets should be modified to include all four halogens in a single basis set.

Table S2: Comparative results for some hybrid density functionals for TS-6.1.1-OH structure using Def2TZVP

	B3LYP	X3LYP	M06-2X
E_A	24.41	22.87	17.86
$\Delta H^{\ddagger}$	23.17	21.61	16.50
$\Delta S^{\ddagger}$	-79.35	-79.47	-80.64
$\Delta G^{\ddagger}$	46.83	45.31	40.54
lnk	-49.59	-47.02	-38.97
lnA	-10.48	-10.54	-11.13

Energies are calculated in gas phase at 298.15K. E_A, $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ in kcal mol^{-1} and $\Delta S^{\ddagger}$ [cal (mol.K)$^{-1}$]

SECTION 2

Table S**3**: Raw thermochemistry values for one step cyclic four-membered mechanism at B3LYP/Def2TZVP level

	MeOH	HOAc	Pc-4.1-OH	TS-4.1-OH	TS-4.2-OH	MeOAc	H$_2$O
E	-115.724656	-229.119450	-344.855759	-344.789412	-344.783251	-268.415035	-76.441815
H	-115.720353	-229.113902	-344.845363	-344.780782	-344.774455	-268.408766	-76.438035
S	57.000	68.551	100.767	83.965	84.939	72.972	45.089
G	-115.747436	-229.146473	-344.893241	-344.820677	-344.814812	-268.443437	-76.459459

	FAc	Pc-4.1-F	TS-4.1-F	TS-4.2-F	HF	ClAc	Pc-4.1-Cl
E	-253.161166	-368.889857	-368.843152	-368.835555	-100.481182	-613.497282	-729.225979
H	-253.155893	-368.879450	-368.834672	-368.827024	-100.477878	-613.491702	-729.215286
S	67.519	101.237	84.345	84.295	41.496	70.317	102.835
G	-253.187973	-368.927551	-368.874747	-368.867075	-100.497594	-613.525112	-729.264146

	TS-4.1-Cl	TS-4.2-Cl	HCl	BrAc	Pc-4.1-Br	TS-4.1-Br	TS-4.2-Br
E	-729.194320	-729.187169	-460.828410	-2727.452388	-2843.181495	-2843.153464	-2843.146472
H	-729.185455	-729.178233	-460.825106	-2727.446598	-2843.170615	-2843.144424	-2843.137325
S	87.349	87.710	44.590	73.377	105.357	90.070	90.781
G	-729.226957	-729.219907	-460.846292	-2727.481462	-2843.220673	-2843.187219	-2843.180458

	HBr	IAc	Pc-4.1-I	TS-4.1-I	TS-4.2-I	HI	
E	-2574.782894	-451.069059	-566.796638	-566.770741	-566.763405	-298.399918	
H	-2574.779589	-451.063116	-566.786114	-566.761563	-566.754211	-298.396613	
S	47.419	75.581	101.337	92.211	92.448	49.330	
G	-2574.802119	-451.099027	-566.834263	-566.805376	-566.798136	-298.420051	

Table S **4**: Relative calculated thermodynamic and kinetic data for the one step cyclic four-membered mechanism at B3LYP/Def2TZVP level

	Reactants	Pc-4.1-OH	TS-4.1-OH	TS-4.2-OH	Products	Pc-4.1-F	TS-4.1-F	TS-4.2-F	Products	Pc-4.1-Cl	TS-4.1-Cl
ΔE	0.00	-7.31	34.32	38.19	-8.00	-2.53	26.78	31.54	-6.52	-2.54	17.33
ΔH	0.00	-6.97	33.55	37.53	-7.87	-2.01	26.09	30.89	-6.52	-2.03	16.69
ΔS	0.00	-24.78	-41.59	-40.61	-7.49	-23.28	-40.17	-40.22	-10.05	-24.48	-39.97
ΔG	0.00	0.42	45.95	49.63	-5.64	4.93	38.07	42.88	-3.53	5.27	28.61
lnk	0.00		-48.11	-54.32			-34.80	-42.92			-18.83
lnA	0.00		8.53	9.02			9.24	9.21			9.34

	TS-4.2-Cl	Products	Pc-4.1-Br	TS-4.1-Br	TS-4.2-Br	Products	Pc-4.1-I	TS-4.1-I	TS-4.2-I	Products
ΔE	21.82	-13.50	-2.79	14.80	19.18	-13.11	-1.83	14.42	19.02	-13.33
ΔH	21.22	-13.69	-2.30	14.14	18.59	-13.43	-1.66	13.75	18.36	-13.75
ΔS	-39.61	-9.76	-25.02	-40.31	-39.60	-9.99	-31.24	-40.37	-40.13	-10.28
ΔG	33.03	-10.78	5.16	26.15	30.40	-10.45	7.66	25.78	30.33	-10.68
lnk	-26.30			-14.69	-21.85			-14.06	-21.73	
lnA	9.52			9.17	9.53			9.14	9.26	

Energies are calculated in gas phase at 298.15K, ΔE, ΔH and ΔG (kcal mol^{-1}) and ΔS [cal (mol.K)$^{-1}$]

SECTION 3

Table S**5**: Raw thermochemistry values for one step cyclic six-membered mechanism at B3LYP/Def2TZVP level

	Pc-6.1.1-OH	Pc-6.1.2-OH	Pc-6.1.3-OH	Pc-6.1.4-OH	TS-6.1.1-OH	TS-6.1.2-OH	TS-6.1.3-OH	TS-6.1.4-OH
E	-460.586844	-460.588725	-460.581576	-460.587354	-460.529856	-460.531470	-460.523661	-460.524706
H	-460.572523	-460.575012	-460.567593	-460.572677	-460.517684	-460.519269	-460.511801	-460.512373
S	120.126	113.017	113.519	127.685	103.204	103.258	99.592	105.488
G	-460.629599	-460.628710	-460.621529	-460.633345	-460.566720	-460.568330	-460.559120	-460.562494
	Pc-6.1.1-F	Pc-6.1.2-F	Pc-6.1.3-F	Pc-6.1.4-F	TS-6.1.1-F	TS-6.1.2-F	TS-6.1.3-F	TS-6.1.4-F
E	-484.624324	-484.623995	-484.621803	-484.622683	-484.584142	-484.584313	-484.580697	-484.576766
H	-484.609353	-484.609009	-484.607876	-484.608885	-484.572079	-484.572205	-484.568913	-484.564890
S	127.891	126.332	114.213	114.230	103.024	103.394	100.002	100.824
G	-484.670118	-484.669033	-484.662142	-484.663160	-484.621029	-484.621331	-484.616427	-484.612794
	Pc-6.1.1-Cl	Pc-6.1.2-Cl	Pc-6.1.3-Cl	Pc-6.1.4-Cl	TS-6.1.1-Cl	TS-6.1.2-Cl	TS-6.1.3-Cl	TS-6.1.4-Cl
E	-844.957820	-844.958829	-844.959666	-844.953019	-844.935176	-844.932211	-844.932424	-844.928822
H	-844.943363	-844.944497	-844.945446	-844.938790	-844.922385	-844.919379	-844.919859	-844.916743
S	119.400	118.123	117.563	115.634	107.442	108.898	105.260	102.044
G	-845.000094	-845.000621	-845.001304	-844.993731	-844.973434	-844.971120	-844.969872	-844.965227

