1. INTRODUCTION

1.1. Asymmetric Desymmetrization

Asymmetric desymmetrization (AD) of *meso* cyclic anhydrides by selective reaction at one of the enantiotopic carbonyls has attracted considerable attention, because many *meso* cyclic anhydrides are available through Diels-Alder reactions of maleic anhydride and because the desymmetrized products which contain chemically differentiated carboxy functions can be easily transferred to other versatile chiral building blocks for numerous synthetic applications.[1] The enantioselectivity in enzyme-catalyzed hydrolyses of this type is often very high.[2] A disadvantage of this enzymatic approach is that most of the time only one enantiomer of the product can be obtained directly. In contrast, anhydride openings with chiral nucleophiles are not limited by this restriction, when both enantiomers of the chiral catalyst are available. Recent advances in the development of nonenzymatic catalysts such as cinchona alkaloids for the asymmetric desymmetrization reactions of *meso* cyclic anhydrides by alcoholytic ring-opening have been recently reported.[3] The mechanisms of these amine catalyzed reactions are still unknown. It is desirable to corroborate the stereoselectivity with computational tools in order to understand the role of the catalyst in the enantioselectivity and assist the design of chiral catalysts which will exibit high levels of stereocontrol.

1.2. Catalytic Asymmetric Synthesis with Cinchona Alkaloids

The overall utility of asymmetric catalysts can be compared by examining 3 main criteria:

i. the variety of reactions that the catalyst can promote
ii. the availability of both enantiomeric antipodes of the catalyst at a reasonable price
iii. the stability of the catalyst.

Cinchona alkaloids fulfill all of these criteria making them one of the most powerful catalysts to date. The family of cinchona alkaloids consists of two pseudoenantiomeric pairs, including cinchonine, cinchonidine, quinine and quinidine. The cinchona alkaloids have found wide use in everything from food flavorings to the treatment of malaria.

Due to their widespread use, all four members are readily available in large quantities from most chemical suppliers. The cinchona alkaloids and their derivatives are benchtop stable, unlike many of the inorganic catalysts, withstanding oxygen, water and moderate amounts of light. The aromatic ring system is a quinoline and the bicyclic ring system is called a quinuclidine.(Figure 1.1.)

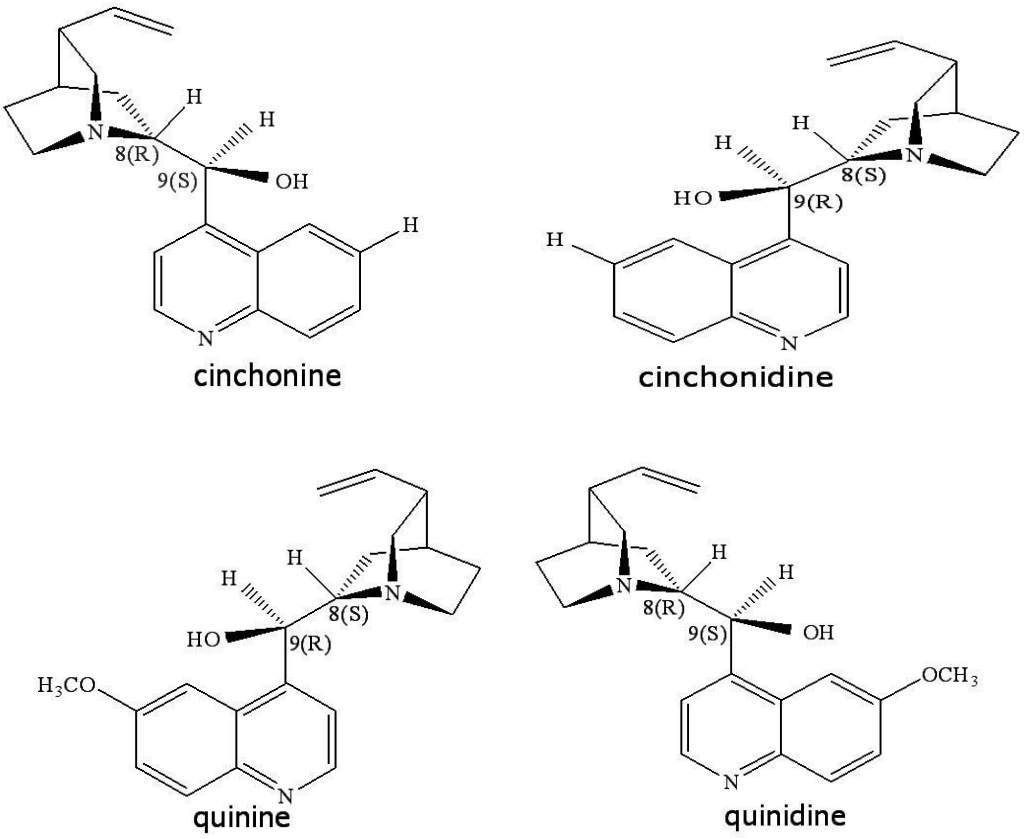


Figure 1.1. The derivatives of cinchona alkaloids

Addition of catalytic amounts of cinchona alkaloid to the reaction mixture leads to preferential reaction or formation of one enantiomer which results in stereoselectivity.

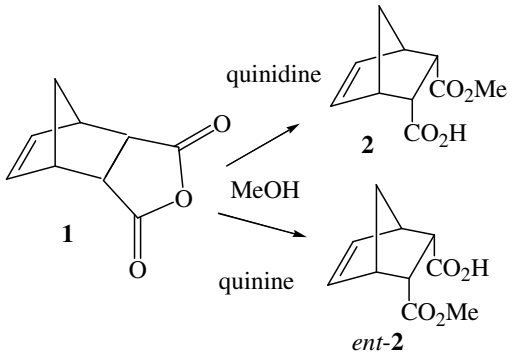


Figure 1.2. Stereoselective hydrolysis of meso cyclic anhydrides

There is a specific interaction of the alkaloid with the reactant molecule, leading to energetic favoring of one diastereomeric complex over the other. This interaction depends on the conformation of the alkaloid itself. There are three important dihedral angles which determine the conformation of a cinchona alkaloid. (Figure 1.3.)

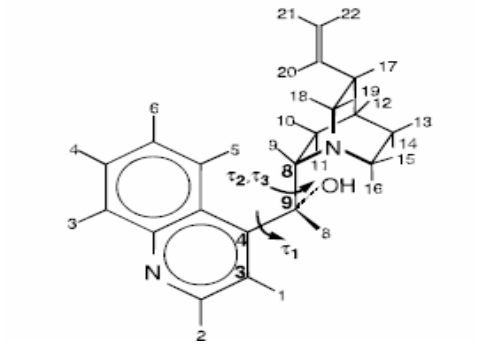


Figure 1.3. Cinchonidine atom numbering and definition of τ1, τ2 and τ3 dihedral angles

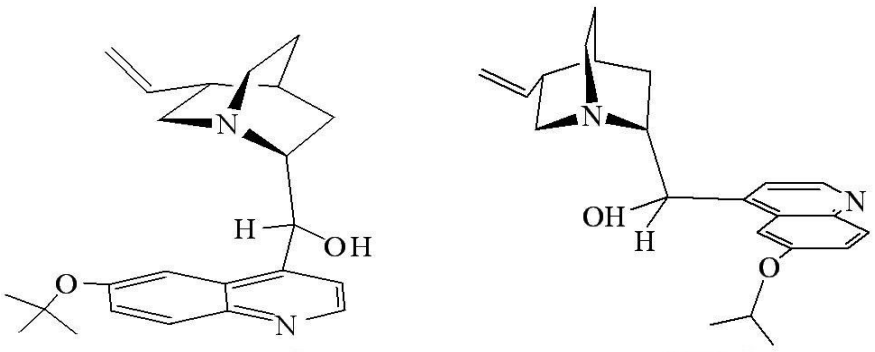
τ1 : C3-C4-C9-C8

τ2: C4-C9-C8-N

τ3: C9-H8-C8-H9.

The cinchona alkaloid conformers are found mainly in two conformations; open and closed. If the lone pair of electrons on the quinuclidine N points towards the quinoline ring, the conformation is referred to as the closed conformation. If the lone pair of electrons on

the quinuclidine N point away from the quinoline ring, the conformation is referred to as the open conformation.



Closed conformation Open conformation

Figure 1.4. Open and closed conformations of cinchonidine

In the two dimensional conformation subspace of τ1 and τ2, six minima corresponding to six conformers exist on the potential energy surface. The calculated dihedral angles for these six minimum energy conformers of cinchonidine are displayed in Table 1.1[19-20]

Table 1.1 Dihedral angles for six conformers of cinchonidine
(B3LYP/6-31G*)

	Closed(1)	Closed(2)	Open(3)	Open(4)	Open(5)	Open(6)
τ1	-107.0	80.4	101.4	-89.3	85.7	-98.7
τ 2	57.5	65.3	153.6	150.1	-48.6	-54.9
τ 3	-176.8	-172.5	-78.3	-77.5	76.2	74.0

The structures of all six conformers were fully optimized with B3LYP/ 6-31G*[19-20].

The four most stable conformers are identified and their relative electronic energies are calculated:

Table 1.2 Relative electronic energies (kcal/mol) of conformers of cinchonidine (B3LYP/6-31G*)

	Closed(1)	Closed(2)	Open(3)	Open(4)
Energies	1.43	2.14	0.00	3.33

According to the table the most stable conformation of the cinchonidine is the Open(3) conformation.(Figure1.5.)

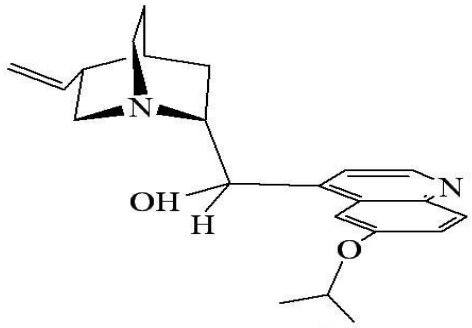


Figure 1.5. The open (3) conformation of cinchonidine

2. EXPERIMENTAL BACKGROUND

The asymmetric desymmetrization (AD) reaction of *meso* compounds by enzymatic[4] and nonenzymatic[3] methods has proven to be a powerful strategy in asymmetric synthesis, because it can provide access to a wide variety of functionalized chiral building blocks for the asymmetric synthesis of many targets [4] (Figure 2.1).

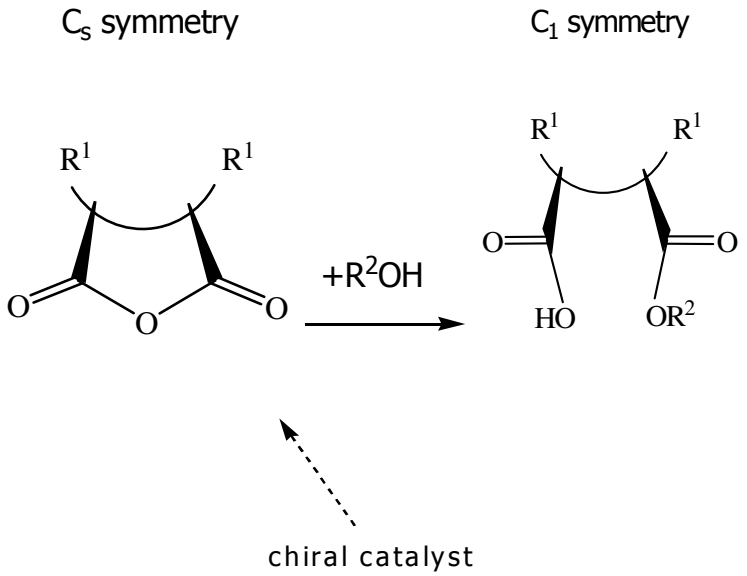


Figure 2.1. Desymmetrization of *meso* anhydrides and diesters.

The asymmetric desymmetrization of *meso* cyclic anhydrides by direct ring-opening with enantiomerically pure alcohols, amines and other nucleophiles has been shown to proceed with high levels of diastereoselectivity.[5] This strategy is limited because stoichiometric quantities of the chiral nucleophile are required, and additional chemical steps must be employed for removal of the chiral group. The enantioselectivity in enzyme-catalyzed hydrolyses is often very high.[6] However, most of the time only one enantiomer of the product can be obtained directly. Recent advances in the development of nonenzymatic catalysts such as chiral tertiary amines for the AD reactions of *meso* cyclic anhydrides by alcoholic ring-opening have been examined by Spivey *et al.*[1] The first nonenzymatic,

catalytic process was reported by Oda and co-workers in 1985 who found that cinchona alkaloids catalyzed the methanolytic AD reaction of cis-dimethylglutaric anhydride.[7]

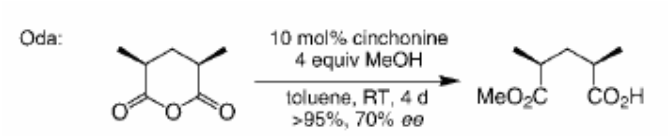


Figure 2.2. The reaction reported by Oda and co-workers

Aitken and co-workers have reported a similar procedure catalyzed by cinchonine in which a *meso* epoxy anhydride was converted into a lactone.[6]

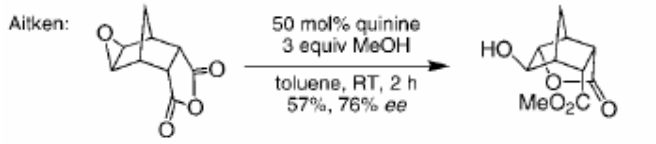


Figure 2.3. The reaction reported by Aitken and co-workers

Two chiral Lewis acid-based protocols for the AD of *meso* cyclic anhydrides were also developed during the 1990s by the groups of Fujisawa[9] and Seebach[10] who utilized a cinchonidine, Et_2Zn complex and diisopropoxytitanium TADDOL-ates, respectively (Figure 2.4.).

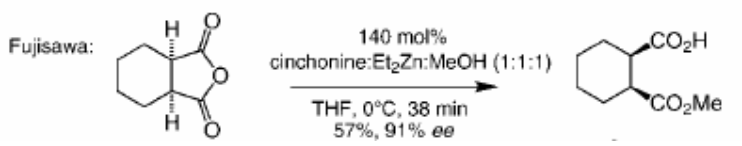


Figure 2.4.The reaction reported by Fujisawa and Seebach using Et_2Zn complex

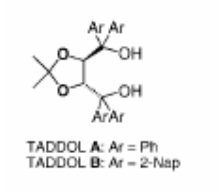


Figure 2.5. The structure of TADDOL

In 1999, Bolm and co-workers[11] developed another enantioselective methanolysis protocol mediated by quinidine

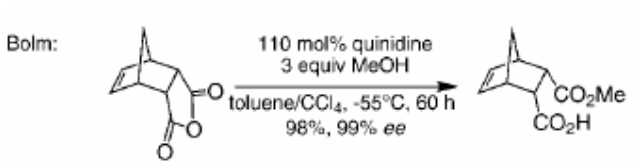
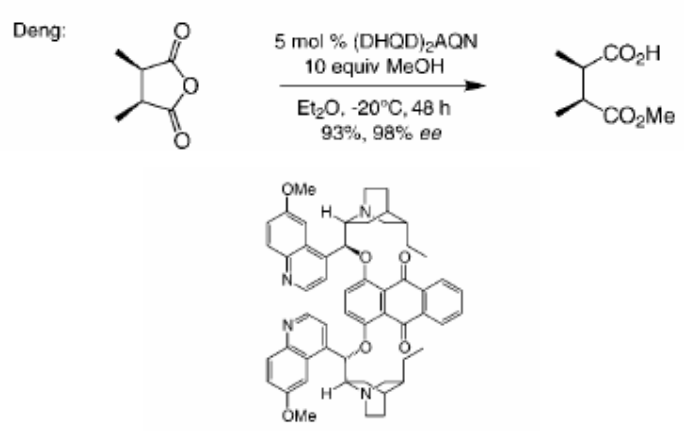


Figure 2.6.The reaction reported by Bolm and co-workers

Deng and co-workers found that the dihydrocinchonidine-based catalyst $(DHQD)_2AQN$ mediated the formation of methyl hemiesters.[12] The corresponding dihydrocinchonine-based catalyst $(DHQ)_2AQN$ provided the antipodal products with comparable enantioselectivities.(Figure 2.7.)



bis-dihydrocinchonidine derivative $(DHQD)_2AQN$

Figure 2.7. Desymmetrization of *meso* cyclic anhydrides mediated by bis-cinchona derivatives.

Deng and coworkers achieved the asymmetric methanolysis of various *meso* cyclic anhydrides using modified bis-cinchona alkaloids as catalysts. A number of ethers of cinchona alkaloids were developed by Sharpless and Corey and their co-workers in their investigations of the asymmetric OsO_4-catalyzed dihydroxylation of simple olefins.[13-15]

3. ALTERNATIVE HYDROLYSIS MECHANISMS

The catalytic effect of amines in asymmetric synthesis has been the subject of many recent investigations.[16-17] A model to explain the stereoselectivities of reductions of activated ketones on chincona alkaloid modified platinum was recently proposed by Vayner and Houk and supported by calculations.[17a] The catalytic effect of amines has been explored theoretically by Houk *et al.*[17b] for the addition of (S)-methyl lactate to methyl phenyl ketene catalyzed by trimethylamine. In the case of amine-catalyzed acylative kinetic resolution of secondary alcohols, the reaction can proceed by the initial attack of the amine on the carbonyl (*nucleophilic catalysis*) or a base catalyzed addition of alcohol to the ketene (*general base catalysis*).

