Michael reaction can be accomplished with a host of alkenes and alkynes activated by conjugation with electron-withdrawing groups (EWG), such as aldehyde, keto, carboxy, cyano, nitro, acid derivatives, sulphonyl, etc. The scope of the reaction was further broadened by discovering that not only carbanionic nucleophiles, but a variety of heteroatomic nucleophiles, such as amines, amides, alcohols, thiols, too could add to the activated alkenes and alkynes affording a number of compounds having pharmaceutical importance and usefulness as building blocks.

The aza-Michael addition acquires much importance due to its ability to make β-aminocarbonyl derivatives accessible, which are useful synthons for the preparation of several nitrogen containing bioactive natural products, antibiotics and chiral auxiliaries.The use of various N-nucleophiles (aliphatic amines, aromatic amines, amides, carbamates, azides) and Michael-acceptors (enones, acrylates, unsaturated nitriles, amides, sulphones, phosphonates, trifluoromethylalkenes, nitroalkenes, alkyl acetylenecarboxylates, etc.) has been reported in literature.

With this background, the present study was undertaken to investigate experimentally and theoretically reactions of some amines with α,β-unsaturated carbonyl compounds.

The results of the present investigations have been presented in the following chapters:

Chapter 1. Aza-Michael Addition: Introduction and Review of Literature

Chapter 2. Experimental and Theoretical Investigation of the Reaction of secondary Amines with Maleic Anhydride

Chapter 3. Aza-Michael Addition of Amines with Methyl Propiolate: Experimental and Theoretical Results

Chapter 4. Diastereoselectivity in Asymmetric Michael Addition of α-Methylbenzylamines to α,β-Unsaturated Carbonyl Compounds

Chapter 5. Synthesis, Characterisation and Bioactivity of New Tin(IV) Complexes withMaleamic Acid Derivatives as Ligands

Chapter 1 Aza-Michael Addition: A Review

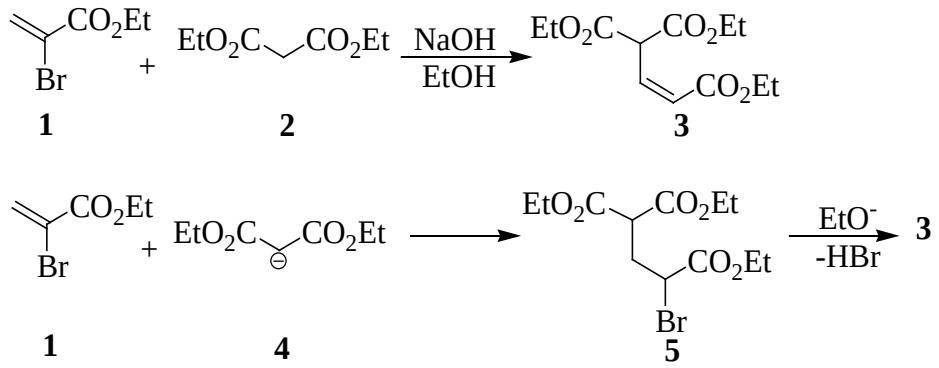
The first Chapter comprises an overview of Michael addition of amines and *N*-heterocycles. This chapter deals with the research work on aza-Michael addition of nitrogen containing nucleophiles with different Michael acceptors reported from 2005 through most recently.

In this review, reactions have been classified on the basis of the nature of the Michael donors.

The review is divided into four subsections.

1.1. Introduction

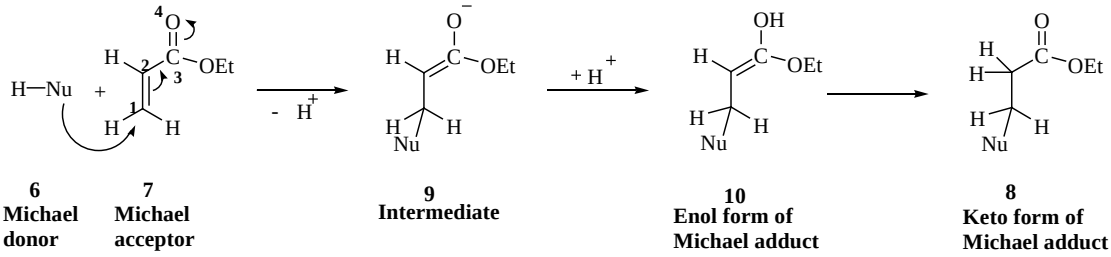
This section includes discovery and general scope of Michael addition reaction.