	Pc-6.1.1-Br	Pc-6.1.2-Br	Pc-6.1.3-Br	Pc-6.1.4-Br	TS-6.1.1-Br	TS-6.1.2-Br	TS-6.1.3-Br	TS-6.1.4-Br
E	-2958.913624	-2958.914561	-2958.916385	-2958.912236	-2958.894733	-2958.894340	-2958.891943	-2958.888685
H	-2958.899061	-2958.900086	-2958.900906	-2958.897530	-2958.881617	-2958.881168	-2958.879051	-2958.876357
S	121.317	120.701	132.320	122.034	111.029	111.782	108.853	105.044
G	-2958.956702	-2958.957435	-2958.963775	-2958.955512	-2958.934371	-2958.934280	-2958.930771	-2958.926267
	Pc-6.1.1-I	Pc-6.1.2-I	Pc-6.1.3-I	Pc-6.1.4-I	TS-6.1.1-I	TS-6.1.2-I	TS-6.1.3-I	TS-6.1.4-I
E	-682.528607	-682.531330	-682.531674	-682.528003	-682.511891	-682.510666	-682.509220	-682.506211
H	-682.513983	-682.516795	-682.517054	-682.513136	-682.498631	-682.498071	-682.496082	-682.493671
S	121.856	122.208	122.682	124.749	112.857	108.270	111.823	107.691
G	-682.571881	-682.574860	-682.575344	-682.572409	-682.552253	-682.549513	-682.549212	-682.544838

Table S6: Relative calculated thermodynamic and kinetic data for one step six-membered ring mechanism using B3LYP/Def2TZVP

	Pc-6.1.1-OH	Pc-6.1.2-OH	Pc-6.1.3-OH	Pc-6.1.4-OH	TS-6.1.1-OH	TS-6.1.2-OH	TS-6.1.3-OH	TS-6.1.4-OH
ΔE	-11.35	-12.53	-8.04	-11.67	24.41	23.40	28.30	27.65
ΔH	-11.24	-12.80	-8.15	-11.34	23.17	22.18	26.86	26.50
ΔS	-62.43	-69.53	-69.03	-54.87	-79.35	-79.29	-82.96	-77.06
ΔG	7.37	7.93	12.43	5.02	46.83	45.82	51.60	49.48
lnk					-49.59	-47.88	-57.64	-54.06
lnA					-10.48	-10.45	-12.29	-9.33

	Pc-6.1.1-F	Pc-6.1.2-F	Pc-6.1.3-F	Pc-6.1.4-F	TS-6.1.1-F	TS-6.1.2-F	TS-6.1.3-F	TS-6.1.4-F
ΔE	-8.69	-8.48	-7.11	-7.66	16.53	16.42	18.69	21.15
ΔH	-8.00	-7.79	-7.08	-7.71	15.39	15.31	17.37	19.90
ΔS	-53.63	-55.19	-67.31	-67.29	-78.49	-78.13	-81.52	-80.70
ΔG	7.99	8.67	12.99	12.35	38.79	38.60	41.68	43.96
lnk					-36.02	-35.70	-40.89	-44.74
lnA					-10.05	-9.86	-11.57	-11.15

	Pc-6.1.1-Cl	Pc-6.1.2-Cl	Pc-6.1.3-Cl	Pc-6.1.4-Cl	TS-6.1.1-Cl	TS-6.1.2-Cl	TS-6.1.3-Cl	TS-6.1.4-Cl
ΔE	-7.04	-7.68	-8.20	-4.03	7.16	9.03	8.89	11.15
ΔH	-6.87	-7.59	-8.18	-4.00	6.29	8.18	7.87	9.83
ΔS	-64.92	-66.19	-66.75	-68.68	-76.88	-75.42	-79.06	-82.27
ΔG	12.48	12.15	11.72	16.47	29.21	30.66	31.45	34.36
lnk					-19.85	-22.30	-23.62	-28.54
lnA					-9.23	-8.50	-10.33	-11.95

	Pc-6.1.1-Br	Pc-6.1.2-Br	Pc-6.1.3-Br	Pc-6.1.4-Br	TS-6.1.1-Br	TS-6.1.2-Br	TS-6.1.3-Br	TS-6.1.4-Br
ΔE	-7.48	-8.07	-9.21	-6.61	4.37	4.62	6.12	8.17
ΔH	-7.38	-8.02	-8.54	-6.42	3.57	3.85	5.18	6.87
ΔS	-66.06	-66.68	-55.06	-65.34	-76.35	-75.60	-78.52	-82.33
ΔG	12.32	11.86	7.88	13.07	26.33	26.39	28.59	31.42
lnk					-14.99	-15.09	-18.80	-23.57
lnA					-8.97	-8.59	-10.06	-11.98

	Pc-6.1.1-I	Pc-6.1.2-I	Pc-6.1.3-I	Pc-6.1.4-I	TS-6.1.1-I	TS-6.1.2-I	TS-6.1.3-I	TS-6.1.4-I
ΔE	-6.42	-8.13	-8.35	-6.04	4.07	4.83	5.74	7.63
ΔH	-6.38	-8.14	-8.30	-5.84	3.26	3.61	4.86	6.37
ΔS	-67.73	-67.37	-67.00	-64.83	-76.72	-81.31	-77.76	-81.89
ΔG	13.82	11.95	11.64	13.49	26.13	27.85	28.04	30.79
lnk					-14.66	-17.56	-17.88	-22.51
lnA					-9.16	-11.46	-9.68	-11.76

Energies are calculated in gas phase at 298.15K, ΔE, ΔH and ΔG (kcal mol^{-1}) and ΔS [cal (mol.K)$^{-1}$]

SECTION 4

Table S7: Raw thermochemistry values for two-step cyclic six-membered mechanism at B3LYP/Def2TZVP level

	Pc-6.2.1-OH	Pc-6.2.2-OH	Pc-6.2.3-OH	Pc-6.2.4-OH	TS-6.2.1-OH	TS-6.2.2-OH	TS-6.2.3-OH	TS-6.2.4-OH	Int-6.2.2-OH
E	-460.587437	-460.587201	-460.588802	-460.589892	-460.539964	-460.540245	-460.541774	-460.543091	-344.837215
H	-460.573588	-460.572253	-460.574004	-460.576079	-460.528211	-460.528418	-460.530068	-460.531871	-344.828606
S	118.366	125.563	122.133	113.078	100.373	100.909	99.505	96.785	83.352
G	-460.629827	-460.631912	-460.632033	-460.629806	-460.575901	-460.576363	-460.577346	-460.577857	-344.868209

	Pc-6.3.1-OH	Pc-6.3.2-OH	TS-6.3.1-OH	TS-6.3.2-OH	Pc-6.2.1-F	Pc-6.2.2-F	Pc-6.2.3-F	Pc-6.2.4-F	TS-6.2.1-F
E	-460.571196	-460.571620	-460.544709	-460.546405	-484.624897	-484.626195	-484.625774	-484.620095	-484.587480
H	-460.558456	-460.558859	-460.532907	-460.534718	-484.611158	-484.611402	-484.610974	-484.606882	-484.576076
S	107.453	107.440	101.825	100.712	113.962	124.850	124.591	109.610	99.586
G	-460.60951	-460.609907	-460.581288	-460.582569	-484.665305	-484.670722	-484.670172	-484.658962	-484.623393

	TS-6.2.2-F	TS-6.2.3-F	TS-6.2.4-F	Int-6.2.2-F	Pc-6.3.1-F	Pc-6.3.2-F	TS-6.3.1-F	TS-6.3.2-F	Pc-6.2.1-Cl
E	-484.587677	-484.585655	-484.582467	-368.884321	-484.619173	-484.618764	-484.605790	-484.604654	-844.959327
H	-484.576267	-484.574463	-484.571244	-368.876258	-484.606609	-484.606103	-484.594267	-484.593051	-844.945024
S	99.515	97.424	98.061	81.495	107.532	108.166	100.182	100.607	117.945
G	-484.623550	-484.620753	-484.617836	-368.914978	-484.657701	-484.657496	-484.641867	-484.640852	-845.001063