In *nucleophilic catalysis*, the nucleophilic attack by the amine nitrogen on the anhydride forms a reactive chiral acylammonium salt. Nucleophilic attack on this salt by the secondary alcohol gives the ester product and regenerates the amine.

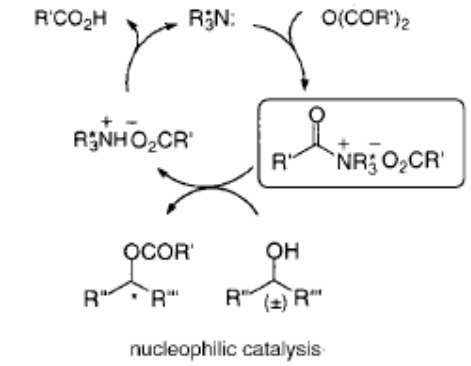


Figure 3.1. The Nucleophilic catalysis of ring opening of meso cyclic anhydrides

Aitken[8] and Bolm[11] predict that the same mechanism operates for cyclic anhydride ring-opening where an acylammonium-type intermediate is formed by nucleophilic attack of the alkaloid on the less-hindered front face of the anhydride. This intermediate is then converted to the product by a rear side attack of methanol to give the desired monoester.If the carbonyls are sterically blocked, no reaction can take place.

However,

i. Neither the quinoline nor the alpha substituted quinuclidine nitrogens of cinchona alkaloids are expected to be very nucleophilic, as nucleophilicity is strongly attenuated by steric factors.
ii. For cyclic anhydrides the leaving carboxylate group has a high effective molarity which makes the equilibrium between anhydride and acylammonium salt very unfavorable towards the latter.
iii. In nonpolar solvents, as used in the cinchona catalyzed reactions, even the position of the equilibrium between the highly nucleophilic amine 4-dimethylaminopyridine and the acylic anhydride Ac_2O is unfavorable, this suggests that an extremely low concentration of acylammonium salt will be present and won't be kinetically useful.

In the *general base catalysis* as proposed by Oda[7] and co-workers the cinchona-catalyzed ring-opening of meso anhydrides involves the quinuclidine nitrogen acting as a chiral general base rather than a nucleophile. Oda and co-workers[9] found that the cinchonine-catalyzed ring-opening of *cis*-2,4-dimethylglutaric anhydride by methanol in toluene displayed a kinetic isotope effect (k_{MeOH}/k_{MeOD}) of 2.3, this value being greater than would be expected for nucleophilic catalysis. They proposed that cinchona-catalyzed ring-opening of *meso* anhydrides involves the quiniclidine nitrogen acting as a chiral general base rather than a nucleophile. On the other hand, Aitken[8] and Bolm[11] claim the nucleophilic catalysis to operate for cyclic anhydride ring opening.

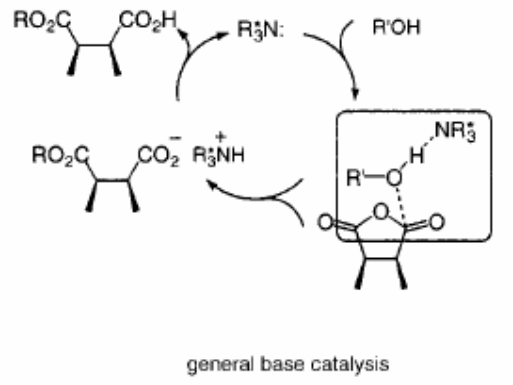


Figure 3.2.General Base Catalysis of Ring Opening of Meso Cyclic Anhydrides

Recently, Vayner modeled the addition of methanol to phenylalkylketenes catalyzed by tertiary amines and "planar-chiral" nitrogen based nucleophiles.[18] In this study, B3LYP/6-31G* calculations on the reactions of methanol with succinic anhydride, using cinchonidine as a model base, will map out energetics for both nucleophilic and base-catalyzed reations. Subsequently, modeling with the whole cinchona alkaloid will be carried out to determine the origins of stereoselectivity.

4. METHODOLOGY

All the geometry optimizations have been carried by using the density functional theory (DFT)[21-22] B3LYP/6-31G*. Harmonic frequencies have been computed in order to identify the stationary points as minima (with all real frequencies) or transition states (with only one imaginary frequency) and to obtain thermal energy and entropy contributions. That the optimized transition states connect the desired minima is verified by intrinsic reaction coordinate calculations. All calculations have been carried out using the Gaussian 98 program[23].

The energetic results are reported as the change in the electronic energy at 0 K (ΔE_0), sum of the electronic energy and zero point energy at 0 K (ΔE_{0+ZPE}), electronic energy at

298 K (ΔE^o_{298}), enthalpy at 298 K (ΔH^o_{298}) and Gibbs free energy at 298 K (ΔG^o_{298}). The change in entropy is referred to as ΔS^o_{298}.

4.1. Density Functional Theory

The DFT functional used is the Becke 3-parameter-Lee-Yang-Parr exchange-correlation functional (B3LYP) [24-25] as implemented in the Gaussian 98 package.

The density functional theory is based on the Kohn-Hohenberg theorems proposed in 1964 [21-22]. The first theorem states that the electron density $\rho(r)$ determines the external potential $v(r)$, i.e. the potential due to the nuclei. The second theorem introduces the variational principle. Hence, the electron density can be computed variationally and the position of nuclei, energy, wave function and other related parameters can be calculated [21-22].

The electron density is defined as:

$$\rho(x) = N \int ... \int \left|\Psi(x_1, x_2, ...x_n)\right|^2 dx_1 dx_2 ... dx_n \tag{3.1}$$

where x represents both spin and spatial coordinates of electrons.

The electronic energy can be expressed as a functional of the electron density:

$$E[\rho] = \int v(r)\rho(r)dr + T[\rho] + V_{ee}[\rho] \tag{3.2}$$

where $T[\rho]$ is the kinetic energy of the interacting electrons and $V_{ee}[\rho]$ is the interelectronic interaction energy. The electronic energy may be rewritten as:

$$E[\rho] = \int v(r)\rho(r)dr + T_s[\rho] + J[\rho] + E_{xc}[\rho] \tag{3.3}$$

with $J[\rho]$ being the coulomb energy, $T_s[\rho]$ being the kinetic energy of the non-interacting electrons and $E_{xc}[\rho]$ is the exchange-correlation energy functional. The exchange-correlation functional is expressed as the sum of an exchange functional $E_x[\rho]$ and a

correlation functional $E_c[\rho]$, although it contains also a kinetic energy term arising from the kinetic energy difference between the interacting and non-interacting electron systems.

In the Kohn-Sham density functional theory, a reference system of independent non-interacting electrons in a common, one-body potential V_{KS} yielding the same density as the real fully-interacting system is considered. More specifically, a set of independent reference orbitals ψ_i satisfying the following independent particle Schrödinger equation are imagined:

$$\left[-\frac{1}{2}\nabla^2 + V_{KS}\right]\psi_i = \varepsilon_i\psi_i \tag{3.4}$$

with the one-body potential V_{KS} defined as:

$$V_{KS} = v(r) + \frac{\partial J[\rho]}{\partial \rho(r)} + \frac{\partial E_{xc}[\rho]}{\partial \rho(r)} \tag{3.5}$$

$$V_{KS} = v(r) + \frac{\rho(r')}{|r - r'|}dr' + v_{xc}(r) \tag{3.6}$$

where $v_{xc}(r)$ is the exchange-correlation potential. The independent orbitals ψ_i are known as Kohn-Sham orbitals and give the exact density by:

$$\rho(r) = \sum_i^N |\psi_i|^2 \tag{3.7}$$

if the exact form of the exchange-correlation functional is known. However, the exact form of this functional is not known and approximate forms are developed starting with the local density approximation (LDA). This approximation gives the energy of a uniform electron gas, i.e. a large number of electrons uniformly spread out in a cube accompanied with a

uniform distribution of the positive charge to make the system neutral. The energy expression is:

$$E[\rho] = T_s[\rho] + \int \rho(r) v(r) dr + J[\rho] + E_{xc}[\rho] + E_b \tag{3.8}$$

where E_b is the electrostatic energy of the positive background. Since the positive charge density is the negative of the electron density due to uniform distribution of particles, the energy expression is reduced to:

$$E[\rho] = T_s[\rho] + E_{xc}[\rho] \tag{3.9}$$

$$E[\rho] = T_s[\rho] + E_x[\rho] + E_c[\rho] \tag{3.10}$$

The kinetic energy functional can be written as:

$$T_s[\rho] = C_F \int \rho(r)^{5/3} dr \tag{3.11}$$

where C_F is a constant equal to 2.8712. The exchange functional is given by:

$$E_x[\rho] = -C_x \int \rho(r)^{4/3} dr \tag{3.12}$$

with C_x being a constant equal to 0.7386. The correlation energy, $E_c[\rho]$, for a homogeneous electron gas comes from the parametrization of the results of a set of quantum Monte Carlo calculations.

The LDA method underestimates the exchange energy by about 10 per cent and does not have the correct asymptotic behavior. The exact asymptotic behavior of the exchange energy density of any finite many-electron system is given by:

$$\lim_{x\to\infty} U_x^{\sigma} = -\frac{1}{r} \tag{3.13}$$

U_x^{σ} being related to $E_x[\rho]$ by:

$$E_x[\rho] = \frac{1}{2}\sum_{\sigma}\int \rho_{\sigma} U_x^{\sigma} dr \tag{3.14}$$

A gradient-corrected functional is proposed by Becke:

$$E_x = E_x^{LDA} - \beta\sum_{\sigma}\int \rho_{\sigma}^{4/3} \frac{x_{\sigma}^2}{1+6\beta x_{\sigma}\sinh^{-1} x_{\sigma}} dr \tag{3.15}$$

where σ denotes the electron spin, $x_{\sigma} = \frac{|\nabla\rho_{\sigma}|}{\rho_{\sigma}^{4/3}}$ and β is an empirical constant (β=0.0042). This functional is known as Becke88 (B88) functional [26].

The adiabatic connection formula connects the non-interacting Kohn-Sham reference system (λ=0) to the fully-interacting real system (λ=1) and is given by:

$$E_{xc} = \int_0^1 U_{xc}^{\lambda} d\lambda \tag{3.16}$$

where λ is the interelectronic coupling-strength parameter and U_{xc}^{λ} is the potential energy of exchange-correlation at intermediate coupling strength. The adiabatic connection formula can be approximated by:

$$E_{xc} = \frac{1}{2}E_x^{exact} + \frac{1}{2}U_{xc}^{LDA} \tag{3.17}$$

since $U_{xc}^{0} = E_x^{exact}$, the exact exchange energy of the Slater determinant of the Kohn-Sham orbitals, and $U_{xc}^{1} = U_{xc}^{LDA}$ [27].

The closed shell Lee-Yang-Parr (LYP) correlation functional [25] is given by:

$$E_c = -a\int \frac{1}{1+d\rho^{-1/3}}\left\{\rho + b\rho^{-2/3}\left[C_F\rho^{5/3} - 2t_w + (\frac{1}{9}t_w + \frac{1}{18}\nabla^2\rho)\right]e^{-c\rho^{-1/3}}\right\}dr \qquad (3.18)$$

where

$$t_w = \frac{1}{8}\frac{|\nabla\rho(r)|^2}{\rho(r)} - \frac{1}{8}\nabla^2\rho \qquad (3.19)$$

and a=0.04918, b=0.132, c=0.2533 and d=0.349.

The mixing of LDA, B88, E_x^{exact} and the gradient-corrected correlation functionals to give the hybrid functionals [24] involves three parameters:

$$E_{xc} = E_{xc}^{LDA} + a_0\left(E_x^{exact} - E_x^{LDA}\right) + a_x\Delta E_x^{B88} + a_c\Delta E_c^{non-local} \qquad (3.20)$$

where ΔE_x^{B88} is the Becke's gradient correction to the exchange functional. In the B3LYP functional, the gradient-correction ($\Delta E_c^{non-local}$) to the correlation functional is included in LYP. However, LYP contains also a local correlation term which must be subtracted to yield the correction term only:

$$\Delta E_c^{non-local} = E_c^{LYP} - E_c^{VWN} \qquad (3.21)$$

where E_c^{VWN} is the Vosko-Wilk-Nusair correlation functional, a parametrized form of the LDA correlation energy based on Monte Carlo calculations. The empirical coefficients are a_0=0.20, a_x=0.72 and a_c=0.81[24].

4.2. Basis Sets

In the present study the geometry optimizations were carried out with B3LYP/6-31G*. The non-scaled frequencies were used to compute zero-point energies (ZPE). All calculations were performed with Gaussian 03.

The 6-31G* basis set for the first row atoms describes the core orbitals by a combination of six primitive Gaussian functions and the valence shell is split into two orbitals consisting of three and one primitive Gaussian functions. This set is augmented by a set of d orbitals. For the hydrogen atoms 6-31G* basis set uses two sets of s orbitals containing three and one primitive Gaussian functions.

5. COMPUTATIONAL STRATEGY

The achiral tertiary amine-catalyzed alcoholysis of *meso* anhydrides is modeled to determine the mechanism of the catalysis of the addition of methanol to anhydrides. The "general base catalysis" (**BC**) (Figure 5.1) and the "nucleophilic catalysis" (**NC**) (Figure 5.2) pathways are adopted for the addition of methanol to *cis*-dimethylsuccinic anhydride in the presence of trimethylamine. The activation energies (Ea) are calculated by subtracting Hartree energies of the transition states from reactant compounds and converting this difference to kcal/mol by multiplying with 627.51.The Ea+ZPE energies are calculated in the same manner as described above but by adding zero correction factors to activation energies of the compounds.

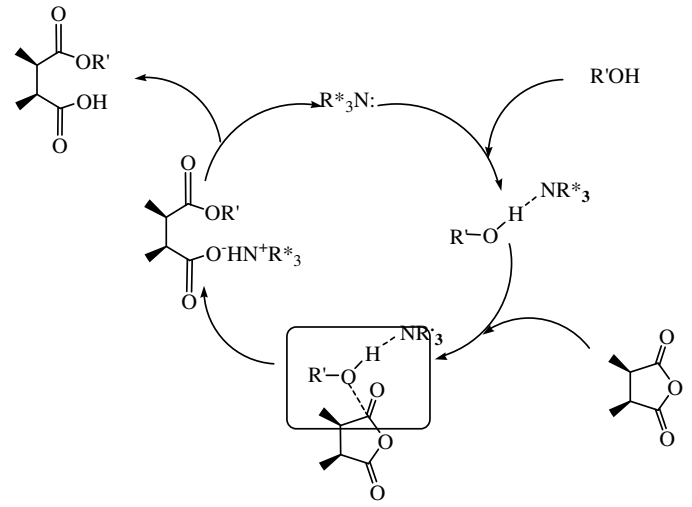


Figure 5.1. General base catalysis (BC)

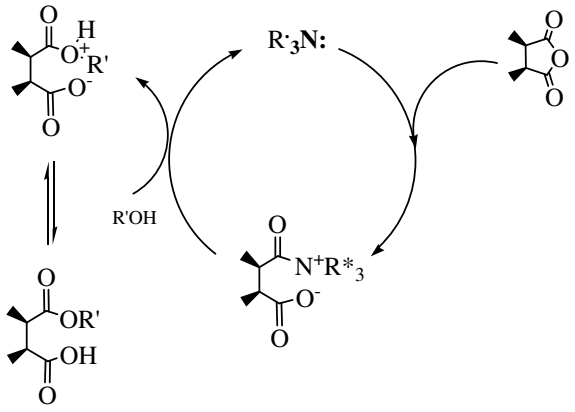


Figure 5.2. Nucleophilic catalysis (NC)

Stationary points (intermediates and transition structures) are located along both reaction paths. The evaluation of the energy barriers for the rate determining steps provides an understanding of these two mechanisms.

The reaction path modeled for *cis*-dimethylsuccinic anhydride with trimethyl amine is reconsidered in the presence of cinchona alkaloids as catalyst to determine the selectivitiy in the presence of cinchona alkaloids. Both the "general base catalysis" (**BC**) and the "nucleophilic catalysis" (**NC**) pathways are modelled by using cinchona alkaloids to determine the activation barriers in order to predict the stereoselectivity and the reaction mechanism of the ring opening of meso cyclic anhydrides by cinchona alkaloids.

The differentiation between the enantiotopic carbonyl groups by the alkaloids is based on the recognition of certain structural components in the anhydride morphology. The most stable conformation of **cinchonidine** which has been identified as "Open (3)" in a non-polar medium[21], will be used for the conformation of the alkaloid **cinchonidine** and the proposed reaction paths are simulated for *cis*-dimethylsuccinic anhydride in the presence of **cinchonidine** and **cinchonine**. The following experiemental results reported by Bolm *et al.*[11] will be modeled.