Scheme 1.1. Michael reaction of diethyl malonate with ethyl α-bromoacrylate.

1.2. Mechanism of Michael Addition

In this Section, two steps mechanism of Michael addition is discussed.

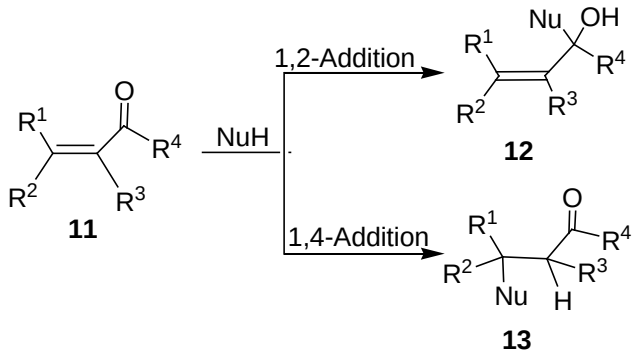


6 **Michael donor** **7** **Michael acceptor** **9** **Intermediate** **10** **Enol form of Michael adduct** **8** **Keto form of Michael adduct**

Scheme 1.3. Mechanism of Michael addition.

1.3. 1,2-Versus 1,4-addition

It is explained that in the reaction with α,β-unsaturated carbonyl compounds, direct addition of the nucleophile across the carbonyl group (1,2-addition)**(12)**is kinetically preferred whereas under thermodynamic control, Michael addition (1,4-addition or conjugate addition) occurs predominantly.



11 **12** **13**

Scheme 1.4. 1,2- Versus 1,4-addition of nucleophile to α,β-unsaturated carbonyl compound.

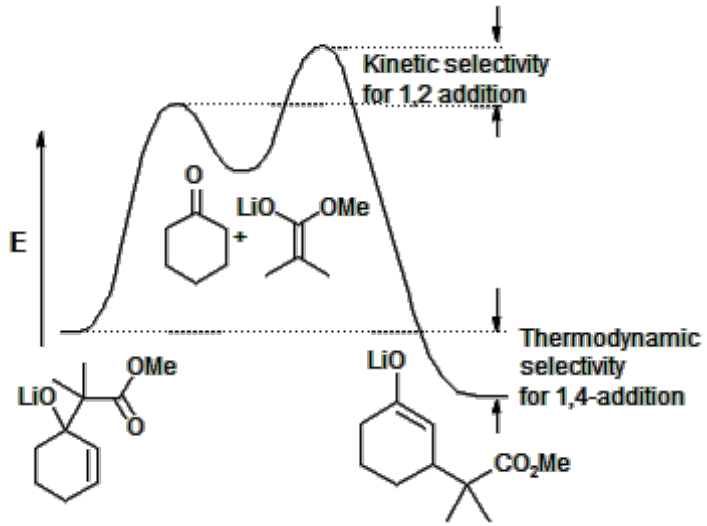


Figure 1.1.1,2- Versus 1,4-addition of enolates of methyl propiolate with 2-cyclohexen-1-one.

1.4. Aza-Michael addition

Reactions have been classified on the basis of the nature of the Michael donors.

1.4.1. Addition of amines

This section includes the use of amines as Michael donors and is further divided on the basis of reaction conditions such as without catalyst and in the presence of catalyst. Use and advantages of different catalytic systems have been discussed in this part.

1.4.1.1. Aza-Michael addition of amines without the use of a catalyst

1.4.1.2. Aza-Michael addition of amines in the presence of a catalyst

1.4.1.2.1. Metal and metal salts as catalyst

1.4.1.2.2. Organocatalysts

1.4.1.2.3. Ionic liquids as catalysts

1.4.1.2.4. Heterogeneous catalysts

1.4.2. Addition of amides and carbamates

Though the amide nitrogen atom exhibits reduced nucleophilicity, these compounds have also been reported to undergo aza-Michael addition under catalytic conditions; it is described in this subsection.

1.4.3. Addition of azides

Aza-Michael addition of azide has been reported in this section.

1.4.4. Addition of hydrazines/hydrazones

Aza-Michael addition of hydrazine as well as hydrazones containing at least one free amino group with various activated alkenes is given in this section.

1.4.5. Addition of aromatic aza heterocycles

Amino ketones and β-amino acid derivatives having an aromatic N-heterocycle are important constituents of drugs. For this reason, the Michael addition of imidazoles, pyrazoles, pyrroles, triazoles and indoles to enones and acrylates has attracted much attention of the chemists and is included in this section.

1.5. Problem statement

Gaps in the study are discussed in this section.