	Pc-6.2.2-Cl	Pc-6.2.3-Cl	Pc-6.2.4-Cl	TS-6.2.1-Cl	TS-6.2.2-Cl	TS-6.2.3-Cl	TS-6.2.4-Cl	Int-6.2.2-Cl	Pc-6.3.1-Cl
E	-844.960250	-844.959820	-844.958671	-844.919687	-844.921346	-844.919412	-844.915310	-729.218340	-844.957695
H	-844.946121	-844.945604	-844.944413	-844.908165	-844.909346	-844.907689	-844.903628	-729.209904	-844.945325
S	116.842	117.498	117.249	99.957	103.203	100.473	100.752	83.772	104.571
G	-845.001636	-845.001431	-845.000121	-844.955657	-844.958381	-844.955427	-844.951498	-729.249707	-844.995010

	Pc-6.3.2-Cl	TS-6.3.1-Cl	TS-6.3.2-Cl	Pc-6.2.1-Br	Pc-6.2.2-Br	Pc-6.2.3-Br	Pc-6.2.4-Br	TS-6.2.1-Br	TS-6.2.2-Br
E	-844.955147	-844.958833	-844.954989	-2958.914527	-2958.916280	-2958.914120	-2958.913055	-2958.879472	-2958.877957
H	-844.942830	-844.946746	-844.942895	-2958.900150	-2958.900856	-2958.899661	-2958.898467	-2958.867781	-2958.865593
S	103.980	104.372	104.196	120.367	132.642	120.834	121.065	101.733	106.904
G	-844.992235	-844.996337	-844.992402	-2958.957340	-2958.963879	-2958.957073	-2958.955989	-2958.916118	-2958.916387

	TS-6.2.3-Br	TS-6.2.4-Br	Int-6.2.2-Br	Pc-6.3.1-Br	Pc-6.3.2-Br	TS-6.3.1-Br	TS-6.3.2-Br	Pc-6.2.1-I	Pc-6.2.2-I
E	-2958.875830	-2958.871089	-2843.174083	-2958.915685	-2958.914526	-2958.921442	-2958.918471	-682.529547	-682.531595
H	-2958.863717	-2958.859050	-2843.165419	-2958.903261	-2958.902056	-2958.909755	-2958.906758	-682.514949	-682.517119
S	104.351	104.411	86.696	106.194	106.525	102.541	102.891	121.352	122.840
G	-2958.913297	-2958.908659	-2843.206612	-2958.953717	-2958.952669	-2958.958475	-2958.955645	-682.572608	-682.575484

	Pc-6.2.3-I	Pc-6.2.4-I	TS-6.2.1-I	TS-6.2.2-I	TS-6.2.3-I	TS-6.2.4-I	Int-6.2.2-I	Pc-6.3.1-I	Pc-6.3.2-I
E	-682.530348	-682.529731	-682.486952	-682.492867	-682.492049	-682.487542	-566.790327	-682.530163	-682.535442
H	-682.515796	-682.514934	-682.475403	-682.480913	-682.480141	-682.475379	-566.781558	-682.517599	-682.522799
S	122.424	124.051	103.060	105.084	104.624	106.606	88.625	108.298	110.166
G	-682.573964	-682.573875	-682.524370	-682.530841	-682.529851	-682.526030	-566.823666	-682.569055	-682.575142

	TS-6.3.1-I	TS-6.3.2-I	Constant values
E	-682.533360	-682.538143	$k_B(J/K) = 1.380662 \times 10^{-23}$
H	-682.521576	-682.526044	$R[cal/(mol.K)] = 1.987$
S	104.396	106.249	$h(JS) = 6.626176 \times 10^{-34}$
G	-682.571178	-682.576527	$T(K) = 298.15$

Table S**8**: Relative calculated thermodynamic and kinetic data for the two-step six-membered ring mechanism using B3LYP/Def2TZVP

	HOAc+2MeOH												
	Pc-6.2.1	Pc-6.2.2	Pc-6.2.3	Pc-6.2.4	TS-6.2.1	TS-6.2.2	TS-6.2.3	TS-6.2.4	Int-6.2.2	Pc-6.3.1	Pc-6.3.2	TS-6.3.1	TS-6.3.2
ΔE	-11.72	-11.57	-12.58	-13.26	18.07	17.89	16.94	16.11	4.32	-1.53	-1.79	15.09	14.03
ΔH	-11.91	-11.07	-12.17	-13.47	16.56	16.43	15.40	14.27	3.54	-2.41	-2.67	13.62	12.48
ΔS	-64.19	-56.99	-60.42	-69.47	-82.18	-81.64	-83.05	-85.77	-42.20	-75.10	-75.11	-80.73	-81.84
ΔG	7.23	5.92	5.84	7.24	41.07	40.78	40.16	39.84	16.13	19.98	19.73	37.69	36.88
lnk					-39.86	-39.37	-38.33	-37.79				-34.16	-32.80
lnA					-11.90	-11.63	-12.34	-13.71				-11.17	-11.73

	Pc-6.2.1	Pc-6.2.2	Pc-6.2.3	Pc-6.2.4	TS-6.2.1	TS-6.2.2	TS-6.2.3	TS-6.2.4	Int-6.2.2	Pc-6.3.1	Pc-6.3.2	TS-6.3.1	TS-6.3.2
					FAc+2MeOH								
ΔE	-9.05	-9.86	-9.60	-6.03	14.43	14.31	15.58	17.58	0.94	-5.46	-5.20	2.94	3.65
ΔH	-9.14	-9.29	-9.02	-6.45	12.89	12.76	13.89	15.91	-0.01	-6.28	-5.96	1.46	2.23
ΔS	-67.56	-56.67	-56.93	-71.91	-81.93	-82.00	-84.10	-83.46	-43.02	-73.99	-73.35	-81.34	-80.91
ΔG	11.01	7.61	7.95	14.99	37.31	37.21	38.96	40.79	12.82	15.78	15.91	25.71	26.35
lnk					-33.52	-33.35	-36.31	-39.40				-13.95	-15.02
lnA					-11.78	-11.81	-12.87	-12.54				-11.48	-11.26
					ClAc+2MeOH								
ΔE	-7.99	-8.57	-8.30	-7.58	16.88	15.84	17.06	19.63	2.26	-6.97	-5.37	-7.68	-5.27
ΔH	-7.92	-8.61	-8.28	-7.53	15.21	14.47	15.51	18.06	1.35	-8.11	-6.54	-9.00	-6.58
ΔS	-66.37	-67.48	-66.82	-67.07	-84.36	-81.11	-83.84	-83.57	-43.55	-79.75	-80.34	-79.95	-80.12
ΔG	11.87	11.51	11.64	12.46	40.37	38.66	40.51	42.98	14.33	15.67	17.41	14.84	17.31
lnk					-38.68	-35.79	-38.92	-43.08				4.41	0.24
lnA					-13.00	-11.36	-12.74	-12.60				-10.78	-10.87