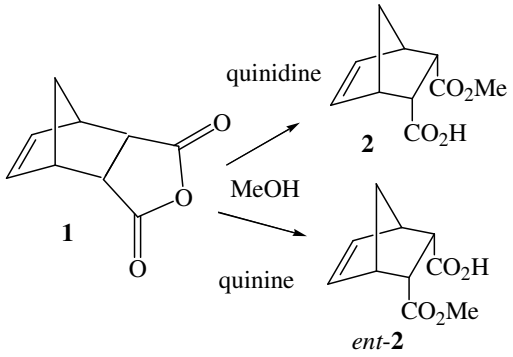


Figure 5.3. Stereoselectivity by cinchona alkaloids

According to the experimental results of Bolm *et al.*[11] compound **2** is the dominant enantiomer in the presence of **cinchonidine** and *ent*-**2** forms in the presence of **cinchonine**. Thus, the behaviour of cis-dimethyl succinic anhydride in the presence of **cinchonidine** and **cinchonine** will be tested along the alcoholysis reaction.

The experimental results with varying solvent polarities suggest that a certain alkaloid conformation is mainly responsible for the asymmetric induction in the ring opening reaction and that a less-pronounced stabilization of this particular conformation by another solvent reduces the selectivity. The influence of the solvent on the **cinchonidine**-mediated ring-opening of *cis*-dimethylsuccinic anhydride will be studied.

The modeling is performed with solvent cavity models that mimic:

- a non polar solvent (toluene);
- a non polar solvent (CCl_4)

Since the experimental results[11] suggest a tremendous decrease in the ee(per cent) due to the polarity of the solvent, this theoretical approach will allow us to understand how the polarity of the solvent affects the stereoselectivity.

6. RESULTS AND DISCUSSION

6.1 Nomenclature

The nomenclature used for the molecules in the nucleophilic catalysis pathway starts with an **N**, followed by one of the following suffixes; a **G** if it represents a ground state and **TS** if it represents a transition state. The compounds used on the base catalyzed pathway are designated by the prefix **B.**

The prefixes **N** and **B** are followed by the numbers 1, 2 and 3 corresponding to the first, second and third ground states along the reaction pathway. The suffix **TS** is followed by the numbers 1 and 2 corresponding to the first and the second transition states of the reaction pathway respectively.

The letters **t** and **c** are used to indicate that the reaction is modelled by using trimethylamine or members of the cinchona alkaloid family; **cqn** is used to represent cinchonine and **cqd** is used to represent cinchonidine. The letter **s** indicates the presence of cis-dimethyl substituents on succinic anhydride. The letters **sos** are used to indicate that the cis-dimethyl groups are bound from the other side of the succinic anhydride. The letters **wm** are used to show that the compounds are stabilized by two additional moles of methanol.

Finally the suffixes **RS** and **SR** are used to indicate the stereochemistry of the compounds. The first letter labels the chiral carbon adjacent to the acid side, the second letter labels the chiral carbon adjacent to the ester side.

For example, **NTS1-cqn-s(RS)** is the first transition state of the nucleophilic pathway which is modelled by using a cinchona alkaloid; cinchonine as the chiral catalyst with cis-dimethylsuccinic anhydride and both the transition states and the products have **RS** stereochemistry.

6.2 Base Catalyzed Mechanism For a Model Compound in the presence of Trimethylamine

The base catalyzed mechanism for the ring opening reactions of meso cyclic anhydrides is first modelled by using succinic anhydride (without substituents), methanol and trimethylamine as the reactants (Figure 6.2.1.a and Figure 6.2.1.b).

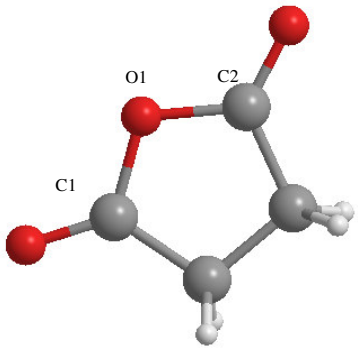


Figure 6.2.1.a. Succinic anhydride

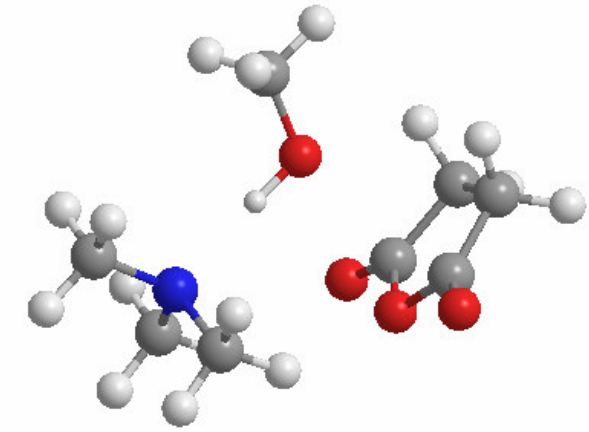


Figure 6.2.1.b Succinic anhydride + methanol + trimethylamine complex

The first transition state and potential energy diagram for the reaction are shown in Figure 6.2.2.a and Figure 6.2.2.b.

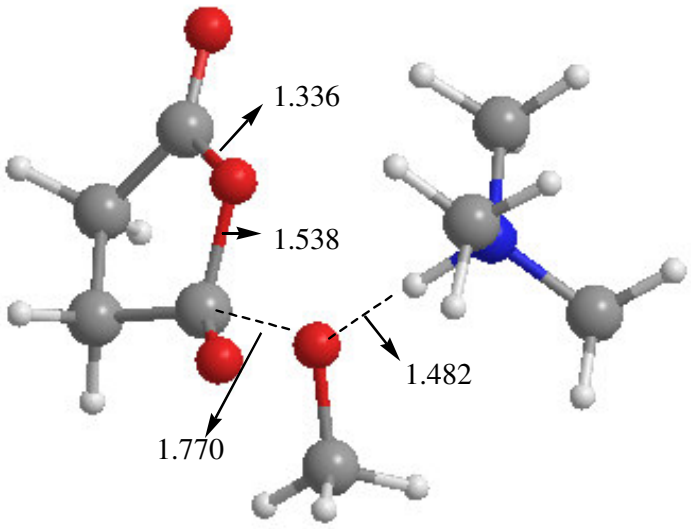


Figure 6.2.2.a. The first transition state for base catalyzed mechanism (BTS1-t)

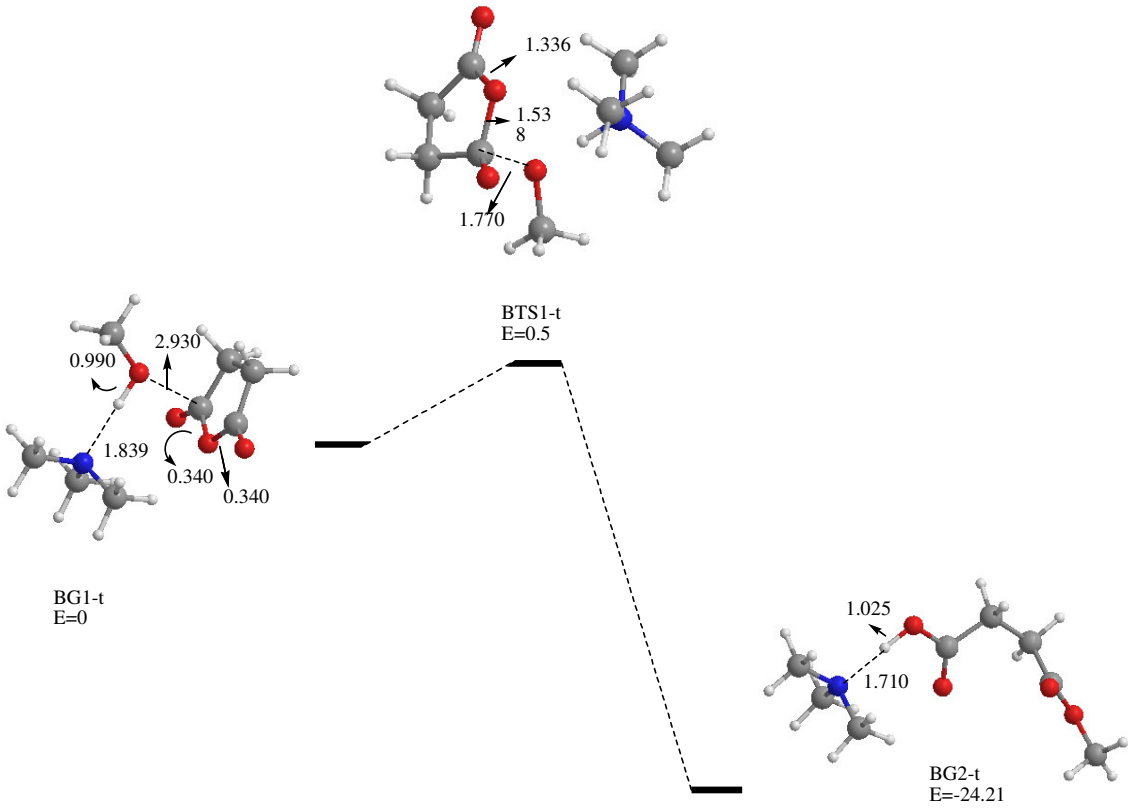


Figure 6.2.2.b.Potential Energy Diagram for the base catalyzed pathway by using succinic anhydride

The first step in general base catalysis is the formation of a complex between succinic anhydride and methanol. This complex is stabilized by formation of a hydrogen bridge of 1.84 Å between the N of trimethylamine and the H of methanol. The next step on the pathway is a nucleophilic attack by trimethylamine-methanol complex to one of the carbonyl carbons (C1) of succinic anhydride forming the first transition state BTS1-t. The energy required for that transition is 0.5 kcal/mol. In first transition state the carbonyl carbon and O bond of succinic anhydride elongates as the methanol comes closer to that carbonyl carbon. This transition state leads to formation of BG2-t which is a hemiester of succinic anhydride by giving off 24.21kcal/mol.

The second reaction model involves the same reactants as in the first case but instead of succinic anhydride, cis-dimethyl succinic anhydride (Figure 6.2.3.) is used in order to

examine the stereochemistry of the products. Two different transition states have been located each corresponding to a different steroisomer of the product.

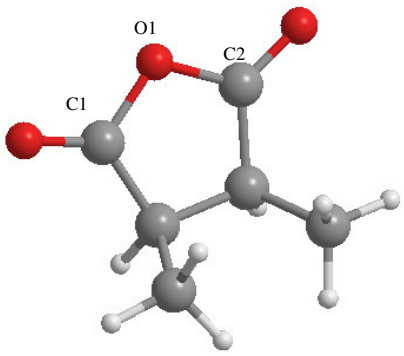


Figure 6.2.3. Cis-dimethyl succinic anhydride

The transition state and the potential energy diagram for the first transition state that leads to the formation of the SR isomer of product are shown in Figure 6.2.4.a and Figure 6.2.4.b. respectively.

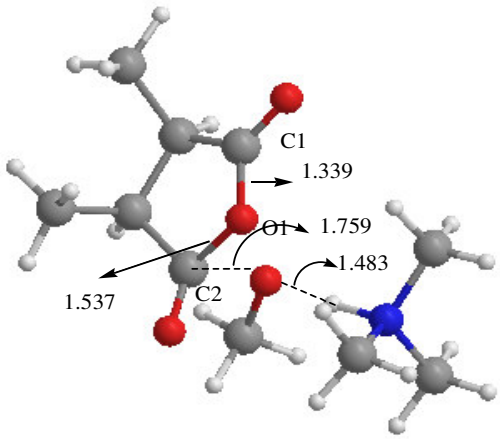


Figure 6.2.4.a.Transition state of the RS product

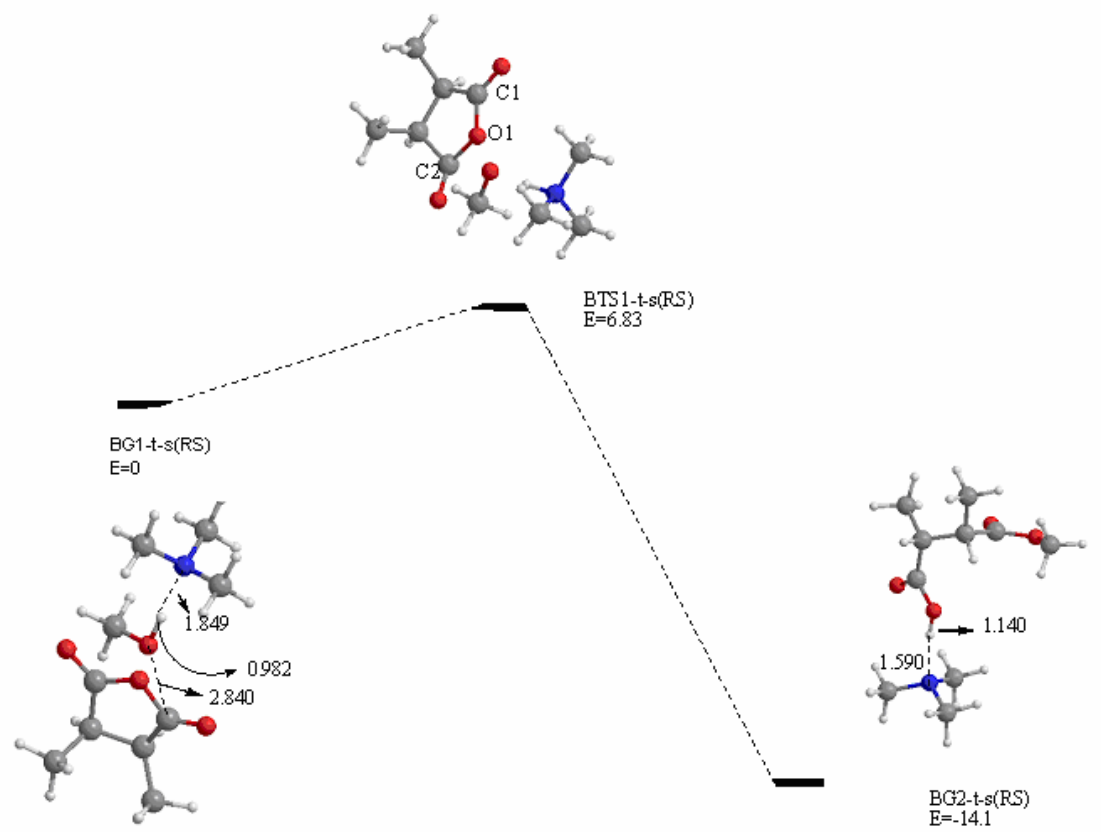


Figure 6.2.4.b Potential Energy Diagram for the RS product via base catalyzed mechanism

The first step along the reaction mechanism is the formation of the methanol-trimethylamine complex with an N-H distance of 1.849 Å and O-H distance of 0.982 Å (BG1-t-s(RS). Formation of the complex is followed by a nucleophilic attack from the O of methanol to the carbonyl carbon of cis–dimethyl succinic anhydride (BTS1-t-s(RS). The stereoselectivity of the reaction is determined in this step when trimethylamine-methanol complex attacks to either one of the carbonyl carbons. The side of this nucleophilic attack determines the stereochemistry of the final product. The transition state of this reaction is a tetrahedral intermediate with C-O distance of 1.759 Å that indicates methanol-trimethylamine complex has started to dissociate and methanol starts binding to the carbonyl carbon of cis dimethyl succinic anhydride. The ring also opens up a little with a C-O distance of 1.537 Å which is longer than normal C-O bonds. The activation energy required for the first step of the reaction is 6.83 kcal/mol. In the final step of the

mechanism the RS isomer of the product is formed and trimethylamine is pushed away with a distance of 1.61 Å, in the end it will be regenerated.

The transition state and the potential energy diagram for the SR isomer of the product are shown in Figure 6.2.5.a and Figure 6.2.5.b. respectively.