1.6. Technology available

This section includes the details of the technology available for the conduction of the research work.

1.7. Objectives

This section includes objectives of the study.

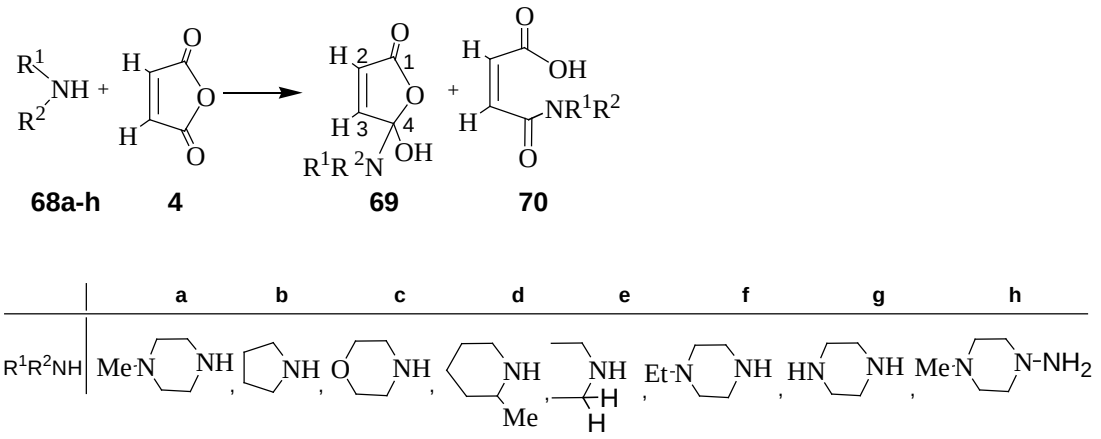
Chapter 2 Experimental and Theoretical Investigation of the Reaction of Secondary Amines with Maleic Anhydride

2.1. Introduction

This chapter comprises the results of the reactions of various amines with maleic anhydride. It is found that under kinetic control, amine adds predominantly across the carbonyl group. The products so formed isomerize to maleimic acid derivatives on heating. It is interesting to find that in contrast to the acyclic α,β-unsaturated carbonyl compounds, in the present case, amine does not add across the C=C functionality in maleic anhydride in Michael addition mode even under thermodynamic control. In order to explain this, computational calculations have been done at the DFT level. This Chapter is divided into following subsections:

2.2. Experimental Results

Amines (**68a-h**) react with maleic anhydride (**4**) in methylene chloride under kinetic control, i.e. at low temperature (-78^{o}C or -15^{o}C) and under thermodynamic control at higher temperature (40^{o}C) to form the corresponding C=O addition products (**69**) and maleimic acids (**70**) respectively.



Scheme 2.23. Reaction of amines with maleic anhydride.

The relative percentages of the products **69** and **70** were calculated on the basis of ^{1}H NMR.

2.2.1. Characterization of the products

The reactions of the amines **68a**, **68b**, **68c** with maleic anhydride at higher temperature afforded white crystalline solids which were chracterized on the basis of high resolution mass spectra (HRMS), heteronuclear single-quantum correlation (HSQC) NMRand other spectral studies. In other cases, the resulting products were found to be mixtures of the C=O addition product and the corresponding maleimic acid, which could not be separated even with column chromatography. But in ^{1}H NMR spectra, the signals could be assigned to these products separately.

2.3 Theoretical Results

In contrast to the acyclic α,β-unsaturated carbonyl compounds, amine does not add across the C=C functionality in maleic anhydride even under thermodynamic control. In order to explain this, we calculated local condensed Fukui functions at different positions of maleic anhydride by following the method

reported earlier. Total energies, ionization potential, electron affinity, global hardness and global softness of maleic anhydride (**4**), acrolein andall amines (**68a-h**), have also been calculated.

Unlike in simple α,β-unsaturated aldehydes or ketones, such as acrolein, the -CH=CH- functionality in maleic anhydride (**4**) is encompassed by the carbonyl groups on both sides, as a result of which in maleic anhydride, the C=O and C=C groups are locked in the S-*trans* conformation and value of the condensed Fukui function for the nucleophilic attack (f^+ r) at the carbonyl carbon atom in maleic anhydride (0.003) is much smaller than in acrolein (0.215) showing much harder character of the former. As compared to the carbonyl carbon atom, β carbon atom (C3) in maleic anhydride is much softer. This difference (difference between the hardnesses of the carbonyl carbon atom and softness of the β carbon atom) in acrolein is much smaller. From this, it may be concluded that under kinetic control conditions, attack at the carbonyl carbon atom in maleic anhydride leading to addition across the C=O group will be much more preferred than in acrolein under similar conditions.