					BrAc+2MeOH								
	Pc-6.2.1	Pc-6.2.2	Pc-6.2.3	Pc-6.2.4	TS-6.2.1	TS-6.2.2	TS-6.2.3	TS-6.2.4	Int-6.2.2	Pc-6.3.1	Pc-6.3.2	TS-6.3.1	TS-6.3.2
ΔE	-8.05	-9.15	-7.79	-7.13	13.95	14.90	16.23	19.21	1.86	-8.78	-8.05	-12.39	-10.52
ΔH	-8.06	-8.50	-7.75	-7.00	12.25	13.62	14.80	17.73	0.96	-10.01	-9.26	-14.09	-12.21
ΔS	-67.01	-54.74	-66.54	-66.31	-85.64	-80.47	-83.03	-82.97	-43.68	-81.18	-80.85	-84.84	-84.49
ΔG	11.92	7.82	12.09	12.77	37.79	37.62	39.56	42.47	13.98	14.19	14.85	11.21	12.98
lnk					-34.32	-34.04	-37.31	-42.23				10.54	7.54
lnA					-13.65	-11.04	-12.33	-12.30				-13.24	-13.06
					IAc+2MeOH								
	Pc-6.2.1	Pc-6.2.2	Pc-6.2.3	Pc-6.2.4	TS-6.2.1	TS-6.2.2	TS-6.2.3	TS-6.2.4	Int-6.2.2	Pc-6.3.1	Pc-6.3.2	TS-6.3.1	TS-6.3.2
ΔE	-7.01	-8.30	-7.52	-7.13	19.72	16.00	16.52	19.35	2.13	-7.40	-10.71	-9.41	-12.41
ΔH	-6.98	-8.34	-7.51	-6.97	17.83	14.38	14.86	17.85	1.20	-8.65	-11.91	-11.14	-13.94
ΔS	-68.23	-66.74	-67.16	-65.53	-86.52	-84.50	-84.96	-82.98	-43.96	-81.28	-79.42	-85.19	-83.33
ΔG	13.36	11.56	12.51	12.57	43.63	39.57	40.19	42.59	14.31	15.59	11.77	14.26	10.90
lnk					-44.19	-37.34	-38.38	-42.43				5.39	11.06
lnA					-14.09	-13.07	-13.30	-12.30				-13.41	-12.48

Energies are calculated in gas phase at 298.15K, ΔE, ΔH and ΔG (kcal mol^{-1}) and ΔS [cal (mol.K)$^{-1}$]

SECTION 5

CH₃ ... O4 ... structures (TS.4-X, TS-6.1-X, TS-6.2-X, TS-6.3-X)

Reference compounds for (X = OH, F, Br, Cl and I).
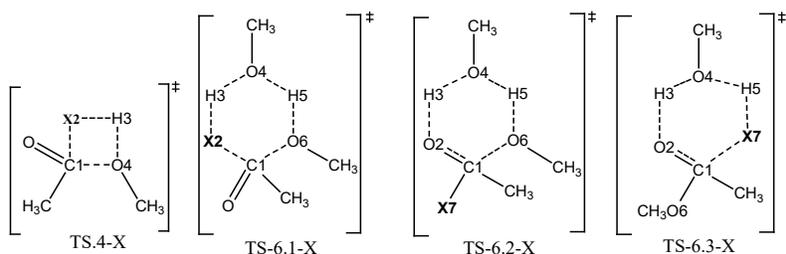
Table S9: Interatomic distances (Å) at B3LYP/Def2TZVP level

Pc	C1-X2	X2-H3	C1-O4	Pc	C1-X2	X2-H3	O4-H5	C1-O6	TS	C1-X2	X2-H3	O4-H5	C1-O6
4.1-OH	1.37	2.23	3.45	6.1.1-OH	1.37	2.08	2.07	2.90	6.1.1-OH	1.73	1.24	1.16	1.73
4.1-F	1.38	2.27	3.45	6.1.2-OH	1.38	1.94	1.87	3.57	6.1.2-OH	1.74	1.24	1.16	1.72
4.1-Cl	1.85	2.64	3.67	6.1.3-OH	1.38	2.18	1.92	2.94	6.1.3-OH	1.75	1.37	1.16	1.64
4.1-Br	2.04	2.75	3.75	6.1.4-OH	1.37	2.11	2.02	3.11	6.1.4-OH	1.64	1.26	1.12	1.73
4.1-I	2.27	3.30	3.25	6.1.1-F	1.39	2.12	1.89	3.31	6.1.1-F	1.95	1.38	1.36	1.65
TS				6.1.2-F	1.39	2.12	1.89	3.12	6.1.2-F	1.94	1.38	1.35	1.65
4.1-OH	1.82	1.21	1.80	6.1.3-F	1.39	2.30	1.93	2.90	6.1.3-F	1.91	1.45	1.32	1.63
4.2-OH	1.84	1.20	1.82	6.1.4-F	1.41	2.00	1.86	3.85	6.1.4-F	1.98	1.41	1.34	1.66
4.1-F	1.93	1.32	1.79	6.1.1-Cl	1.87	2.72	1.88	3.16	6.1.1-Cl	2.49	2.03	1.51	1.71
4.2-F	1.96	1.30	1.82	6.1.2-Cl	1.87	2.60	1.87	3.32	6.1.2-Cl	2.45	2.09	1.41	1.75
4.1-Cl	2.52	1.86	1.78	6.1.3-Cl	1.87	2.57	1.85	3.80	6.1.3-Cl	2.47	2.09	1.47	1.69
4.2-Cl	2.59	1.83	1.79	6.1.4-Cl	2.00	2.52	1.98	2.76	6.1.4-Cl	2.55	2.12	1.51	1.68
4.1-Br	2.73	2.05	1.78	6.1.1-Br	2.04	2.70	1.82	3.19	6.1.1-Br	2.66	2.22	1.53	1.73
4.2-Br	2.81	2.00	1.79	6.1.2-Br	2.05	2.63	1.87	3.45	6.1.2-Br	2.64	2.23	1.53	1.72
4.1-I	2.99	2.27	1.77	6.1.3-Br	2.06	2.61	1.85	3.87	6.1.3-Br	2.64	2.29	1.49	1.71
4.2-I	3.09	2.23	1.78	6.1.4-Br	2.05	2.80	1.93	3.02	6.1.4-Br	2.70	2.28	1.52	1.70
				6.1.1-I	2.28	3.10	1.88	2.82	6.1.1-I	2.90	2.47	1.55	1.75
				6.1.2-I	2.28	2.85	1.85	3.82	6.1.2-I	2.89	2.45	1.58	1.74
				6.1.3-I	2.26	2.91	1.84	3.69	6.1.3-I	2.88	2.52	1.50	1.74
				6.1.4-I	2.26	3.21	1.92	2.94	6.1.4-I	2.94	2.52	1.53	1.71

Pc	C1-O6	O4-H5	O2-H3	TS	C1-O6	O4-H5	O2-H3	Pc	C1-X7	H5-X7	H3-O4
6.2.1-OH	3.79	1.85	1.86	6.2.1-OH	1.86	1.18	1.19	6.3.1-OH	1.45	2.00	1.89
6.2.2-OH	3.14	1.87	1.92	6.2.2-OH	1.85	1.14	1.23	6.3.2-OH	1.44	2.00	1.88
6.2.3-OH	3.21	1.98	2.05	6.2.3-OH	1.84	1.15	1.25	6.3.1-F	1.46	2.15	1.86
6.2.4-OH	2.84	1.94	1.99	6.2.4-OH	1.77	1.17	1.29	6.3.2-F	1.45	2.17	1.86
6.2.1-F	3.19	1.85	2.00	6.2.1-F	1.66	1.19	1.37	6.3.1-Cl	2.16	2.38	1.71
6.2.2-F	3.07	1.87	2.02	6.2.2-F	1.66	1.18	1.35	6.3.2-Cl	2.04	2.49	1.74
6.2.3-F	3.11	1.88	2.03	6.2.3-F	1.67	1.18	1.37	6.3.1-Br	2.32	2.40	1.69
6.2.4-F	2.86	1.71	1.82	6.2.4-F	1.69	1.18	1.35	6.3.2-Br	2.29	2.47	1.70
6.2.1-Cl	3.03	1.87	2.21	6.2.1-Cl	1.60	1.15	1.46	6.3.1-I	2.67	2.72	1.66
6.2.2-Cl	3.22	1.88	2.05	6.2.2-Cl	1.60	1.18	1.45	6.3.2-I	3.11	2.47	1.48
6.2.3-Cl	3.28	1.87	2.08	6.2.3-Cl	1.61	1.16	1.46	**TS**			
6.2.4-Cl	3.10	1.89	2.13	6.2.4-Cl	1.65	1.17	1.40	6.3.1-OH	1.85	1.29	1.22
6.2.1-Br	3.20	1.89	2.04	6.2.1-Br	1.56	1.17	1.57	6.3.2-OH	1.81	1.27	1.19
6.2.2-Br	3.73	1.86	2.02	6.2.2-Br	1.53	1.18	1.59	6.3.1-F	2.02	1.38	1.34
6.2.3-Br	3.12	1.82	2.25	6.2.3-Br	1.56	1.14	1.54	6.3.2-F	2.00	1.38	1.32
6.2.4-Br	3.08	1.91	2.27	6.2.4-Br	1.61	1.16	1.44	6.3.1-Cl	2.54	2.06	1.50
6.2.1-I	2.80	1.97	2.24	6.2.1-I	1.86	1.44	1.59	6.3.2-Cl	2.53	2.03	1.45
6.2.2-I	3.70	1.83	2.06	6.2.2-I	1.56	1.13	1.59	6.3.1-Br	2.90	2.13	1.34
6.2.3-I	3.12	1.82	2.23	6.2.3-I	1.53	1.13	1.65	6.3.2-Br	2.91	2.18	1.42
6.2.4-I	3.19	1.89	2.21	6.2.4-I	1.60	1.15	1.46	6.3.1-I	3.18	2.48	1.39
								6.3.2-I	3.46	2.21	1.25