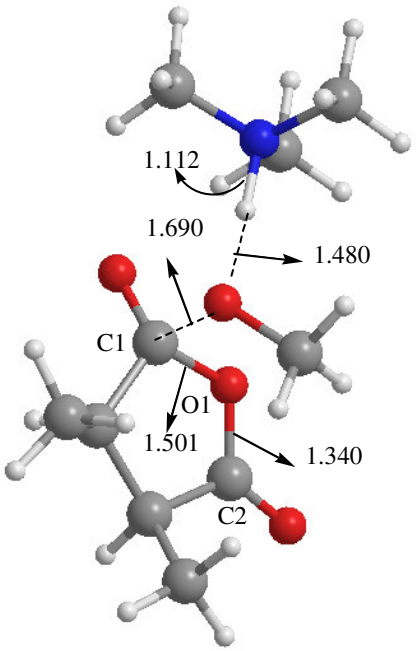


Figure 6.2.5.a.Transition state of the SR product

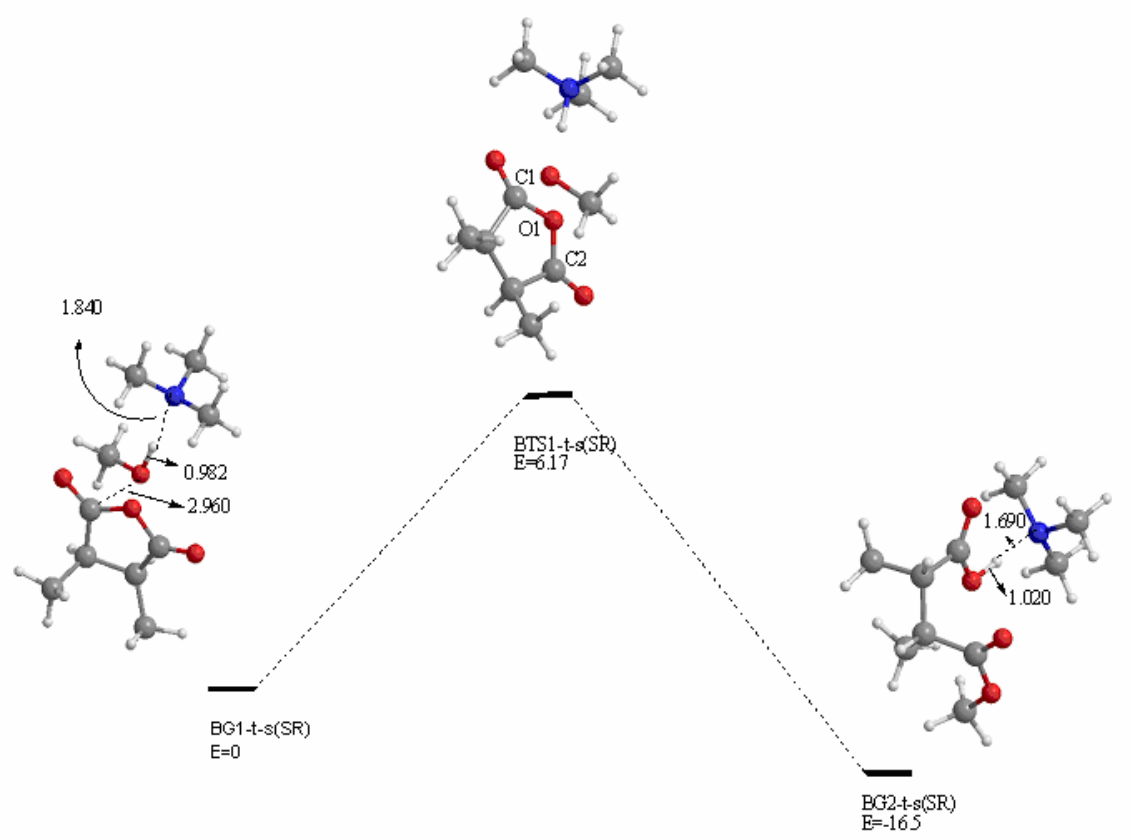


Figure 6.2.5.b. Potential Energy Diagram for the SR product via base catalyzed mechanism

In this reaction the mechanism is modelled in exactly the same way as the previous reaction with one exception. In the first ground state BG1-t-s(SR), trimethylamine-methanol complex is attacking to the other carbonyl carbon of cis-dimethyl succinic anhydride which explains the formation of SR isomer of the product. The energy barrier for that reaction is 6.17 kcal/mol.

Both of these pathways have activation energy barriers that are very close to each other. This is the main reason for the absence of stereoselectivity of ring opening of meso cyclic anhydrides in the presence of trimethylamine.

The same reactions are modelled by changing the orientation of two methyl groups in order to understand the effect of these two methyl groups on the activation barrier of the reaction. The reaction pathways are shown in Figure 6.2.6.a to 6.2.7.b.

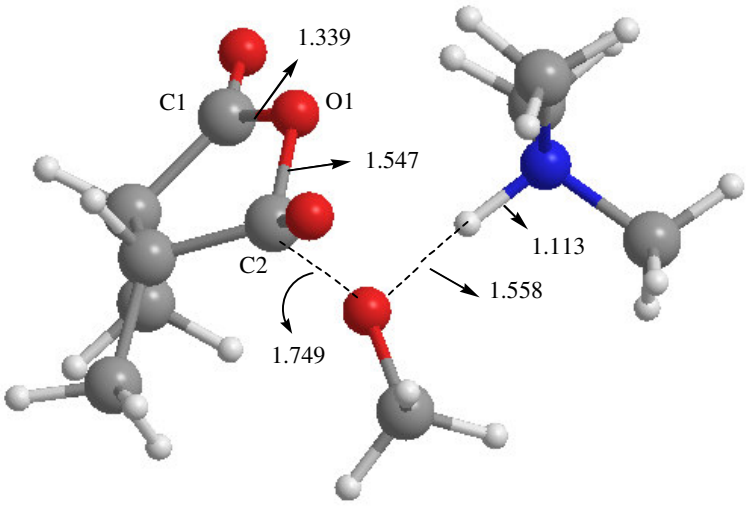


Figure 6.2.6.a Transition state of the SR product with the two methyl groups towards the reactants

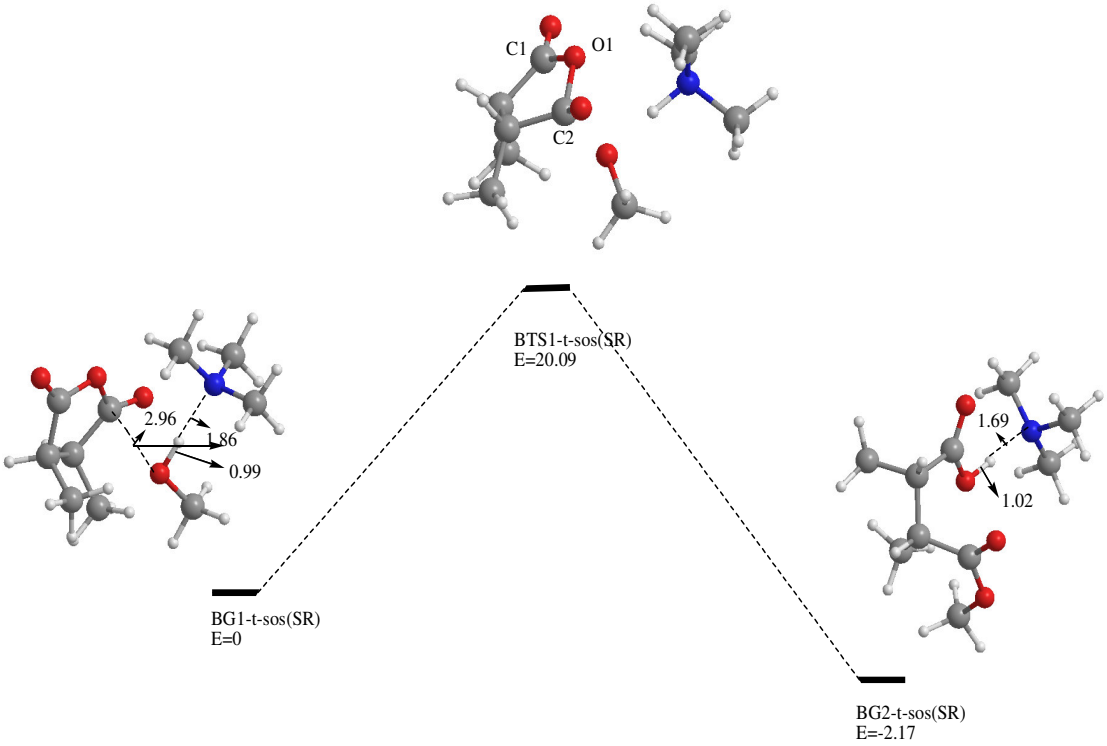


Figure 6.2.6.b Potential Energy Diagram for the SR product with the two methyl groups towards the reactants

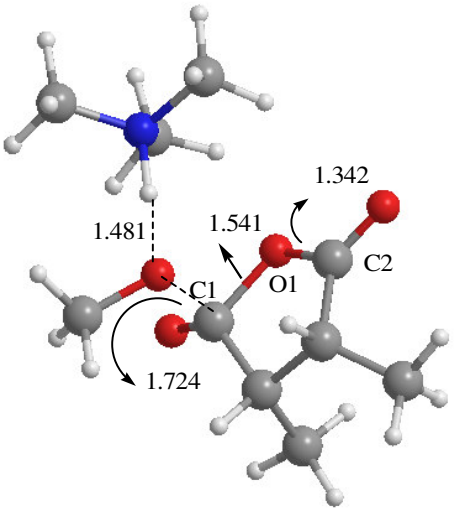


Figure 6.2.7.a. Transition state of the RS product with the two methyl groups towards the reactants

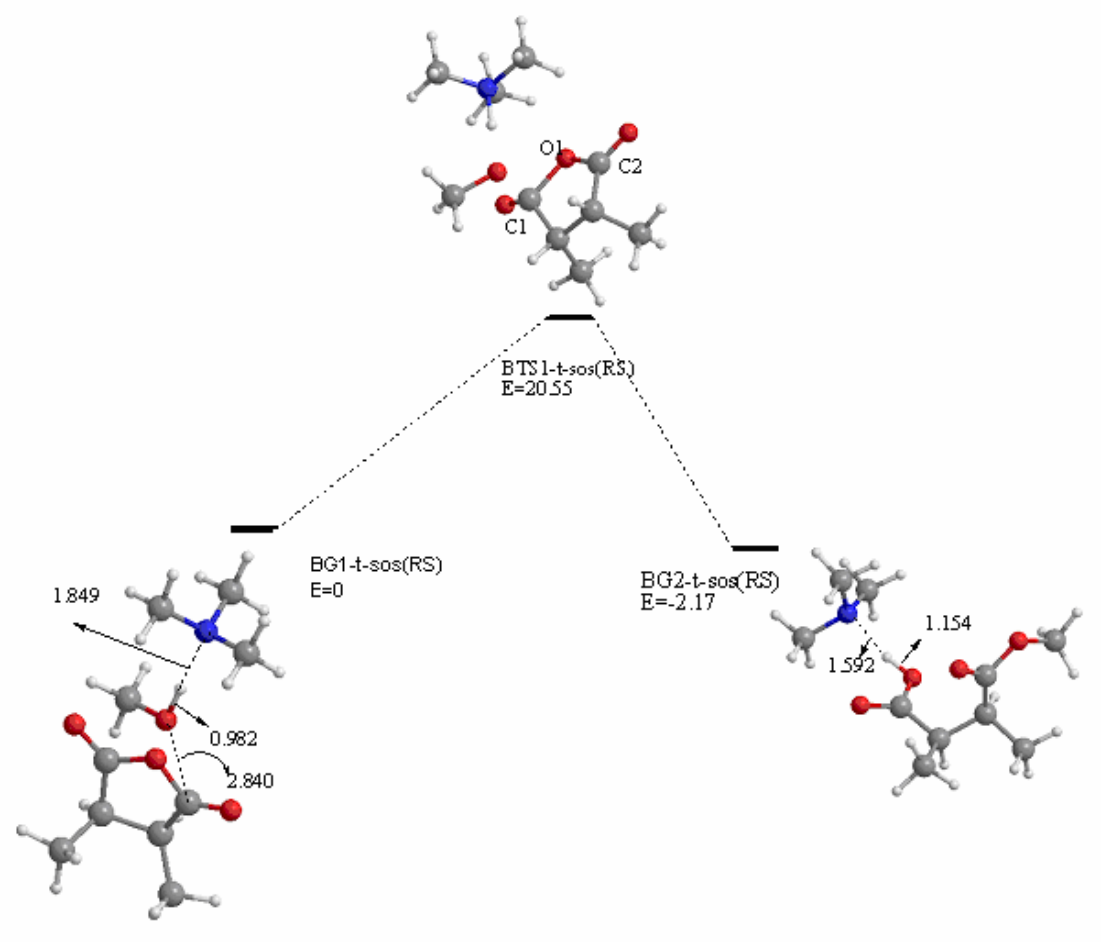


Figure 6.2.7.b Potential Energy Diagram for the RS product with the two methyl groups towards the reactants

The energies of activation barriers for both of these two reactions are higher than the reactions shown in Figure 6.4.b and Figure 6.5.b. The reason for that increase is the steric effect of these two methyl groups. Because the methyl groups are on the same side of the attack on these reactions they have a tendency to hinder the attack of methanol-trimethylamine complex.

6.3. Base Catalyzed Mechanism In the Presence of Cinchona Alkaloids

The ring opening reaction in the presence of cinchona alkaloids is modelled by using a cinchona alkaloid, cinchonidine, instead of trimethylamine for further investigation of effects of chiral catalysts on stereoselectivity. The transition state and potential energy diagram of the reaction are shown in Figure 6.3.1.a and Figure 6.3.1.b. respectively. The reaction is modelled using the same strategy as employed in reactions with trimethylamine.

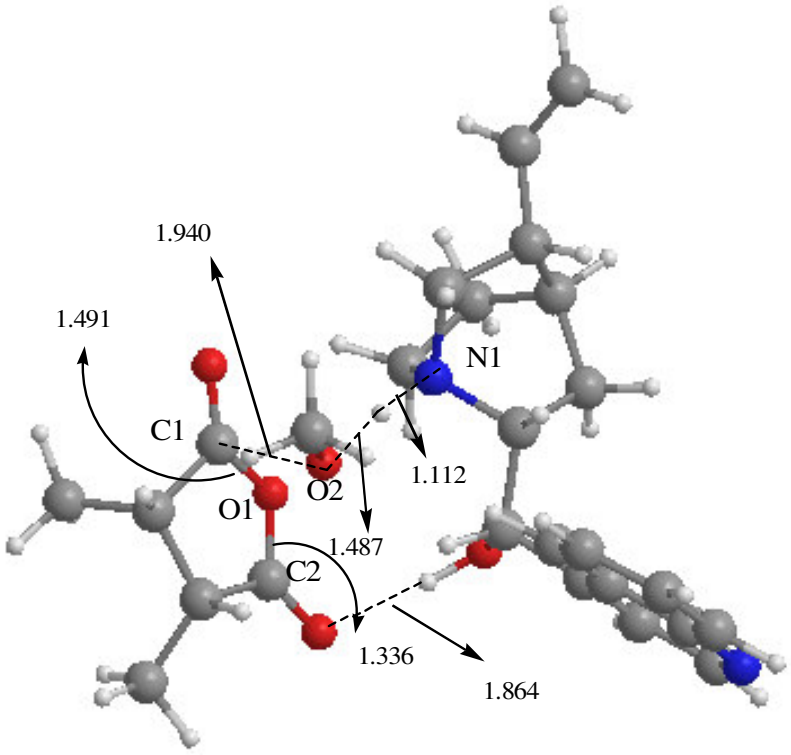


Figure 6.3.1.a. Transition state for base catalyzed mechanism with cinchona alkaloids

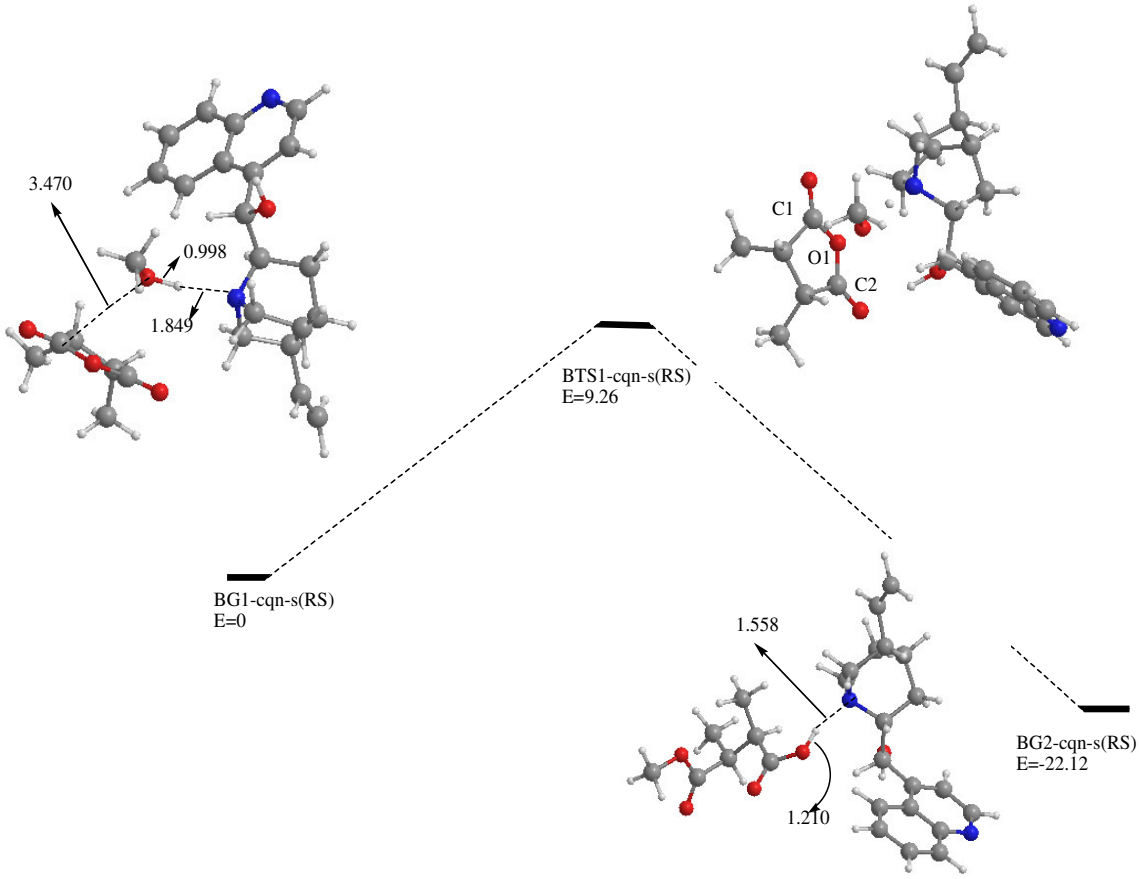


Figure 6.3.1.b. Potential Energy Diagram for base catalyzed mechanism by cinchona alkaloids

6.4 Nucleophilic Mechanism For A Model Compound

A similar approach is used to model the catalytic asymmetric desymmetrization of meso cyclic anhydrides via nucleophilic pathway. In this model, trimethylamine or cinchona alkaloid is acting as a nucleophile rather than a base. The mechanism is first modelled by using same reactants as in the base catalyzed pathway; trimethylamine, succinic anhydride and methanol. The transition state and potential energy diagram for this reaction are shown in Figure 6.4.1.a and Figure 6.4.1.b respectively.