FMO analysis

Inspection of the frontier molecular orbitals (FMO) of maleic anhydride shows that lowest unoccupied molecular orbital (LUMO) of maleic anhydride molecule is composed of the π^*C=O and π^*Cα=Cβ orbitals merged together. In view of this, the attacking nucleophile has both opportunities, i.e. either to attack the carbonyl carbon atom or the Cβ atom of the C=C functionality. This preference will, however, be determined by the relative condensed Fukui functions for the

nucleophilic attack (f^+r) at these two sites as well as conditions. Amines are known to have intermediate hardness and can attack either of the two sites depending upon the conditions. Thus under kinetic control, i.e. at low temperature, the carbonyl carbon atom which is the harder site (f^+r = 0.003) is attacked giving the C=O addition product. The preferential attack of amine on the carbonyl carbon atom is in accordance with the electrostatic potential map also which shows highest electron deficiency at this site.

Comparison of the relative stabilities of the carbonyl nucleophilic addition products and the corresponding maleimic acid

Total energies of the carbonyl addition products and the corresponding maleimic acids were calcultated at the B3LYP/6-311++G**// B3LYP/6-31+G* level. It is found that maleimic acids are thermodynamically more stable than the respective C=O addition products by ca. 11- 18 kcal mol^{-1}. The greater stability of maleimic acid as compared to the corresponding C=O addition product could be rationalized on the basis of the NBO analysis.

2.4. Experimental Details

Reaction procedure and experimental techniques used during the synthesis of maleimic acid derivatives and their purification are given in this section.

2.5. Computational Methods

Various computational software and techniques used in the theoretical investigation are described in this section.

2.6. Conclusions

From experimental and computational studies of the reactions of amines with maleic anhydride, it can be concluded that the reaction of secondary amines with maleic anhydride under kinetic control conditions occurs across the carbonyl group (C=O) almost exclusively, which may be attributed to the much harder nature of its carbonyl carbon atom as compared with that in an acyclic α,β-unsaturated carbonyl compound, such as acrolein. It could be rationalized theoretically on the basis of the condensed Fukui functions which reveal much harder nature of the carbonyl carbon atom in maleic anhydride than in acrolein. Theresulting carbonyl addition products isomerize to the *N*-substituted maleimic acid derivatives, which are stabilised due to amidic delocalization of the nitrogen lone pair. Thus, in contrast to the acyclic α,β-unsaturated carbonyl compound, no addition occurs across the C=C functionality of maleic anhydride.

Chapter 3 Aza-Michael Addition of Amines with Methyl Propiolate: Experimental and Theoretical Results

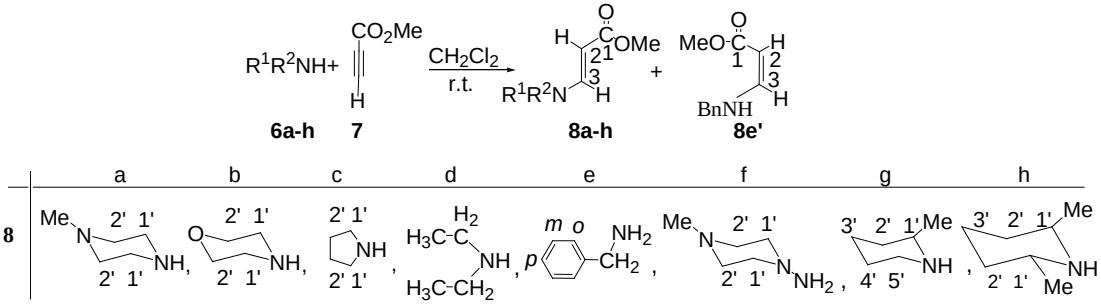
3.1. Introduction

In the first chapter, a comprehensive review on aza-Michael addition was presented, in which its utility for the synthesis of a large number of bioactive and other useful precursors was highlighted. In this context, it was found that the reaction of amines with acetylenecarboxylic acid esters has attracted much attention owing to two reasons-firstly, its *cis-trans*stereoselectivity and secondly, the mechanism of the *cis-trans* isomerisation.