SECTION 6

Cartesian coordinates of optimized lowest energy transition structure for each model in gas phase at B3LYP/Def2TZVP level.

Four-membered ring transition states

TS-4.1-OH, E(RB3LYP) = -344.899499068 A.U.

Imaginary frequency (-1189.58)

C,0.598945394,-0.0719282286,0.325652921\
C,1.6232171605,-0.9356426885,-0.3255247538\
H,2.609529398,-0.585777588,-0.0204568766\
H,1.4790760476,-1.9565160887,0.0300354011\
H,1.5385988297,-0.9056918185,-1.4063535536\
O,0.3670504975,0.1539142274,1.4610555588\
C,-2.0761948949,-0.3331090818,0.0225510949\
H,-2.4634599812,-1.3526507738,0.0638239788\
H,-2.8068527348,0.3036646989,-0.4811748889\
H,-1.9268025398,0.0330212589,1.0434048401\
O,-0.8542763365,-0.3243491911,-0.6982441122\
H,-0.3953713575,0.756689443,-0.961986267\

O,0.6042009743,1.4090667364,-0.7362295319\
H,0.4158095433,2.1310380945,-0.1223118107\

TS-4.1-F, E(RB3LYP) = -368.942633173 A.U.

Imaginary frequency (-575.03)

C,0.600778945,-0.2180964083,0.3284420101\
C,1.706317232,-0.7166991521,-0.5208932905\
H,2.6340371345,-0.2939495328,-0.1371944473\
H,1.7373019851,-1.8040947791,-0.4270851952\
H,1.570093203,-0.4319671013,-1.5568865754\
O,0.3433323832,-0.243041653,1.4611158974\
C,-2.0758311712,-0.3327619658,-0.0654565651\
H,-2.394590481,-1.3736658622,-0.0835414719\
H,-2.8103825778,0.285033032,-0.5814234061\
H,-1.9728419924,0.0046860777,0.9675286398\
O,-0.826453629,-0.2321272816,-0.7552937919\
H,-0.481846568,0.7856383552,-0.8268722144\
F,0.4910965365,1.5671402714,-0.4021135895\

TS-4.1.Cl, E(RB3LYP) = -729.293853708 A.U.

Imaginary frequency (-280.02)

C,-0.047894743,0.8444941551,0.2610357706\
C,-0.8769356827,1.6236945484,-0.6869724777\
H,-1.8167857874,1.855081842,-0.1888222658\
H,-0.3378106164,2.5507725872,-0.9035727354\
H,-1.0684313865,1.0725602108,-1.5986938355\
O,0.3484825295,0.9843725782,1.3417249336\
C,2.2156226465,-0.5660845751,-0.0769197391\
H,2.8595934648,0.2882485403,0.1143670197\
H,2.7236600819,-1.2798788465,-0.7228656981\
H,1.9265385655,-1.0402608833,0.8601730534\
O,1.0505413935,-0.0944217136,-0.7824665271\
H,0.3434283947,-0.8438316757,-0.7984604735\
Cl,-1.2785958605,-1.3408127679,-0.0244140251\

TS-4.1-Br, E(RB3LYP) = -2843.25277420 A.U.

Imaginary frequency (-238.77)

C,0.0502227734,1.2303760858,0.0216932166\
C,1.1136414579,2.1863240413,0.4064616477\

H,1.4789574512,2.656601886,-0.5046882747\
H,0.6502989929,2.9409983703,1.0500887505\
H,1.9295596726,1.6954619266,0.9215022467\
O,-0.9360481775,1.2684728587,-0.5861724303\
C,-1.2120747513,-0.7147184033,1.3784483415\
H,-1.4020482511,-1.1551890631,0.4006948104\
H,-2.0184051273,-0.0420085166,1.656720003\
H,-1.0939366266,-1.4916485309,2.1311585108\
O,0.0124350799,0.0511722998,1.3526260137\
H,0.7358109792,-0.511185831,0.8990458777\
Br,1.7333785267,-0.7187811236,-0.8759667136\

TS-4.1-I, E(RB3LYP) = -566.869736741 A.U.

Imaginary frequency (-220.03)

C,0.5259960793,-0.56915662,0.278124249\
C,1.6985902973,-0.7074376102,-0.6159314621\
H,2.593292946,-0.6116120216,-0.0035709969\
H,1.6543273587,-1.7125704794,-1.0492420691\
H,1.7026093992,0.0429390951,-1.3964082077\

82

O,0.1511246678,-1.0624149375,1.2580937454\

C,-2.0952606271,-0.2325101247,-0.1926495628\

H,-2.1365849764,0.2646885507,0.7753818755\

H,-2.259499745,-1.3003466583,-0.083065398\

H,-2.826519488,0.1948533298,-0.8753673073\

O,-0.7904412683,-0.0494758108,-0.7908244686\

H,-0.5435221972,0.9361708755,-0.7201844418\

I,0.6716851838,2.4106450413,0.5010431744\

One step six-membered ring transition states

TS-6.1.1-OH, E(RB3LYP) = -460.691736334 A.U.

Imaginary frequency (-1240.20)

C,-1.2894708774,-0.2525198166,0.1498695945\

H,-0.1710310916,-1.0450970987,1.7990662622\

C,-1.8099570108,-1.0985304886,-0.9748503009\

H,-2.4601861049,-0.4798633993,-1.5925873084\

H,-1.0050950795,-1.498827927,-1.5856124076\

H,-2.3863905323,-1.9187799247,-0.5485171669\

O,-1.9117070037,0.3295932609,0.9886503461\

O,-0.1672756423,0.7684979628,-0.6830473871\

O,-0.1208287787,-1.3104108278,0.8716236527\

O,1.7639213134,-0.604358246,-0.3975267245\

C,2.956132686,-0.1131977102,0.2040717315\

H,3.4764826481,0.5370271149,-0.500440608\

H,2.7496655785,0.4504975295,1.1199326477\

H,3.6064376542,-0.9544930713,0.4474156909\

H,0.9733209036,-1.0752069005,0.3444015989\

H,0.9474614198,0.186547121,-0.6416557525\

C,-0.1366034873,2.1035294488,-0.2001597991\

H,-0.3293498486,2.7920990947,-1.0253897501\

H,-0.9058381998,2.2300511485,0.5643871127\

H,0.8370884533,2.3390477296,0.2403505681\

TS-6.1.1-F, E(RB3LYP) = -484.736916302 A.U.