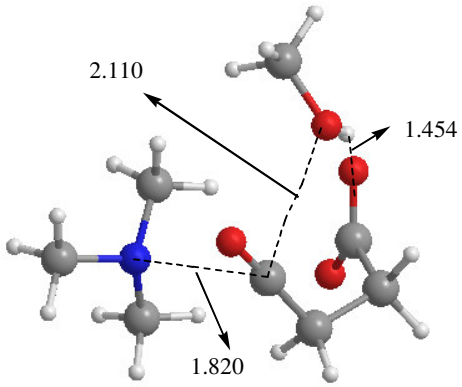


Figure 6.4.1.a The second transition state for nucleophilic mechanism by using trimethylamine

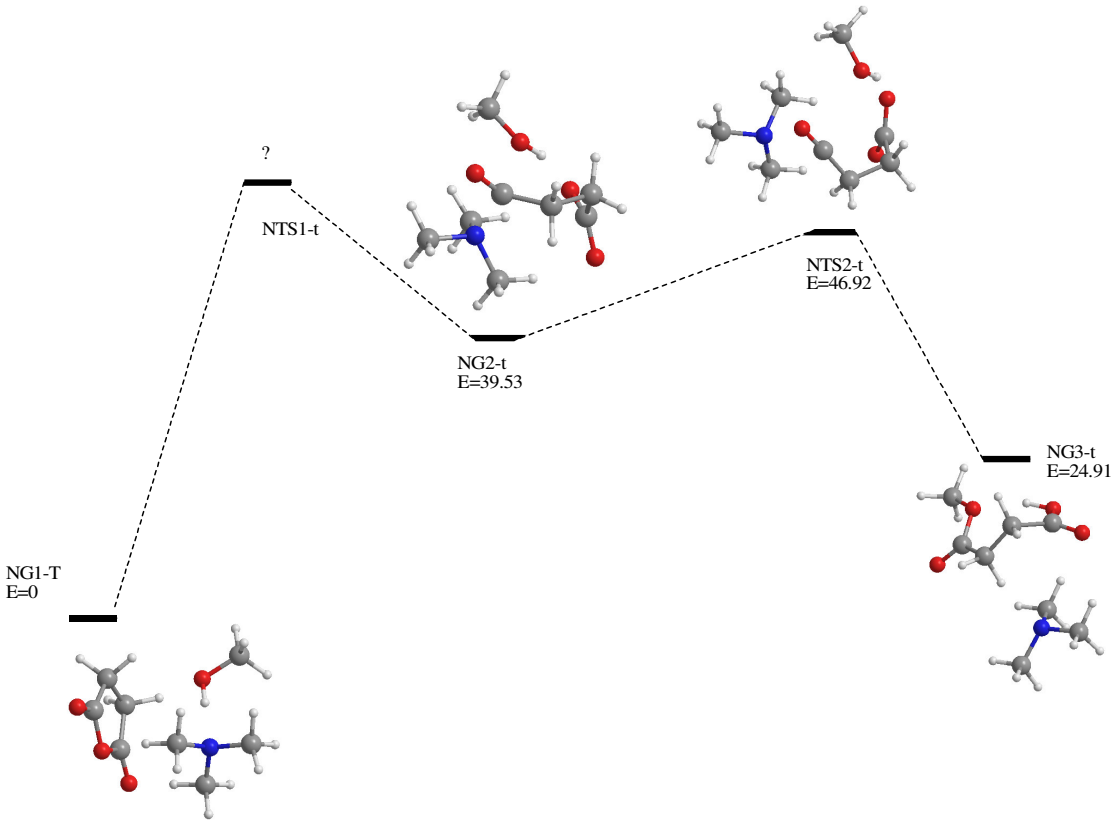


Figure 6.4.1.b Potential Energy Diagram for nucleophilic pathway by using trimethylamine

The first step in the reaction mechanism is assumed to be a nucleophilic attack by trimethylamine to one of the carbonyl carbons of succinic anhydride. In the first transition state NTS1-t; as trimethylamine approaches succinic anhydride, the bond between the carbonyl carbon which is attacked and O elongates leading to opening of the ring. Methanol is used both in NTS1-t and NG2-t , to stabilize the negative charge that is formed on the O as the ring opens. The second transition state shows first of all deprotonation of methanol as it gives its proton to the carboxylic acid end of the product and then a second nucleophilic attack by the deprotonated methanol, methoxide ion, to the C1 of succinic anhydride which now has opened up. As methoxide ion approaches C1 of anhydride it pushes away trimethylamine simultenously and in the NG3-T ground state, the product as it is formed in the base catalyzed mechanism is formed.

The first transition state NTS1-t could not be located therefore an assumption regarding the activation energy of the first transition state has been made. As it can be seen from Figure 6.4.1.b, there is 39.53 kcal/mol energy difference between the reactant and the product of the first transition state. Since the reaction is highly endothermic, the transition state must be located near the product side and it should have an energy higher than 39.53 kcal/mol. This activation energy is much more higher than the activation energy required for the base catalyzed mechanism. Therefore it can be said that according to these results the base catalyzed mechanism is preferred over the nucleophilic catalyzed mechanism when trimethyl amine is used as a catalyst.

6.5 Nucleophilic Mechanism In the Presence of Cinchona Alkaloids

The nucleophilic mechanism is modelled by using cinchona alkaloid to study the effect of cinchona alkaloid as a catalyst on the activation barrier of ring opening of meso cyclic anhydrides. The transition state and potential energy diagram of the reaction are shown in Figure 6.5.1.a and Figure 6.5.1.b.

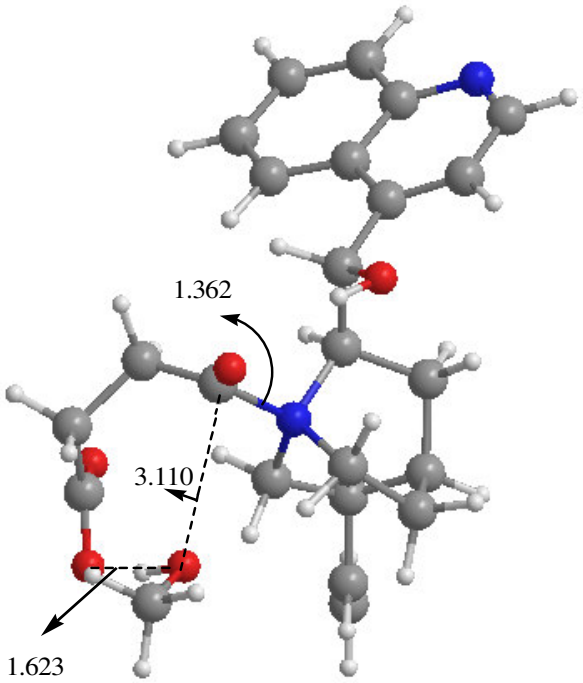


Figure 6.5.1.a The second transition state for the nucleophilic mechanism catalyzed by using cinchona alkaloids

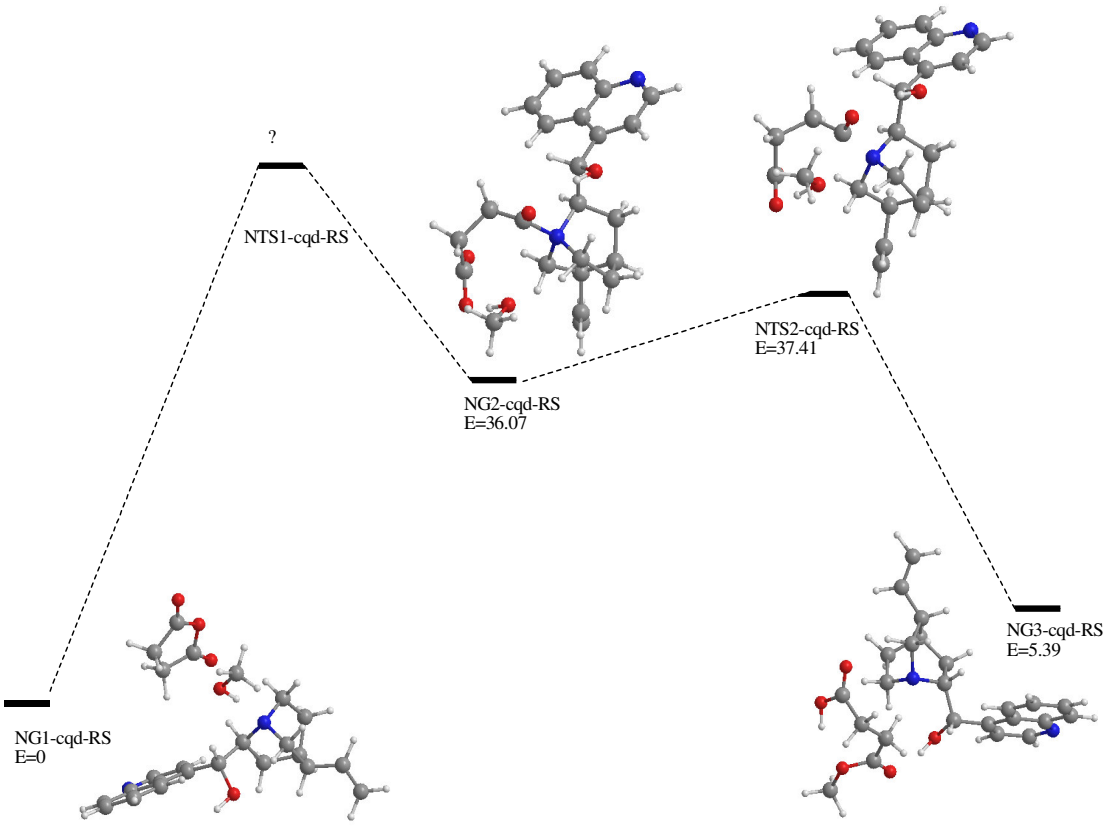


Figure 6.5.1.b Potential Energy Diagram for nucleophilic pathway by using cinchona alkaloids

The first transition state NTS1-cqd-RS cannot be located. However the same assumption which was applied for nucleophilic mechanism for a model compound can be used for cinchona alkaloids. The energy difference between the reactants and the products of the first transition state is 36.07 kcal/mol. Therefore the first transition state, NTS1-cqd-RS must be located higher than 36.07 kcal/mol. This activation barrier is much higher than the activation barrier of the base catalyzed mechanism. Based on this comparison, the base catalyzed mechanism is preferred over nucleophilic catalyzed mechanism in the presence of cinchona alkaloids.

6.6 Comparison of Base versus Nucleophilic Mechanisms

Both base and nucleophilic catalyzed mechanisms are modelled by using trimethylamine and cinchona alkaloids as catalysts respectively. The results show that in either case the activation barriers of first transition states in nucleophilic catalyzed pathways are significantly higher than the activation energies of the base catalyzed pathways. Therefore among the two proposed mechanisms, the base catalyzed mechanism is preferred over nucleophilic catalyzed mechanism. As a result the stereoeselectivity of ring opening of meso cyclic anhydrides is modelled via the base catalyzed mechanism.

6.7 Determination of Stereoselectivity

The stereoselectivity of the products is determined by examining the stereochemistry on C1 and C2. Figure 6.7.1 and Figure 6.7.2 show the two stereoisomers; SR and RS products.

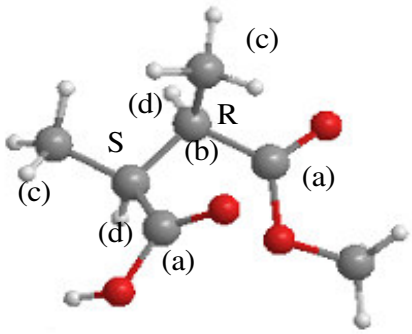


Figure 6.7.1 SR isomer of the product

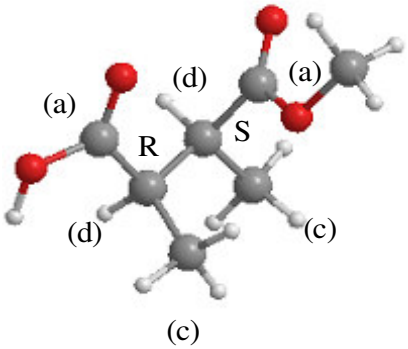


Figure 6.7.2 RS isomer of the product

6.8. Stereoselectivity

In order to investigate and understand the stereoselectivity on ring opening reactions of meso cyclic anhydrides, four different reaction pathways are modelled with cinchona alkaloids. Two enantiomers of cinchona alkaloids; cinchonine and cinchonidine are used in modelling these reactions. Two reactions are modelled by using cinchonine forming two steroisomers of the product and the other two reactions are modelled with cinchonidine leading to the formation of both stereoisomers of the product.

In the first two reactions cinchonine is used to model both the pathways to the RS and SR products. The transition states and potential energy diagrams of these reactions are shown in Figures 6.8.1.a, Figure 6.8.1.b, Figure 6.8.2.a and Figure 6.8.2.b respectively.

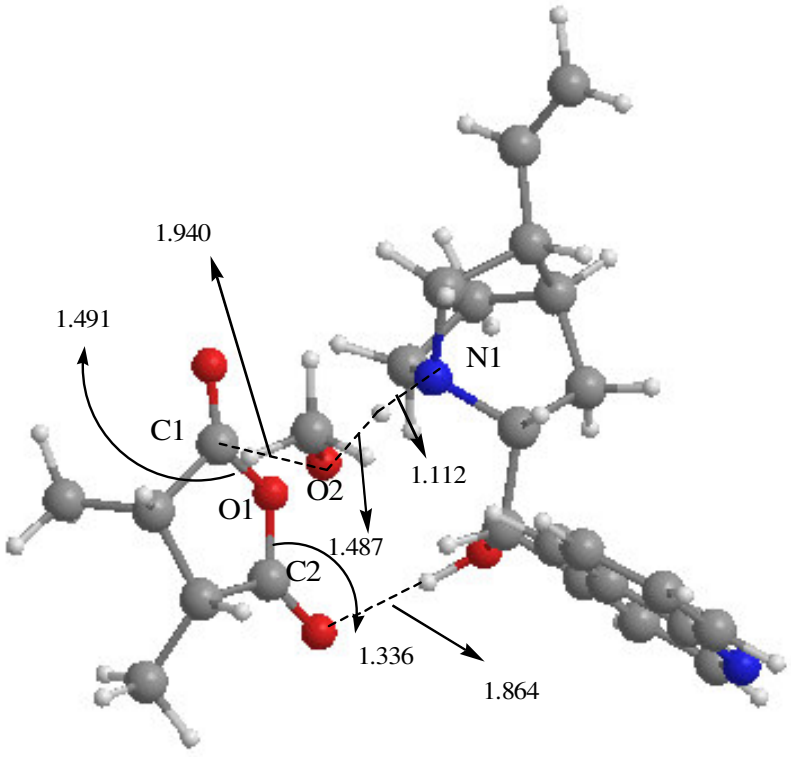


Figure 6.8.1.a. Transition state leading to the formation of the RS product with cinchonine.

In the transition state as the methanol cinchonine complex breaks down and quinuclidine nitrogen of cinchonine (N1) pulls the hydrogen to itself leaving the methanol more available for a nucleophilic attack, the O2 of methanol makes a nucleophilic attack to C1 of cis-dimethyl succinic anhydride. As a result of that attack the C1-O1 bond elongates from 1.336 Å to 1.491 Å indicating that the ring has started to open. The C2-O1 bond as compared to its initial length of 1.336 Å, shortens up a little due to an increased interaction between C2 and O1 which is formed due to the breaking of C1-O1 bond leaving O1 with a negative sign.