Considering the above facts, we undertook a systematic experimental and theoretical investigation of the Michael addition of secondary amines and benzylamine to methyl propiolate The results are presented in this chapter under the following sections:

3.2. Experimental Results

The amines (**6a-h**) react with methyl propiolate (**7**) in methylene chloride at ambient temprature (~25^{o}C) to give the products (**8**). The reactions are moderately exothermic and are complete in 4-8 hrs. at ambient temperature (~ 25 °C). In each case, a single product was obtained, except in the reaction with benzylamine which afforded a mixture of two compounds **8e** and **8e'**. All the products are crystalline colorless solids with low melting points.



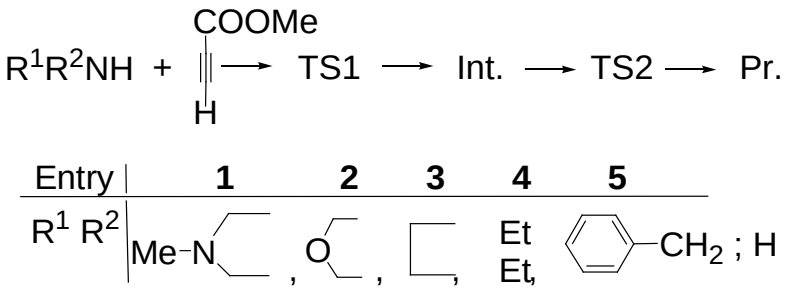
Scheme 3.4. Aza-Michael addition of amines to methyl propiolate.

The products are obtained in high yields, and are colourless crystalline solids or viscous mass, soluble in common organic solvents, such as chloroform, ethyl acetate, and methanol. Theycould be well characterized on the basis of elemental analysis, IR and ^{1}H and ^{13}C NMR spectral studies. In the ^{1}H NMR spectrum, two doublets at ~ δ 7 ppm and ~ δ 4.5 ppm with a $^{3}J_{HH}$of ~13 Hz resulting from an AB spin system confirm the presence of twovinylic protonsH2 and H3 in the product **8a-**

e; a large $^{3}J_{HH}$coupling constant of ~ 13 Hz confirms their *trans*-orientation.In the ^{1}H NMR spectrum of the product obtained from the reaction of benzylamine with methyl propiolate, two sets of signals were observed indicating it to be a mixture of the *trans*- and *cis*- isomers. In this case, the proton H2 gives a doublet (d) due to its coupling with H3, whereas the latter gives a double doublet (dd) due to its coupling with H2 and the NH protons. A set of d and dd with the $^{3}J_{HH}$coupling constant of ca. 13.2 Hz could be assigned to the *trans*-isomer, whereas another set of d and dd with $^{3}J_{HH}$coupling constant of 8.1 Hz is given by the *cis*- isomer.

3.3 Theoretical Results

With a view to investigate the mechanism of the reaction of amines with methyl propiolate, to rationalize relative reactivities of different amines and to look into the role of the N-H proton in the *trans-cis* isomerization of the initially formed product following model reactions were computed (**Scheme 3.5**) at the DFT level.



Scheme 3.5. Theoretically investigated model reactions of amines with methyl propiolate.

Scanning of the potential energy surface (PES) reveals that the reaction occurs in two steps.

(1) **First step**– This step leads to the `formation of a zwitterionic intermediate (**Int.)**and is rate determining. In this context, we computed following three possible modes of the occurrence of the first step:

(i) Direct reaction of amine with methyl propiolate and

(ii) Initial formation of a reactant-complex of methyl propiolate with a molecule of amine followed by the attack of amine on this reactant-complex and subsequent progress of the reaction.

(iii) We explored a third route also, which involved attack of 1-methylpiperazine (**15a**) on methyl propiolate from the side opposite to the complexing amine molecule. However, on optimization, it changed into the same transition structure $\mathbf{TS_{comp}1a}$ that was obtained in route 2.

It was found that the reaction path initiated by the attack of the amine **15a** on the reactant-complex is a lower energy path, the activation energy barrier being lower than the one involved in the direct attack by 4.3 kcal mol^{-1}. In fact, formation of the complex results in lowering of the energies of all species, but the transition state of the rate determining step, i.e. the first step ($\mathbf{TS_{comp}1a}$) is stabilized much more than the reactant, thus making overall the reaction faster.All reactions are accompanied by decrease in entropy. However due to exothermicities, $\Delta H°$ ranging from -54 to -59 kcal mol^{-1}, standard Gibbs free energy of all the reactions has negative value revealing their exergonic nature. Moreover, free energy of activation ($\Delta G^{\neq}$) also has moderate value, ca. 27 to 37 kcal mol^{-1}. Thus all reactions are expected to occur at ambient temperature (~25 °C) as observed experimentally.