Imaginary frequency (-450.19)

C,-1.4533786176,-0.0834103746,0.0417437322\

C,-1.7060066452,-1.2565177509,-0.8404923046\

83

H,-2.1752378688,-2.0286298184,-0.2355282324\

H,-2.3931434731,-0.9427213482,-1.6295106784\

H,-0.7934109166,-1.6432781589,-1.2818918151\

O,-2.1574215012,0.5430785188,0.7391569896\

O,-0.2896755853,0.8104931314,-0.7113179415\

O,1.6383392528,-0.647591558,-0.387513516\

C,2.9208661314,-0.2228307293,0.0609244944\

H,3.4409718706,0.2507376202,-0.7719907386\

H,2.8462411619,0.4883106664,0.8890692656\

H,3.5028651803,-1.0854258288,0.3909789137\

H,1.0236502691,-0.9625101075,0.4020721875\

H,0.6523780386,0.2497224368,-0.6660256559\

C,-0.1222502305,2.1103981105,-0.113966\

H,0.169032019,2.0147286139,0.931396571\

H,0.6441107675,2.6291140242,-0.6871099311\

H,-1.0655946403,2.6436378376,-0.1822471705\

F,-0.1309542125,-0.9801932853,1.15944883\

TS-6.1.1-Cl, E(RB3LYP) = -845.088960974 A.U.

C,1.4742116361,-0.0838166045,0.3988888726\

C,0.25700029,2.0963814366,-0.3993922129\

H,-0.5068288736,2.8268816354,-0.1395923788\

H,1.2394956738,2.5566821103,-0.3717090994\

H,0.0732741346,1.6566747468,-1.3790592963\

C,1.2931562825,-1.0654377407,1.5007280942\

H,1.7433179408,-0.6337171917,2.3994281153\

H,0.2497464575,-1.2975906611,1.6797131897\

H,1.8264452593,-1.9713433638,1.2225666805\

O,2.4075205753,0.3690309482,-0.1342606982\

O,0.2279917237,1.0638763856,0.6098486688\

O,-1.922482054,-0.284669088,0.4915100295\

C,-3.2111523248,0.1595350811,0.0672444171\

H,-3.1657028566,0.6471332986,-0.910035446\

H,-3.9026537812,-0.6834292995,0.0139464743\

H,-3.5782930351,0.8688622885,0.8076021956\

H,-1.4966981912,-0.8558784322,-0.2060676634\

H,-0.6895230104,0.5881353,0.5956013077\

Cl,0.1507051533,-1.3270928497,-1.3023782502\

TS-6.1.1-Br, E(RB3LYP) = -2959.04808712 A.U.

Imaginary frequency (-163.85)

C,1.350423772,0.8639148427,0.5515572873\

C,1.1523482135,0.5380792684,1.9882125026\

H,1.8838942491,-0.2209524591,2.2553765059\

H,1.3437888058,1.4532109549,2.5570343289\

H,0.1537806,0.1708733782,2.1937096722\

O,2.2592824462,1.2199157958,-0.0846039004\

O,-0.1171897745,1.6398526853,0.0693543389\

O,-1.9893052421,-0.0209687508,0.5899451744\

C,-3.2912407656,-0.1011830946,0.0069899235\

H,-3.828509361,0.8071283906,0.275098756\

H,-3.237820466,-0.183254553,-1.0814621374\

H,-3.8316692661,-0.9615902118,0.4057098989\

H,-1.4282839353,-0.7855243036,0.3000677441\

H,-0.9201001499,1.0269809751,0.2587631967\

C,-0.1094794498,2.0250614286,-1.3215439229\

H,0.7811622658,2.621918811,-1.4915146593\

H,-0.0927016738,1.1354659717,-1.9506282512\

H,-1.0006091178,2.6239191497,-1.5009612484\

Br,0.5579068493,-1.486134279,-0.4147002099\

TS-6.1.1-I, E(RB3LYP) = -682.665125628 A.U.

Imaginary frequency (-172.56)

C,0.8025475272,0.0062922841,0.235560732\

C,0.1907803446,0.028782049,1.590199873\

H,-0.119473601,-0.9865985888,1.8263038497\

H,0.9686024093,0.3509365397,2.2902987224\

H,-0.6628820248,0.693909745,1.6453114083\

O,1.6756582554,-0.5847009642,-0.2589228871\

O,0.8062902991,1.6855521636,-0.2617524266\

O,-1.6140687937,2.5323793134,-0.0899371685\

C,-2.1877174162,3.6889005515,-0.7052080983\

H,-1.6559516675,4.5588797003,-0.3237489705\

H,-2.0909897885,3.6520307572,-1.7929290526\

85

H,-3.2427286666,3.7749078262,-0.4397727812\

H,-2.0205321377,1.7092500742,-0.4528637149\

H,-0.1375570308,2.0763215611,-0.2158765066\

C,1.361649763,1.8759389005,-1.578527893\

H,1.477295783,2.9467077931,-1.7378441601\

H,2.3327575536,1.3906864016,-1.5969857863\

H,0.7040843165,1.4306694256,-2.3250511203\

I,-1.6160769749,-0.599424143,-1.2389778794\

Two steps six-membered ring transition states

First step

TS-6.2.2-OH, E(RB3LYP) = -460.703275307 A.U.

Imaginary frequency (-1289.39)

C,-0.9223015207,-0.6982588218,0.2062068639\

C,-1.9652598232,-1.0145916222,-0.8355089901\

H,-2.4991589232,-1.914140878,-0.5207255949\

H,-2.6839202648,-0.203378207,-0.9577773618\

H,-1.4773099771,-1.2056433804,-1.7869512165\

O,-1.4011089259,-0.2273551881,1.4008284881\

O,-0.1683698049,0.8097799223,-0.5462236599\

O,0.0807563278,-1.4800292703,0.3090970263\

O,1.8616147832,0.0791889775,0.4800007059\

H,1.0975101845,-0.8353762405,0.5447335904\

H,1.0134450383,0.6249650799,-0.0483173692\

C,-0.7614232959,2.0504980309,-0.2453783845\

H,-0.1915067484,2.851554216,-0.7251914464\

H,-1.7840779392,2.0984426175,-0.6400746127\

H,-0.7890285609,2.2509322584,0.8323413613\

H,-2.2223443833,0.2594734435,1.2620356726\

C,2.9662226511,-0.1925655083,-0.3810440754\

H,2.634238176,-0.6135300164,-1.3342519171\

H,3.5142090717,0.7319619408,-0.568461738\

H,3.6324989351,-0.9020663538,0.1103466581\

TS-6.2.2-F, E(RB3LYP) = -484.739378092 A.U.