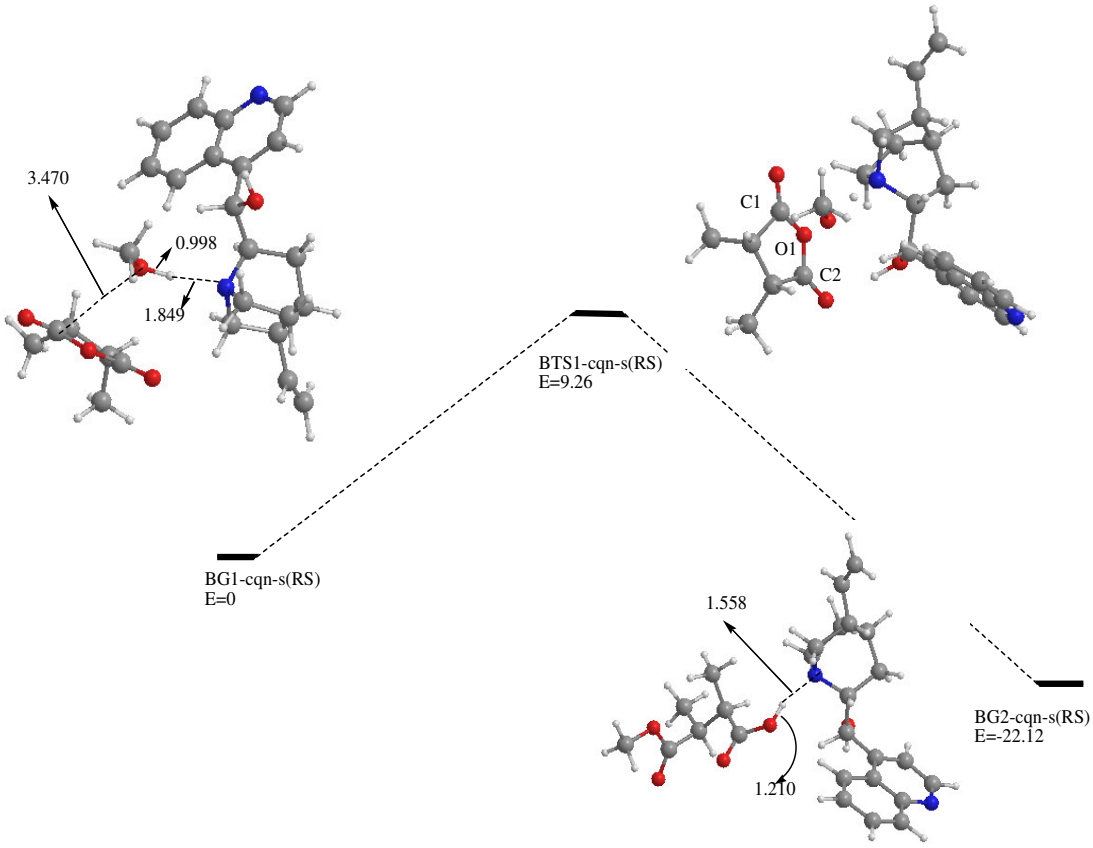


Figure 6.8.1.b Potential Energy Diagram for the formation of the RS product with cinchonine

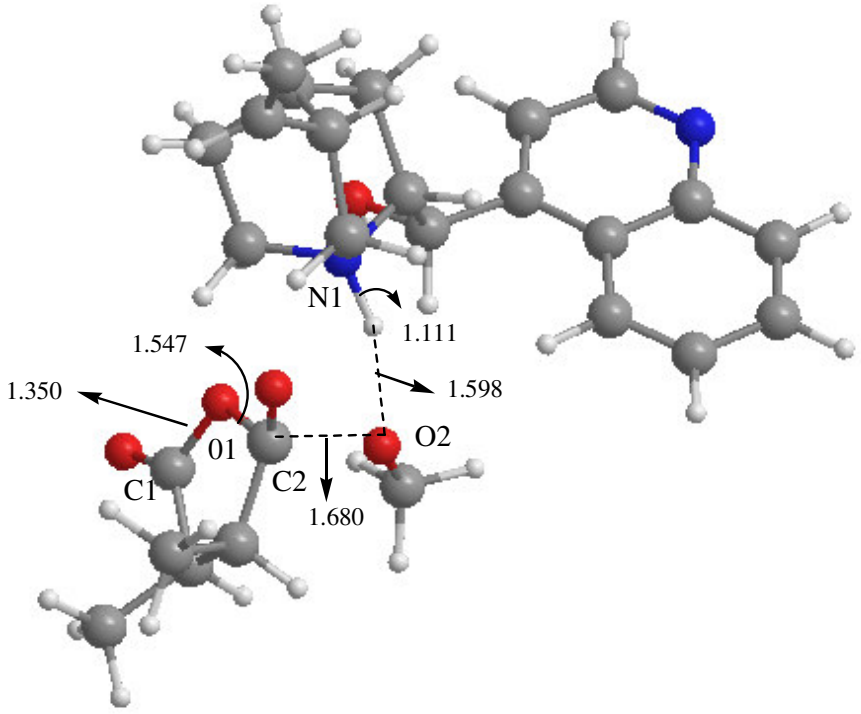


Figure 6.8.2.a. Transition state leading to the formation of SR product with cinchonine.

The transition state for the formation of the SR product is very similar to the transition state of the RS product. The primary difference between these two transition states is the carbonyl carbon which is attacked by methanol. In this transition state the methanol, after breaking of the methanol- cinchonine complex, makes a nucleophilic attack to C2 of cis-dimethyl succinic anhydride. As a result, the bond between C2-O1 elongates, from 1.350 Å to 1.547Å indicating the ring opening and the C1-O1 bond shortens due to the formation of the negative charge on O1.

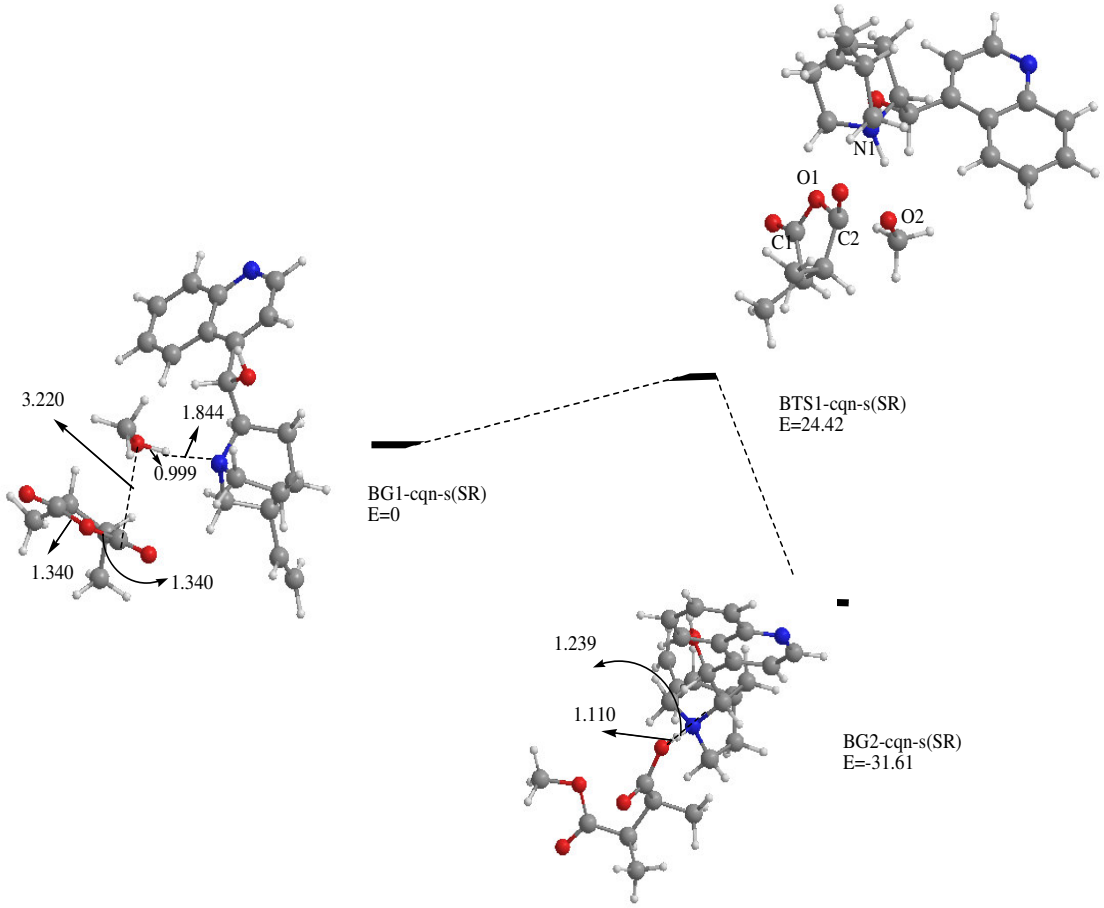


Figure 6.8.2.b Potential Energy Diagram for the formation of the SR product with cinchonine

Both of these reactions are exothermic, so they are thermodynamically favorable; however the activation energies of transition states are very different from each other. The activation barrier for the formation of the RS product is 9.26 kcal/ mol, whereas the activation barrier for the formation of the SR product is 24.42 kcal/ mol. As a result when cinchonine is used as a chiral catalyst in ring opening reactions of meso cyclic anhydrides the formation of the RS enantiomer of the product is favored. The main reason for that difference in the energies of the isomers is that the transition state of the RS product has a formation of H bonding between the O of the cinchonine and one of the carboylic oxygen's of the anhydride with a distance of 1.864 Å which stabilizes the transition state.

The same reactions are then modeled by using cinchonidine, the enantiomer of cinchonine. The transition states and potential energy diagrams are given in Figure 6.8.3.a, Figure 6.8.3.b, Figure 6.8.4.a, Figure 6.8.4.b respectively.

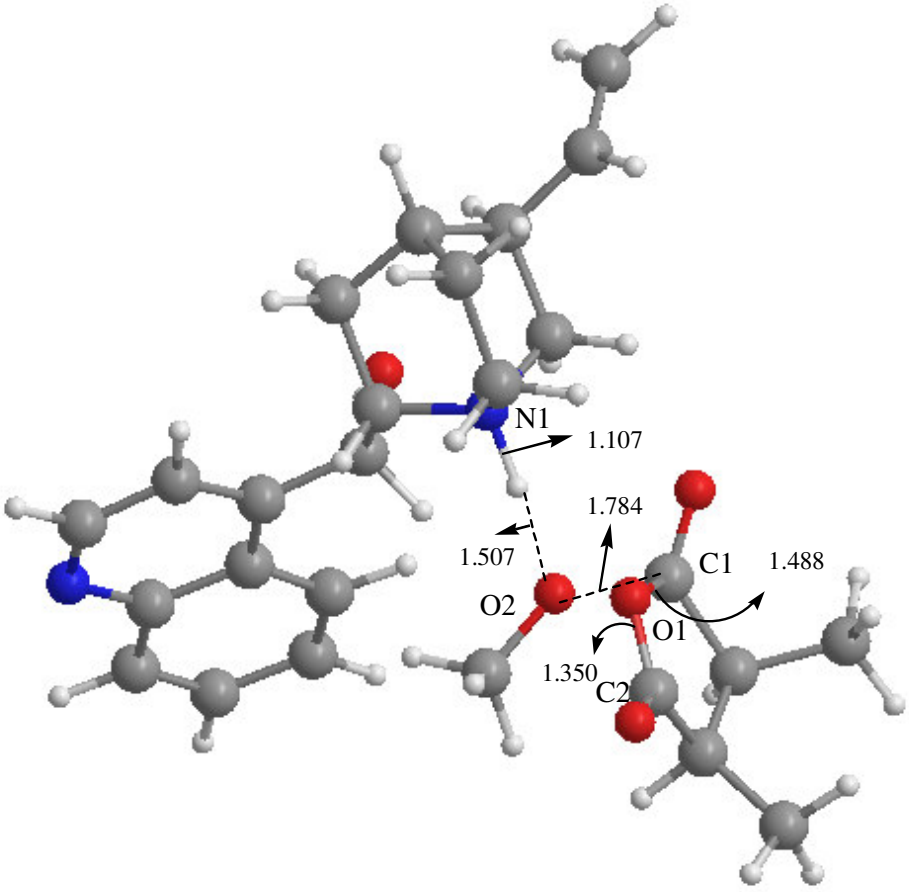


Figure 6.8.3.a. Transition state leading to the formation of the RS product with cinchonidine.

The transition state on Figure 6.8.3.a is very similar to the transition state on Figure 6.8.1.a. The only difference is instead of cinchonine, cinchonidine has formed a complex with methanol that dissociates in the transition state leading to formation of the product. The attack of methanol is to C1 of cis-dimethyl succinic anhydride, RS product is formed.

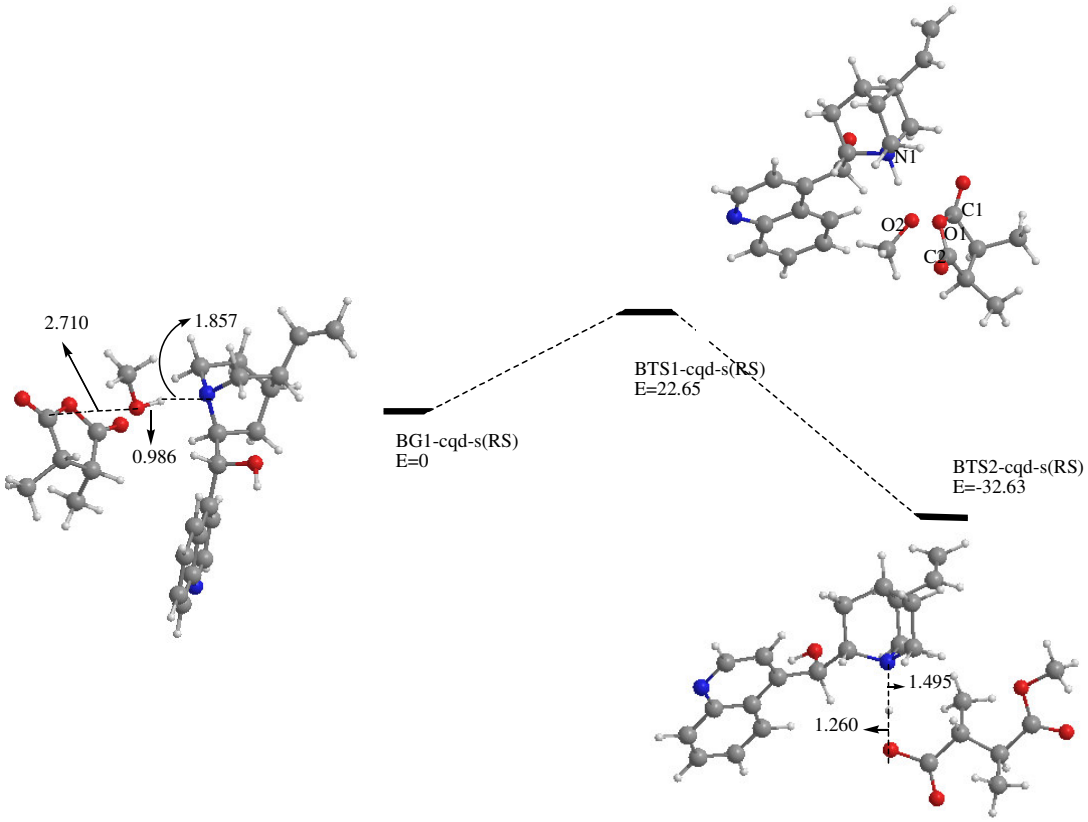


Figure 6.8.3.b Potential Energy Diagram for the formation of the RS product with cinchonidine.

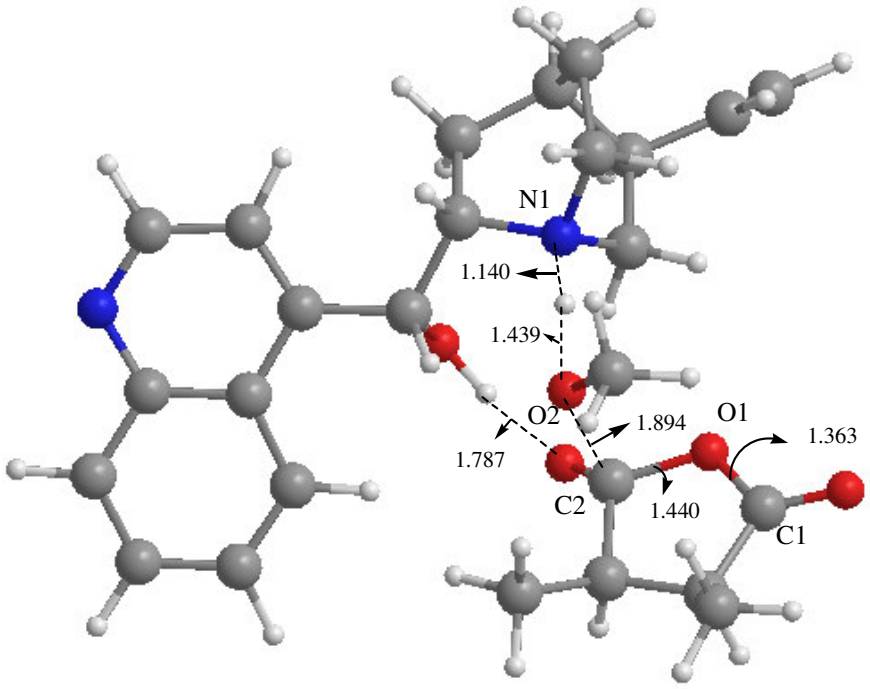


Figure 6.8.4.a. Transition state leading to the formation of the SR product with cinchonidine.