In order to check the effect of the solvent on the rate of the reaction, single point energies of the reactant-complex and the transition structure **TS_{comp}1a** in methylene chloride were also calculated at the MPW1B95/6-31+G(d,p) level and total energies were obtained by adding to these energies the zero-point corrections computed at the B3LYP/6-31+G(d) level. It is found that the activation barrier is slightly raised to 11.2 kcal mol^{-1}. Thus solvent is expected to affect the rate of the reaction marginally only.

(2) Second step -This step involves 1,3-prototropic shift of the NH proton to the carbanioniccentre C2 of the intermediate to furnish the final product.

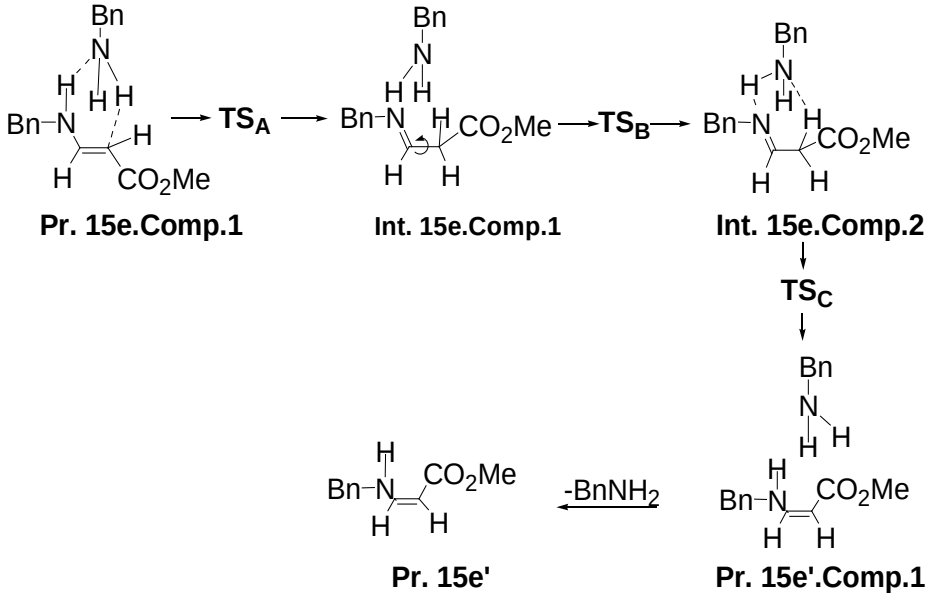
1,3-Prototropic shift in the second step may take place directly or through the intermediate complex. The activation energy barrier for the second step occurring through the intermediate complex is also lowered from 9.1 to 1.8 kcal mol^{-1} only.

Reaction with benzylamine and mechanism of trans-cis isomerization

The reaction with benzylamine (**13e**) afforded a mixture of two products**15e** and **15e'**.As mentioned earlier, under kinetic control, *trans*- and *cis*- isomers are formed in 28:72% ratio, as revealed by the ^{1}H NMR spectrum of the product obtained after 2 hrs. The *cis*- isomer is expected to be thermodynamically more stable due to intramolecular hydrogen bonding between NH proton and the C=O group. In view of this, we calculated theoretically the percentages of the two isomers under thermodynamic control. A difference of 0.5 kcal mol^{-1} corresponds to 30% of the *trans*- isomer by applying the formula, $k1/k2=e^{-\Delta E/RT}$.

The possible mechanism of isomerization of the initially formed *trans*product of benzylamine to the *cis* isomer was investigated and whole sequence

of events has been proposed. It is found that the initially formed *trans*enamine forms a complex with a molecule of benzylamine, the latter sitting in the cavity, -NH-C(3)H=C(2)H- of the enamine product. In this complex, lone pair of the nitrogen atom of the amine faces the NH proton of the enamine on the one side while on the other side, NH proton of the amine sits just opposite to the =C(2) atom of enamine. This arrangement facilitates transfer of the NH proton to the =C(2)- atom via the amine molecule. The proton transfer results in changing of enamine -NH-C(3)H=C(2)H- to imine –N=C(3)H-C(2)H_2- group, thus making free rotation about –C(3)-C(2)H_2- possible. After rotation of –C(3)-C(2)H_2- through 180°, a proton of –C(2)H_2- is transferred back to the nitrogen atom of imine –N=C(3)- intermediate through the amine molecule thus generating enamine –NH-C(3)H=CH- part of the *cis*-isomer. The whole sequence of events involved in *trans*-*cis* isomerization is shown below.