Imaginary frequency (-1159.02)

C,-0.5870219283,-0.8494144518,0.1605272134\

86

C,-1.4127734852,-1.5893064283,-0.8605944882\

H,-1.8446547717,-2.4625129304,-0.3708419398\

H,-2.2205171904,-0.974884953,-1.2541142585\

H,-0.768282475,-1.9203561266,-1.6720846584\

O,-0.0404389016,0.5145417525,-0.6207422467\

O,0.4277341487,-1.4098433098,0.6618930985\

O,1.8883856635,0.4854630312,0.7691253638\

H,1.3696617622,-0.4755410232,0.9332333938\

H,1.012247646,0.7157575894,0.0109694516\

C,-0.9208050145,1.6301036586,-0.7483220264\

H,-0.4026598932,2.3953172125,-1.3279800291\

H,-1.8193988765,1.33154389,-1.2890425577\

H,-1.2040440497,2.030710539,0.2252672277\

C,3.1653297258,0.2959846319,0.1490910519\

H,3.0888105556,-0.3693898324,-0.7140751904\

H,3.5455824697,1.2659123593,-0.1692260421\

H,3.8517856747,-0.1336712423,0.8779829086\

F,-1.4516070602,-0.2628403666,1.1022317281\

Imaginary frequency (-948.89)

C,0.6511156094,-0.5884612868,0.3083443516\

C,0.5560943419,2.064910936,0.3542802898\

H,-0.1830621763,2.8387172175,0.5622764713\

H,1.3709451039,2.1539901463,1.0718049748\

H,0.942058391,2.1672543408,-0.6582281258\

C,1.7204555193,-0.7028007518,1.3662542755\

H,2.2696819138,-1.6246970058,1.1848922702\

H,2.4197301302,0.1286815567,1.346916843\

H,1.232875638,-0.7630462809,2.3409323228\

O,-0.1011623411,0.8054223302,0.5259301419\

O,-2.0218013575,-0.0446525191,-0.5865766913\

C,-3.2458491285,-0.1251527809,0.1628545346\

H,-3.7575829773,0.8315591549,0.0793151354\

H,-3.8686900225,-0.9059504519,-0.2701825889\

H,-3.0462902385,-0.3511975064,1.2119101797\

H,-1.4048498365,-0.8899809756,-0.4030273269\

H,-1.1808117285,0.5969285519,-0.0715259211\

Cl,1.6101520099,-0.2728733522,-1.4027046143\

O,-0.2223198506,-1.475455323,0.2044434776\

TS-6.2.2-Br, E(RB3LYP) = -2959.02901939 A.U.

Imaginary frequency (-728.65)

C,-0.1038007502,0.5341272154,-0.7505621035\

C,-1.0482002275,1.6269461486,-1.1696929754\

H,-1.6661995316,1.2398531722,-1.9756119322\

H,-1.69263162,1.9610227596,-0.3627775799\

H,-0.4506452155,2.4632339226,-1.5460115696\

O,0.7011658728,0.9467903815,0.4867603927\

O,0.6272094869,-0.0508569464,-1.5516048814\

O,2.2453334307,-0.8360631187,0.1743202423\

H,1.7233793756,-0.8298369505,-0.7097191573\

H,1.5721674768,0.0504297735,0.5544158428\

C,0.0765871384,1.4615265415,1.6753431879\

H,0.8364199673,1.4572934784,2.4552216002\

H,-0.2491800046,2.4848017558,1.4952785302\

H,-0.7621670386,0.8265892395,1.9555849269\

C,3.6259843191,-0.479938744,-0.0465247051\

H,3.6997155007,0.4503733751,-0.6111173032\

H,4.0960207857,-0.3681912412,0.9274372619\

H,4.1072635099,-1.288410586,-0.5925542947\

Br,-1.5633824757,-1.0169021769,0.2266945174\

TS-6.2.2-I, E(RB3LYP) = -682.643758324 A.U.

Imaginary frequency (-626.13)

C,0.378135,0.75335,-0.701528\

C,-0.18308,2.101584,-1.111665\

H,-0.821609,1.948512,-1.984274\

H,-0.772629,2.579965,-0.32888\

H,0.659904,2.747255,-1.392897\

O,1.22955,0.92832,0.595517\

O,1.031376,0.066599,-1.521813\

O,2.471039,-1.074118,0.154907\

H,1.96121,-0.941781,-0.718811\

H,1.996248,-0.14402,0.586819\

C,0.673333,1.364428,1.848364\

H,1.517114,1.709166,2.45346\

H,-0.015214,2.194186,1.679448\

H,0.144968,0.545627,2.342746\

C,3.903847,-0.95639,-0.048562\

H,4.136476,-0.029699,-0.581422\

H,4.369443,-0.963449,0.937568\

H,4.232627,-1.82375,-0.622603\

I,-1.582975,-0.505024,0.073213\

Second step

TS-6.3.2-OH, E(RB3LYP) = -460.709527137 A.U.

Imaginary frequency (-1323.51)

O,0.0858612349,-0.2031315739,-1.1225591664\

O,-1.9274181968,0.3864553421,-0.0024777243\

H,-1.0190352856,0.1606601972,-0.7371946811\

H,-1.2119101708,0.0241135713,0.8251739861\

O,-0.1326973288,-0.4439177107,1.3126282948\

H,0.2776992031,0.1079169649,1.9881383183\

C,0.9245899591,-0.3120232777,-0.1512153841\

C,1.7156854095,-1.5865075878,-0.0275648888\

H,1.0368295013,-2.4349184486,-0.0162277655\

H,2.3230012679,-1.585971055,0.8749460487\

H,2.3701950833,-1.6634934742,-0.8982543219\

O,1.7086445402,0.7660456293,0.1626801197\

C,-3.0427764924,-0.4793006778,-0.2051949307\

H,-2.7317863276,-1.5269797262,-0.2456376327\

H,-3.753862884,-0.3486736979,0.6115547196\

H,-3.5324677863,-0.2162524554,-1.1433711011\

C,1.2341002008,2.0524989025,-0.2439399601\

H,2.0130405663,2.7551349923,0.0424155721\

H,1.0742125499,2.0835884462,-1.3209965205\

H,0.302068956,2.3109056394,0.2637850178\

TS-6.3.2-F, E(RB3LYP) = -484.757759428 A.U.

Imaginary frequency (-588.31)

O,-0.193852,0.306578,1.086654\

O,1.912064,0.836277,0.072881\

H,0.876981,0.488754,0.815809\

H,1.322297,0.573358,-0.759948\

C,-0.780834,-0.470768,0.254932\

C,-0.414718,-1.911594,0.101188\

H,0.663732,-2.030507,0.13817\

H,-0.798251,-2.300163,-0.837\

H,-0.859803,-2.46229,0.935069\

O,-2.015527,-0.205444,-0.089689\

C,3.125168,0.095841,0.138446\

H,2.949259,-0.984017,0.106658\

H,3.770927,0.370049,-0.697594\

H,3.632181,0.344959,1.070468\

C,-2.464886,1.160296,0.029427\

H,-3.472934,1.162377,-0.374087\

H,-2.4653,1.472256,1.071691\

H,-1.811663,1.801401,-0.558753\

F,0.198079,0.091321,-1.401467\

TS-6.3.2-Cl, E(RB3LYP) = -845.109271710 A.U.

Imaginary frequency (-133.72)

O,-0.0879160164,0.1787057914,1.2643256808\

O,2.0278054897,0.3798572991,-0.0161686231\

H,0.8244995517,0.3996550536,0.7844029471\

H,1.596221764,-0.2119520904,-0.6970368431\

C,-1.1256027022,0.0484898817,0.510024136\

C,-2.1452442993,-0.9686489358,0.8883516239\

H,-1.6521567606,-1.9038666245,1.1324436228\

H,-2.8538729764,-1.1132200172,0.0789695566\

H,-2.6746439187,-0.5988967655,1.7729947943\

O,-1.5950164646,1.03666343,-0.2098861416\

C,3.1473688463,-0.2982486967,0.5659925944\

H,3.9358476339,-0.4208975031,-0.1778563233\

H,3.5197848785,0.3196829125,1.3811128303\

H,2.8572353965,-1.2775717501,0.9526304651\

C,-0.7282921289,2.1141794548,-0.6057794199\

H,-1.3819175491,2.8592674304,-1.0482161704\

90

H,-0.2062946379,2.5265654637,0.2565331616\

H,-0.0210245483,1.7380015752,-1.3434961016\

Cl,-0.0298885582,-1.2204199091,-1.3784927898\

TS-6.3.2-Br, E(RB3LYP) = -2959.07229314 A.U.