In Figure 6.8.4.a, as the methanol-cinchonidine complex dissociates leaving the hydrogen to N1 of cinchonidine, the methanol attacks to C2 of cis-dimethyl succinic anhydride instead of C1. As a consequence instead of the RS product, the SR isomer of the product is formed.

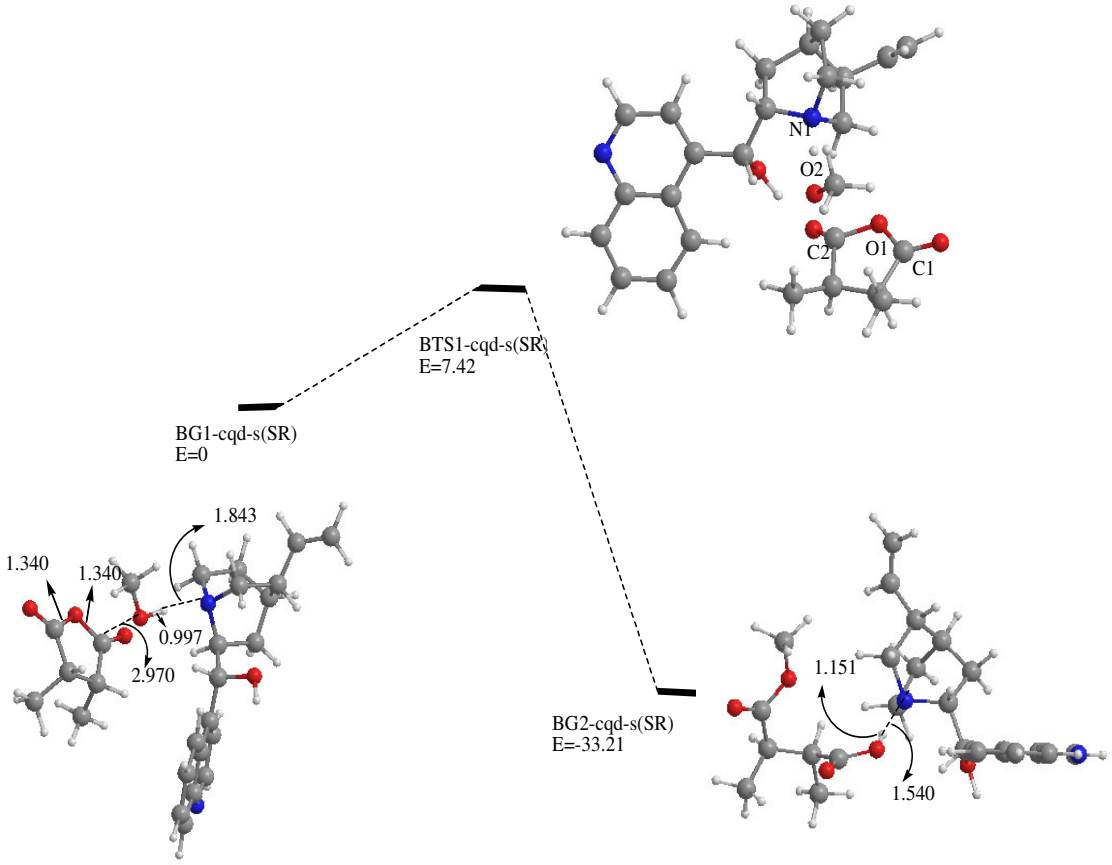


Figure 6.8.4.b Potential Energy Diagram for the formation of the SR product with cinchonidine.

Both of these reactions are also exothermic reactions and at the same time like the first two they have different activation energies. The activation barrier for the formation of the RS product is 22.65 kcal/ mol and activation barrier for the SR product is 7.42kcal/ mol. Therefore when cinchonidine is used in ring opening reaction of cis-dimethyl succinic anhydride formation of SR enantiomer of the product is favored. The main reason for that energy difference is the same as the reason which accounts for cinchonine also; the formation of the H bond between the O on the cinchonidine and one of the carboxylic O 's of the anhydride which can be seen in Figure 6.8.4.a.This information is also in line with the experiment and earlier findings because by using different enantiomers of the same

chiral catalyst, both enantiomers of the same product can be obtained directly in excess amounts.

The ring opening reactions of cis-dimethyl succinic anhydride are modelled by using both trimethylamine and cinchona alkaloids. In the reactions catalyzed by trimethylamine both enantiomers of the product are obtained directly. However the activation barriers of these reactions are very close to each other 6.17 kcal/mol and 6.83 kcal/ mol respectively. As a result neither of these enantiomers can be obtained separately in excess amounts. That is the main reason for usage of cinchona alkaloids in these type of reactions. Since the activation barriers of the reactions forming different enantiomers catalyzed by cinchonine and cinchonidine are different than each other stereoselectivity can be obtained much more easily by using cinchona alkaloids and two enantiomers of the product can be separated from each other. The following table (Table 6.8.1) shows a comparison of the activation energies (Ea) of all the reactions that are mentioned with zero point energy correction factors (Ea +ZPE), Gibb's free energies (G) and the heat of formation (H).

Table 6.8.1. Energies of activation (Ea), energies of activation with zero point energies (Ea+ZPE), Gibbs free energies (G), Enthalpies (H) values for all the transition states (kcal/mol)

	Ea	Ea+ZPE	H	G
BTS1-t	0.48	2.3	2.05	3.66
BTS1-t-s(SR)	6.17	6.72	5.24	4.81
BTS1-t-s(RS)	6.83	6.60	5.32	4.55
BTS1-cqn-s(RS)	9.26	8.54	6.95	12.81
BTS1-cqn-s(SR)	24.42	24.71	23.19	28.40
BTS1-cqd-s(RS)	22.65	22.85	21.41	26.52
BTS1-cqd-s(SR)	7.42	7.91	8.34	7.79
BTS1-cqn-swm (RS)	5.68	4.22	3.75	6.59
BTS1-cqn-swm (SR)	20.10	22.90	21.74	20.43
BTS1-cqd-swm (RS)	18.40	18.18	17.53	19.34
BTS1-cqd-swm(SR)	3.82	3.35	4.25	4.08

The second reason, besides the H bonding, for the difference between activation energies of reactions catalyzed by either cinchonine or cinchonidine is a result of their different stereochemistries on C8 and C9. (Figure 6.8.5.a and Figure 6.8.5.b). Because of that difference when they form a complex with methanol the orientation of these complexes are almost opposite to each other. As a result the complex with cinchonine prefers to react with C1 of cis-dimethyl succinic anhydride forming the RS isomer of the product because it can approach C1 much more easily as compared to C2 and cinchonidine prefers to attack C2 of cis-dimethyl succinic anhydride forming SR isomer of the product.

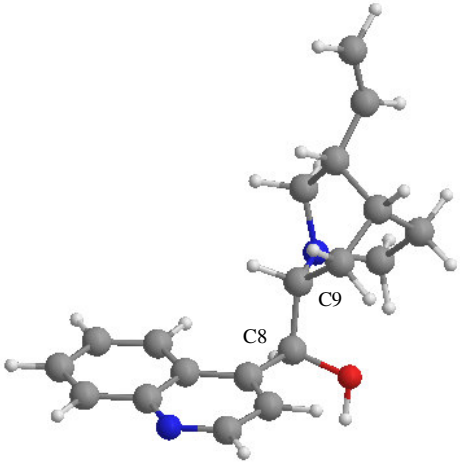


Figure 6.8.5.a. Cinchonine

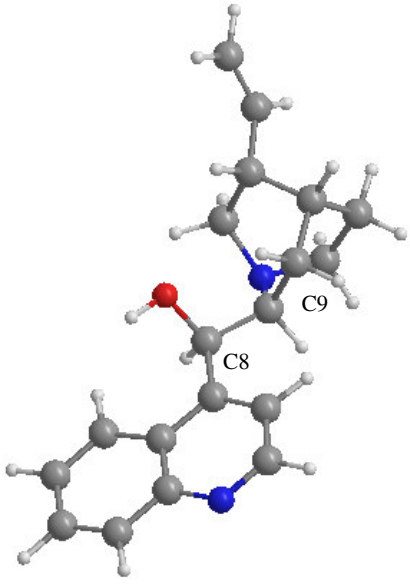


Figure 6.8.5.b Cinchonidine

The stereoselectivity of ring opening of cis-dimethyl succinic anhydride is then modeled by changing the orientation of the two methyl groups. The aim is to understand the effects of these methyl groups on the activation barriers of the stereoselectivity reactions. Two examples of transition states of these reactions are shown in Figure 6.8.6 and Figure 6.8.7.

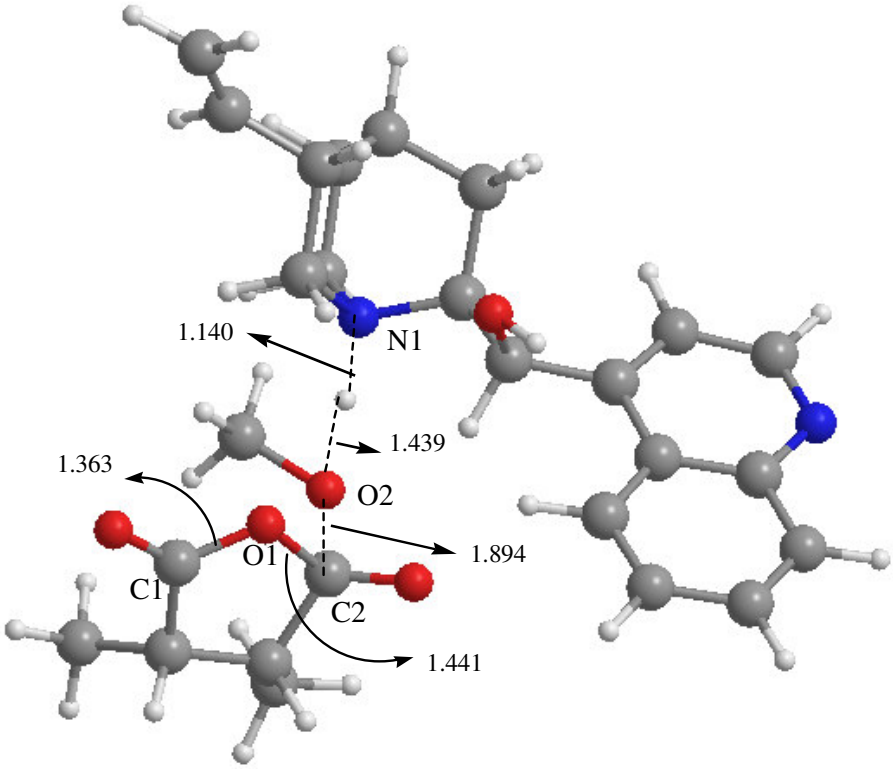


Figure 6.8.6. Transition state of the SR product with cinchonidine and methanol with the methyl groups towards the reactants.

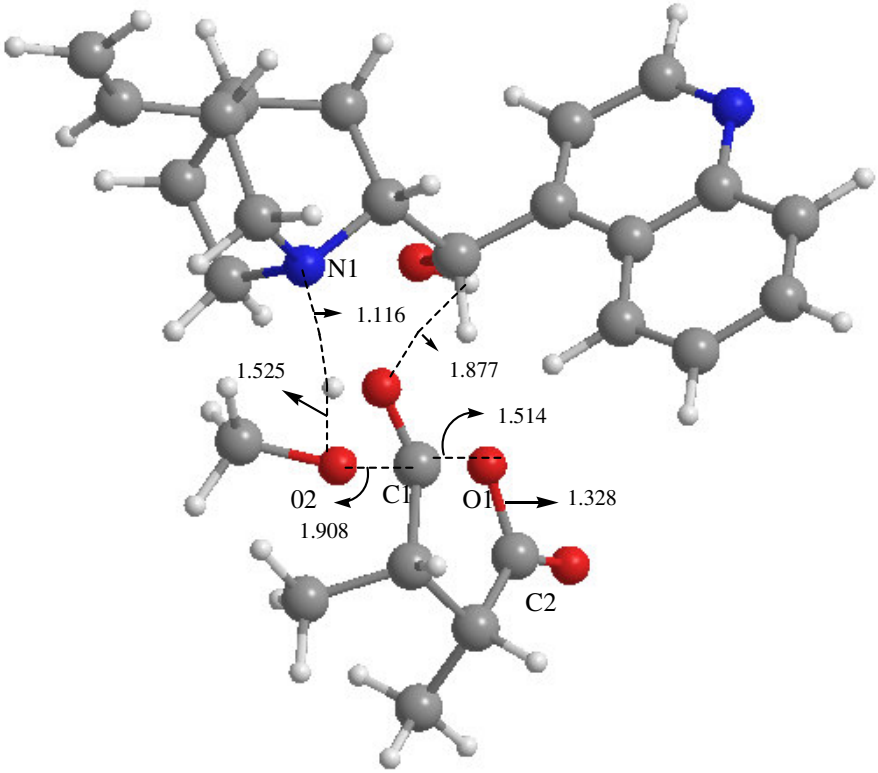


Figure 6.8.7. Transition state of the RS product with cinchonine and methanol with the methyl groups towards the reactants.

Table 6.8.2 shows the differences between the activation energies of the reactions depending on the side of the methyl groups.

Table 6.8.2. The comparison of activation energies (kcal/mol), depending on the direction of the methyl groups.

BTS1-cqn-s(RS)	BTS1-cqn-sos(RS)
9.26	14.72
BTS1-cqn-s(SR)	BTS1-cqn-sos(SR)
24.42	32.96

As it can be understood from Table 6.8.2 there is a significant difference between the activation barriers of the reactions depending on how the methyl groups are attached to the

cis-dimethyl succinic anhydride. When two methyl groups are attached on the side of anhydride which is looking towards the cinchona alkaloid or the side that is closer to the cinchona alkaloid the activation energies of the reactions are increasing. The reason for that increase is the steric hindrance caused by the methyl groups. Because two methyl groups on these reaction pathways are located on the same side of the attack of the cinchona alkaloid, it is much more difficult for the alkaloid to approach cis-dimethyl succinic anhydride.

6.9 Effect of Excess Methanol on the Energetics of the Reactions

According to the experimental results, cinchona alkaloids react with meso cyclic anhydrides in the presence of excess amount of methanol. Therefore methanol can be used in these reactions as a stabilizer. It can stabilize both carbonyl carbons of cis-dimethyl succinic anhydride which will result in a decrease in the activation barriers of the reactions. All four reactions modeled with cinchonine and cinchonidine are modeled with three equivalent moles of methanol and the additional two moles are placed near the carbonyl carbons of cis-dimethyl succinic anhydride to compare the difference in activation energies. One example for this reaction pathway and the corresponding transiton states are given in Figure 6.9.1.a and Figure 6.9.1.b.

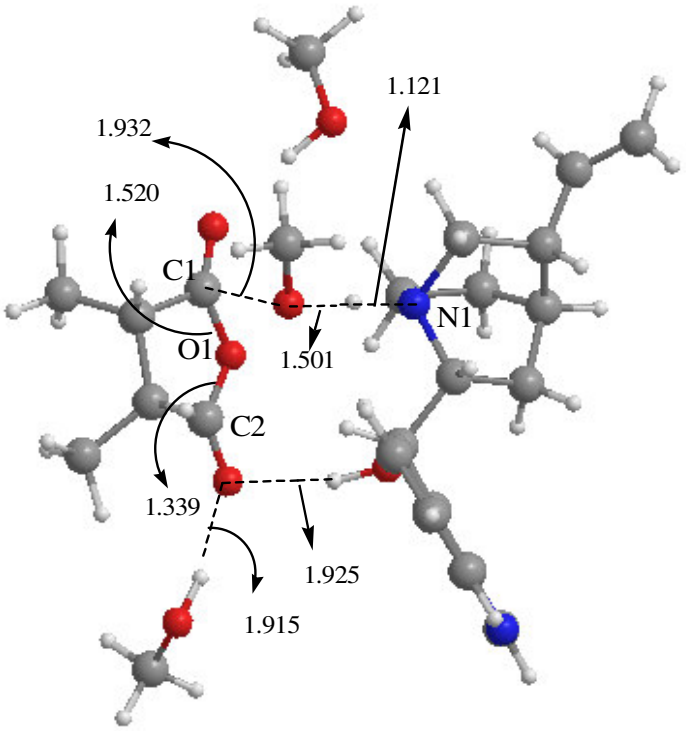


Figure 6.9.1.a Transition state of the RS product with cinchonine and excess methanol

This transition state is very similar to the transition state BTS1-cqn-s(RS).As methanol (O2) approaches C1 of cis-dimethyl succinic anhydride the bond between C1 and O1 elongates from 1.340 Å to 1.520 Å which indicates the opening of the ring. The methanols are used to stabilize the carbonyl oxygens on both sides of the cis-dimethyl succinic anhydride.