3.4. Experimental Details

Reaction procedure and experimental techniques used during the synthesis of maleimic acid derivatives and their purification are given in this section.

3.5. Computational Methods

The computational software and techniques used in the theoretical investigation are described in this section.

3.6. Conclusions

Secondary amines add to methyl propiolate with complete stereoselectivity to afford *trans*-methyl β-(dialkylamino)acrylate. However, reaction with a primary amine, namely benzylamine leads to the formation of a mixture of *trans*- and *cis*-methyl β-(benzylamino)acrylate in 26:74% ratio.

Theoretical investigation of the reaction mechanism reveals thataza-Michael addition of amines to methyl propiolate follows a step-wise mechanism, formation of a zwitterionic intermediate being followed by 1,3-prototropic shift. Initial formation of the amine-methyl propiolate complex followed by the attack of the amine is found to be the lower energy path for the overall addition reaction. The solvent, namely methylene chloride is expected to have almost no effect on the reaction rate. Furthermore, it is found that*trans* → *cis* isomerization of the initially formed product from the reaction of benzylamine occurs via an “enamine-imine-enamine” sequence mediated by a molecule of amine.

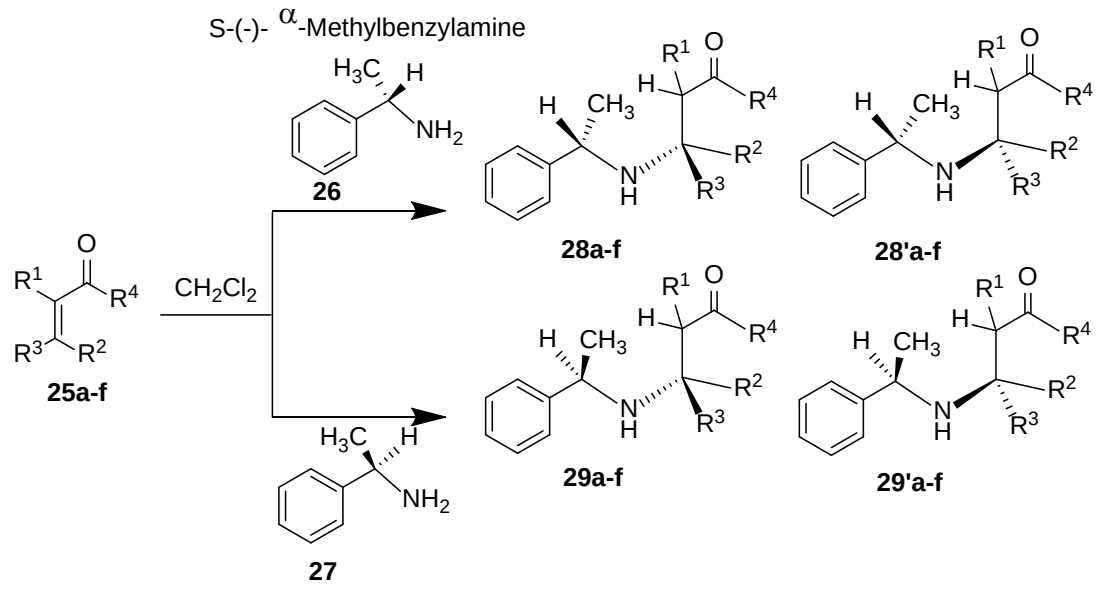
Chapter 4 Diastereoselectivity in Asymmetric Michael Addition of α-Methylbenzylamines to α,β-Unsaturated Carbonyl Compounds

4.1. Introduction

Aza-Michael addition represents one of the most attractive and straightforward procedures for the asymmetric synthesis of β-amino carbonyl compounds or related derivatives. The resulting chiral-nitrogen containing organic molecules display interesting biological activities and are useful building blocks for organic synthesis.It has been possible to induce asymmetry in these reactions by using various chiral auxiliaries and adopting different strategies. In this context, the different strategies employed in order to achievethe desired high stereo-control can be classified according to the reactant in which chiral induction is incorporated.In order to illustrate these strategies, some examples are given in this section; it is, however, not a comprehensive review on the asymmetric aza-Michael reactions.

4.2 Experimental Results and Discussion

(S)-(-)-α-Methylbenzylamine (**26**) and (R)-(+)-α-methylbenzylamine(**27**) reacted with β-substituted α,β-unsaturated carbonyl compounds (**25**) in dichloromethane at r.t. to afford mixtures of the diastereomers **28+28'** and **29+29'** respectively (**Scheme 4.9**).