Imaginary frequency (-75.46)

O,0.467553,-1.496752,-0.627766\

O,-1.917583,-0.920938,-0.853598\

H,-0.60022,-1.416862,-0.642132\

H,-1.691462,0.04407,-0.670915\

C,1.035714,-0.949662,0.386185\

C,0.54961,-1.102358,1.7926\

H,-0.538973,-1.083537,1.826711\

H,0.947857,-0.305145,2.419268\

H,0.905859,-2.075228,2.1636\

O,2.268624,-0.553518,0.263878\

C,-3.064997,-1.322867,-0.094869\

H,-3.958885,-0.833281,-0.494226\

H,-3.167243,-2.404928,-0.205269\

H,-2.95331,-1.064919,0.965419\

Br,-0.344019,1.592049,0.069165\

C,2.782922,-0.307229,-1.07328\

H,3.789245,0.07629,-0.913725\

H,2.798221,-1.23568,-1.646327\

H,2.141332,0.439852,-1.547118\

TS-6.3.2-I, E(RB3LYP) = -682.688792178 A.U.

Imaginary frequency (-373.50)

O,1.833193,0.794085,-0.693565\

O,0.144329,2.142007,0.338549\

H,1.110862,1.509543,-0.131088\

H,-0.543172,1.384968,0.305146\

C,1.946402,-0.444582,-0.451641\

C,2.177167,-1.412858,-1.568827\

H,1.528923,-1.14517,-2.405839\

H,1.971572,-2.432328,-1.240224\

H,3.222616,-1.339859,-1.893468\

O,2.087594,-0.960587,0.768072\

C,-0.320835,3.235667,-0.489729\

H,-1.241048,3.629998,-0.053384\

H,0.455328,4.002255,-0.48059\

H,-0.508493,2.886745,-1.509668\

C,1.90991,-0.135728,1.943288\

H,2.301458,-0.735465,2.764002\

H,2.465553,0.799594,1.843509\

H,0.839258,0.042642,2.075697\

I,-1.479239,-0.601169,0.015527\

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APPENDIX B

Supporting Information for Chapter Three

A Density Functional Theoretical Study on Acid-Catalyzed Esterification Reaction

Cartesian coordinates of optimized transition structures for acid-catalyzed esterification of acetic acid and its halide derivatives in gas phase at M06-2X/def2-TZVP level.

TS-6-OH, E(RM062X) = -460.875911824 A.U.

Imaginary frequency (-223.25)

C,-1.073914,-0.34962,-0.003936\
H,-0.132897,-0.385461,1.831271\
C,-1.287758,-1.497809,-0.960347\
H,-1.602095,-2.393129,-0.416503\
H,-2.049271,-1.2121 51,-1.690619\
H,-0.362399,-1.726688,-1.494124\
O,-2.12955,-0.003149,0.79238\
O,-0.568914,0.751511,-0.675692\
O,0.035553,-0.820395,0.96861\
O,2.00 3954,-0.218603,-0.298043\
C,3.377633,0.017953,0.154756\
H,3.991879,0.169 353,-0.732224\
H,3.410523,0.883756,0.818361\
H,3.680868,-0.89047,0.672596\
H,1.158841,-0.532566,0.43112\

H,1.612755,0.509182,-0.837577\
C,-0.844071,2.069994,-0.137211\
H,-0.365816,2.758711,-0.832927\
H,-1.918824,2.249774,-0.109815\
H,-0.41905,2.185708,0.865428\
H,-2.764209,-0.734029,0.877403\

TS-6-F, E(RM062X) = -484.883364663 A.U.

Imaginary frequency (-327.15)

C,1.075443,-0.262749,-0.065374\
C,1.831441,-1.111372,0.917651\
H,2.433691,-1.854927,0.385086\
H,2.463192,-0.461013,1.5291\
H,1.138818,-1.649173,1.568357\
O,1.79643,0.312428,-1.047838\
O,0.282003,0.650242,0.579843\
O,-1.951759,-0.560722,0.412826\
C,-3.140313,0.032846,-0.227913\
H,-3.502589,0.795079,0.458871\
H,-2.866623,0.445573,-1.19962\
H,-3.861409,-0.777194,-0.317795\
H,-1.350611,-1.101593,-0.200107\
H,-1.182447,0.152976,0.714857\
C,0.398848,2.061252,0.186096\
H,-0.564882,2.511811,0.425082\
H,1.178692,2.522046,0.794178\

H,0.622926,2.15439,-0.874043\

H,2.730525,0.049015,-1.013959\

F,0.083868,-1.146937,-0.743491\

TS-6-Cl, E(RM062X) = -845.229574842 A.U.

Imaginary frequency (-172.96)

C,1.165103,-0.039961,0.18989\

C,1.562851,-0.730711,1.469697\

H,2.125608,-1.641578,1.248578\

H,2.181168,-0.039869,2.052847\

H,0.68999,-1.002968,2.0662\

O,2.161976,0.360749,-0.615511\

O,0.271012,0.997907,0.419251\

O,-1.993558,-0.187903,0.694138\

C,-3.219691,0.18248,-0.05575\

H,-3.737849,0.906431,0.56962\

H,-2.939306,0.590981,-1.026496\

H,-3.800104,-0.73237,-0.155508\

H,-1.505933,-0.972346,0.27346\

H,-1.224494,0.495897,0.635056\

C,0.360883,2.175656,-0.446682\

H,-0.487553,2.79773,-0.163268\

H,1.294394,2.698085,-0.241738\

H,0.305663,1.879516,-1.49625\

H,2.974353,-0.154437,-0.471393\

Cl,0.081985,-1.395052,-0.836298\

TS-6-Br, E(RM062X) = -2959.23056612 A.U.

Imaginary frequency (-109.57)

C,1.499266,0.433525,0.440671\

C,1.42898,0.221263,1.916917\

H,1.675333,-0.808958,2.18212\

H,2.170983,0.890454,2.376411\

H,0.443438,0.470423,2.308964\

O,2.509193,-0.000247,-0.262827\

O,0.815187,1.45249,-0.039233\

O,-2.02249,0.79268,0.626547\

C,-3.403737,0.902661,0.126686\

H,-3.879504,1.706483,0.686304\

H,-3.403575,1.086544,-0.948626\

H,-3.858055,-0.05614,0.363713\

H,-1.391707,-0.111949,0.270936\

H,-1.462879,1.543913,0.409233\

C,0.981031,1.805154,-1.453629\

H,0.332762,2.666534,-1.600265\

H,2.022267,2.067519,-1.64134\

H,0.66863,0.948281,-2.054559\

H,2.978077,-0.745375,0.157624\

Br,-0.278404,-1.365506,-0.32258\

TS-6-I, E(RM062X) = -682.662953986 A.U.

Imaginary frequency (-70.34)

C,0.612593,1.25355,0.35466\

C,0.759291,1.309495,1.848424\

H,1.707586,0.87313,2.153622\

95

H,0.726477,2.364137,2.134135\

H,-0.045909,0.773862,2.345174\

O,1.548611,1.858937,-0.379287\

O,-0.626054,1.631533,-0.05659\

O,-2.216065,-0.271254,0.749778\

C,-3.444362,-0.612303,0.02282\

H,-4.149922,0.187363,0.221104\

H,-3.220246,-0.706851,-1.036699\

H,-3.795668,-1.548352,0.443078\

H,-1.450839,-0.932369,0.58252\

H,-1.801643,0.604223,0.473165\

C,-0.785674,1.936138,-1.46296\

H,-1.84687,2.121813,-1.601706\

H,-0.212022,2.82314,-1.712009\

H,-0.451211,1.083772,-2.056876\

I,0.747144,-1.101433,-0.169319\

H,2.438634,1.657048,-0.060494\