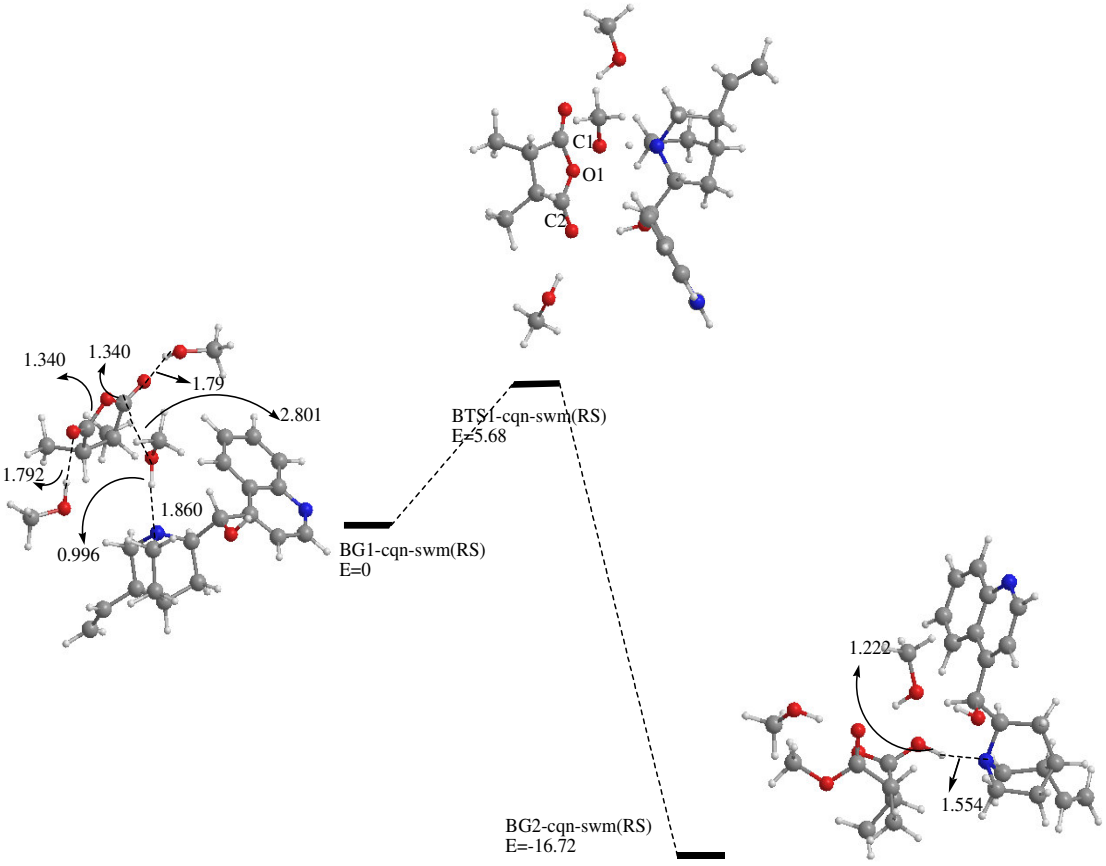


Figure 6.9.1.b Potential Energy Diagram for the formation of the RS product with cinchonine and excess methanol

As it can be seen on Table 6.8.1, addition of two methanol as stabilizers to carbonyl carbons of cis-dimethyl succinic anhydride lowers the activation barriers of all four reactions. The effect can be seen much better with reactions modeled with cinchonine since then activation energy differences between the reactions with and without methanol are much higher than the reactions modeled with cinchonidine.

6.10 Solvent Effect on Stereoselectivity

The effect of two non-polar solvents; toluene (2.38) and CCl_4 (2.23) on stereoselectivity is investigated by using cinchona alkaloids and cis-dimethyl succinic anhydride as the model compounds. Since the experimental results[13] suggest a tremendous decrease in the ee(per cent) in the presence of cinchonidine, due to the polarity of the solvent, this theoretical approach will allow us to understand how the polarity of the solvent affects the stereoselectivity.

The results are shown in Table 6.10.1.

Table 6.10.1. The effect of solvents on stereoselectivity

	Toluene	CCl_4
BTS1-cqn-s(RS)	10.28	10.27
BTS1-cqn-s(SR)	28.23	28.60
BTS1-cqd-s(RS)	27.49	27.48
BTS1-cqd-s(SR)	8.99	8.98

As it can be seen from Table 6.10.1, both toluene and CCl_4 have not changed the activation energies of the reactions mediated by cinchona alkaloids significantly. These results are in accordance with the experimental results which are displayed in Table 6.11.1.The activation energies of the reactions did not change significantly due to the usage of two non-polar solvents, therefore the increase in the ee per cent of the reactions will not be very significant.

6.11 Comparison with Experimental Results

The ee per cent of the enantiomers formed in the presence of either cinchonine or cinchonidine is given in Table 6.11.1.The experimental results based on Bolm *et al.*[11] are given in Table 6.11.2.

The ee per cent of the enantiomers is calculated by the formula:

$$\frac{N_j}{N} = \frac{e^{-\varepsilon_j/KT}}{\sum_i e^{-\varepsilon_i/KT}}$$

Table 6.11.1. The ee(per cent) of the enantiomers in the gas phase and in the presence of toluene

	ee(per cent) of RS product	ee(per cent) of SR product
Cinchonine	93.46	6.54
Cinchonidine	4.49	95.51
Cinchonine+Toluene	94.07	5.93
Cinchonidine+Toluene	4.40	95.60

Table 6.11.2. Influence of the solvent on the quinidine mediated opening of anhydride **1** by Bolm *et al.*[11]

	Yield of 2(per cent)	Ee(per cent)
Acetone	73	49
THF	79	72
Diethyl ether	87	75
di-n-butyl ether	83	79
Toluene	82	78
Mesitylene	78	72
p-xylene	85	80
Benzene	77	83
CCl_4	84	86
n-pentene	76	61
Toluene/ CCl_4	83	83

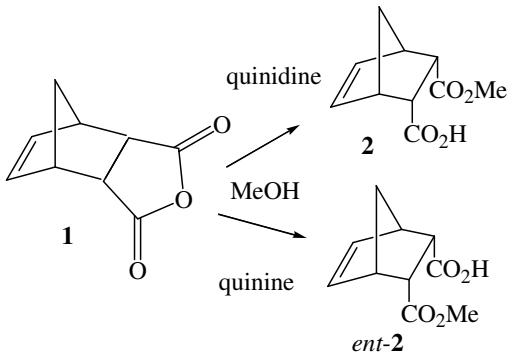


Figure 6.11.1 Stereoselective hydrolysis of meso cyclic anhydrides

According to the experimental results of Bolm *et al.*[11] the ee per cent of the enantiomers formed after reacting the anhydride with quinidine and methanol in the presence of toluene is 78 per cent. In our calculations the ee per cent of the enantiomers are found as 93.46 per cent and 94.07 per cent for cinchonine and cinchonidine respectively. These percentages although higher than the results of Bolm *et al.*[11] they reflect the same trend.

The reactions of Bolm *et al.*[11] are not performed in the gas phase therefore no comparison can be made with the computational results and the experimental results for that case.

6.12 Conclusion

The following conclusions can be drawn from this study:

1. There are two alternative mechanisms for the ring opening of meso cyclic anhydrides; the general base catalysis and the nucleophilic catalysis. Between these two mechanisms, the general base catalysis is preferred energetically over the nucleophilic catalysis.
2. Stereoselectiviy in the asymmetric desymmetrization of meso cyclic anhydrides cannot be obtained by using trimethylamine.
3. The asymmetric desymmetrization of meso cyclic anhydrides can be obtained by using one enantomeric pair of cinchona alkaloids; cinchonine and cinchonidine.
4. In the presence of cinchonine the RS isomer of the product can be obtained in excess amounts. In the presence of cinchonidine, the enantiomer of cinchonine, the SR isomer of the product can be obtained in excess amounts.
5. Addition of excess methanol decreases the activation barriers of the reactions by forming H bonds and therefore stabilizing the meso cyclic anhydrides during the reaction
6. Decreasing the polarity of the reaction medium by adding non polar solvents have increased the ee per cent of the enantiomers.

6.13 Suggestions for Future Work

The following items are suggested for future work:

1. The reaction of sterically hindered anhydrides will be modeled using the same strategy. High reaction barriers are expected in the reaction pathway for these species, since sterically hindered anhydrides did not react at all.[11].
2. The reactions will be modelled by changing the configurations of cinchonine and cinchonidine.
3. Conformer searches on the transitions states of the reactions will be performed.
4. Further solvent calculations can be done by using polar solvents like acetone and THF.
5. The assistance of the OH group on cinchona derivatives will be investigated systematically.

REFERENCES

1. Spivey, A. C. and B. I. Andrews, "Catalysis of the Asymmetric Desymmetrization of Cyclic Anhydrides by Nucleophilic Ring-Opening with Alcohols," *Angew. Chem. Int. Ed.* **2001**, *40*, 3131-3134.

2. Wong, C. H. and G. M. Whitesides, in *Enzymes in Synthetic Organic Chemistry*, J. E. Baldwin and P. D. Magnus, Eds., Oxford: Elsevier, **1994**.

3. Willis, M. C., "Enantioselective Desymmetrisation," *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765-1784.

4. Ho, T. L., *Symmetry: A Basis for Synthesis Design*, New York: Wiley Interscience, **1995**.

5. a) Theisen P. D. and C. H. Heathcock, : "Prochiral Recognition in the Reaction of 3- substituted Glutaric Anhydrides with Chiral Secondary Alcohols," *J. Org. Chem.* **1993**, *58*, 142-146. b) Hibbs, D. E.; M. B. Hursthouse, I.G. Jones, W. Jones, K. M. Abdul Malik and M. North, "Synthesis of Enantio- and Diastereomerically Pure, Tetra- and Penta-Substituted Cyclopentanes by the Desymmetrization of endo-Norborn-5-ene-2,3-dicarboxylic Anhydrides," *J. Org. Chem.* **1999**, *64*, 5413-5421.

6. a)Gais, H. J., in *Enzyme Catalysis in Organic Synthesis*, Vol. 1, K. Drauz and H. Waldmann, Eds., Weinheim: VC, **1995**, pp. 165-261. b) Procter, G, in *Asymmetric Synthesis*, Oxford: Oxford University Press, **1996**, p. 215.

7. a) Hiratake, J., Y. Yamamaoto and J. Oda, "Catalytic Asymmetric Induction from Prochiral Cyclic Acid Anhydrides Using Cinchona Alkaloids," *J. Chem. Soc. Chem. Commun*. **1985**, 1717-1719. b) Hiratake, J.; M. Inagaki, Y. Yamamoto and J. Oda, "Enantiotopic-Group Differentiation. Catalytic Asymmetric Ring-Opening of Prochiral Cyclic Acid Anhydrides with Methanol, Using Cinchona Alkaloids," *J. Chem. Soc. Perkin Trans.* **1987**, 1053-1058.

8. a) Aitken, R. A., J. Gopal and J. A. Hirst, "Catalytic Asymmetric Synthesis of Highly Functionalised Compounds with Six Contiguous Stereocentres," *J. Chem. Soc. Chem. Commun* **1988**, 632. b) Aitken, R. A. and J. Gopal, "Catalytic Asymmetric Ring-Opening of Bridged Tricyclic Anhydrides," *Tetrahedron: Asymmetry* **1990**, *1*, 513-516.

9. Shimizu, M., K. Matsukawa and T. Fujisawa, "Enantioselective Esterification of Cyclic Dicarboxylic Anhydrides Using Chiral Amino Alcohols as Auxiliairies," *Bull. Chem. Soc. Jpn*. **1993**, *66*, 2128-2130.

10. a) Seebach, D., G. Jaeschke, K. Gottwald, K. Matsuda, R. Formisano, C. David, A. M. Breuning and G. Bringmann, "Resolution of Racemic Carboxylic Acid Derivatives by Ti-TADDOLate Mediated Esterification Reactions - A General Method for the Preparation of Enantiopure Compounds," *Tetrahedron* **1997**, *53*, 7539-7556. b) Jaeschke, G. and D. Seebach,, "Highly Enantioselective Ring Opening of Cyclic Meso-Anhydrides to Isopropyl Hemiesters with Ti-TADDOLates: An Alternative to Hydrolytic Enzymes?" *J. Org. Chem.* **1998**, *63*, 1190–1197.

11. a) Bolm, C., A. Gerlach and C. Dinter, *Synlett* **1999**, 195-197. b) Bolm, C., I. Schiffers, C. L. Dinter and A. Gerlach, "Practical and Highly Enantioselective Ring Opening of Cyclic *Meso*-Anydrides Mediated by Cinchona Alkaloids." *J. Org. Chem.* **2000**, *65*, 6984-6991, and references therein.

12. Chen, Y., S. K. Tian and L. Deng, "A Highly Enantioselective Catalytic Desymmetrization of Cyclic Anhydrides with Modified Cinchona Alkaloids," *J. Am. Chem. Soc.* **2000**, *122*, 9542-9543.

13. Kolb, H. C., M. S. Van Nieuwenhze and K. B. Sharpless, "Catalytic Asymmetric Dihydroxylation," *Chem. Rev.* **1994**, *94*, 2483-2547.

14. Kolb, H. C., P. G. Andersson and K. B. Sharpless, "Toward an Understanding of the High Enantioselectivity in the Osmium-Catalyzed Asymmetric Dihydroxylation (AD). 1. Kinetics," *J. Am. Chem. Soc.* **1994**, *116*, 1278-1291.

15. a) Corey, E. J. and M. C. Noe, "Rigid and Highly Enantioselective Catalyst for the Dihydroxylation of Olefins Using Osmium Tetraoxide Clarifies the Origin of Enantiospecificity," *J. Am .Chem. Soc.* **1993**, *115*, 12579 – 12580; b) E. J. Corey and Mark C. Noe, "Kinetic Investigations Provide Additional Evidence That an Enzyme-like Binding Pocket Is Crucial for High Enantioselectivity in the Bis-Cinchona Alkaloid Catalyzed Asymmetric Dihydroxylation of Olefins," *J. Am .Chem. Soc.* **199**, *118*, 319-329. c) Corey, E. J., M. C. Noe, "A Critical Analysis of the Mechanistic Basis of Enantioselectivity in the Bis-Cinchona Alkaloid Catalyzed Dihydroxylation of Olefins," *J. Am. Chem. Soc.* **1996**, *118*, 11038-11053.

16. Mizuta, S., M. Sadamori, T. Fujimoto and I. Yamamoto, "Asymmetric Desymmetrization of *meso*-1,2-Diols by Phosphinite Derivatives of Cinchona Alkaloids," *Angew. Chem. Int. Ed.* **2003**, *42*, 3383-3385.

17. a) Vayner, G., K. N. Houk and Y. K. Sun, "Origins of Enantioselectivity in Reductions of Ketones on Cinchona Alkaloid Modified Platinum," *J. Am. Chem. Soc.* **2004**, *126*, 199-203. b) Cannizzaro, C. E., T. Strassner and K. N. Houk, "The Origin of 1,4-Asymmetric Induction in the Additions of Chiral Alcohols to Ketenes," *J. Am. Chem. Soc.* **2001**, *123*, 2668-2669.

18. Vayner, G., Ph. D. thesis, **2003** (supervised by K. N. Houk).

19. a) Dijkstra, G. D. H., R. M. Kellogg and H. Wynberg, "Conformational Study of Cinchona Alkaloids. A Combined NMR and Molecular Orbital Approach," *J. Org. Chem.* **1990**, *55*, 6121-6131. b) Dijkstra, G. D. H., R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko and K. B. Sharpless, "Conformational Study of Chinchona Alkaloids. A Combined NMR, Molecular Mechanics, and X-ray Approach," *J. Am. Chem. Soc.* **1989**, *111*, 8069-8076.

20. Burgi, T. and A. Baiker, "Conformational Behavior of Cinchonidine in Different Solvents: A Combined NMR and ab Initio Investigation," *J. Am. Chem. Soc.* **1998**, *120*, 12920-12926.

21. Parr, R. G. and W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, New York, **1989**.

22. Handy, N. C., "Density Functional Theory", in: B. O. Roos (ed.), Lecture Notes inQuantum Chemistry, Vol. 2, pp. 91-123, Springer-Verlag, Berlin, **1994**.

23. Frisch, M. J. *et al.*, Gaussian 98 Revision A.7, Gaussian, Inc., Pittsburgh PA, **1998**.

24. Becke, A. D., "Density Functional Thermochemistry III. The Role of ExactExchange", *Journal of Chemical Physics*, Vol. 98, pp. 5648-5652, **1993**.

25. Lee, C., W. Yang and R. G. Parr, "Development of Colle-Salvetti Correlation EnergyFormula into a Functional of the Electron Density", *Physical Reviews B*, Vol. 37, pp. 785-789, 1988.

26. Becke, A. D., "Density-Functional Exchange Energy Approximation with Correct Asymptotic Behavior", *Physical Reviews A*, Vol. 38, pp. 3098-3103, 1988.

27. Becke, A. D., "A New Mixing of Hartree-Fock and Local Density Functional Theories", *Journal of Chemical Physics*, Vol. 38, pp. 1372-1377, 1993.