25,28,29	a	b	c	d	e	f
R^1	H	H	H	H	H	CH_3
R^2	H	H	H	H	H	CH_3
R^3	C_6H_5	CH_3	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	C_6H_5	H
R^4	H	H	OH	H	OCH_3	H

Scheme 4.9. Reaction of α-methylbenzylamines to α,β-unsaturated carbonyl compounds.

4.2.1. Characterization of the products

In all cases, the resulting products were found to be mixtures of two diastereomers, which could not be separated even by column chromatography. But in ^{1}H NMR spectra, the signals could be assigned to the two diastereomers. Furthermore, high resolution mass spectra (HRMS) and other spectral studies confirmed formation of the expected compounds.

^{1}H NMR signals for the aldehydic protons are observed in the most downfield region of δ 8-9 ppm. In the case of the diastereomers **28a**,**28'a** obtained from the reaction of (S)-(-)-α-methylbenzylamine (**26)** with cinnamaldehyde, a

double doublet (dd) at δ 9.71 ppm ($^3J_{HH}$=7.7, $^3J_{HH}$=1.0 Hz) results due to the aldehydic proton of the major diastereomer. Another dd slightly upfield at δ8.12 ppm ($^3J_{HH}$=7.7, $^3J_{HH=0.0}$) is found due to the minor diastereomer. On the basis of the relative intensities of these two signals, the calculated percentages of the two diastereomers (**28a** and **28a'**) were found to be 78 % and 22 %respectively. These relative percentages are in conformity with the relative percentages obtained from HPLC.

The methylene protons at C3 are diastereotopic and constitute an ABC spin system with the proton H_C present at C4. Thusthree characteristic double doublets (dds) are observed for the methylene protons H_A and H_B and proton H_C in the region of δ 2.15-2.52 ppm.

Diastereoselectivity

As discussed earlier, diastereoselectivity of the two diastereomers in each case was calculated on the basis of the relative intensities of the aldehydic or other appropriate protons. In one case, namely **28a, 28a',** the diastereoselectivity was determined by general HPLC. It is observed that the overall diastereoselectivity is 52%.It is interesting to find that the *de* of the two diastereomers formed from the reaction of (S)-(-)-α-methylbenzylamine with cinnamaldehyde determined on the basis of HPLC (52 %) is very close to that calculated on the basis of the relative intensities of the aldehydic protons (56 %) in the ^{1}H NMR spectrum.

4.3. Theoretical Results and Discussion

We attempted to rationalize the experimentally observed diastereoslectivity of the reaction theoretically at the B3LYP/6-31+G* level using GAUSSIAN 03

Package and computed the reactions involving the attack of (R)-(+)-α-methylbenzylamine and (S)-(-)-α-methylbenzylamine on *Si* and *Re* faces of *trans*-cinnamaldehyde and other α,β-unsarurated carbonyl compounds. The model reactions were computed for the attack of (S)-(-)-α-methylbenzylamine and (R)-(+)-α-methylbenzylamine on *Re* and *Si* faces of cinnamaldehyde.

Our repeated efforts to locate the transition structures failed and hence it has not been possible to determine which product is preferred kinetically. However, it may be seen that product **31** formed from the attack on the *Re* face is thermodynamically more stable than the product **30** formed from the attack on the *Si* face by 2.84 kcal mol^{-1} which corresponds to 100% diastereoselectivity. Thus the observed stereoselectivity based on ^{1}H NMR cannot be rationalized on the basis of the relative thermodynamic stabilities of the two diastereomers determined theoretically.

4.3.1. Rationalization of the chemical shifts of the aldehydic protons of the products 30 and 31

The chemical shifts of the aldehydic protons of the two diastereomers formed from the reaction of (S)-(-)-α-methylbenzylamine with *trans*-cinnamaldehyde are distinctly different, i.e. δ8.12 (minor) and δ 9.71 (major) ppm. We tried to rationalize this difference theoretically. It is interesting to find that the aldehydic proton of the minor product (**30**) falls in the shielding zone of the phenyl ring whereas that of the major product (**31**) comes in the deshielding zone.

4.4. Experimental Details

Reaction procedure and experimental techniques used for the reactions of chiral amines with β-substituted α,β-unsaturated carbonyl compounds are described in this section.

4.5. Computational Methods

Various computational software and techniques used in the theoretical investigation are described in this section.

4.6. Conclusions

The aza-Michael addition of (R)-(+)- and (S)-(-)-α-methylbenzylamines with α,β-unsaturated carbonyl compounds occur with high diastereoselectivity ranging from 52 to 98%, except in the reactions of the amines with *trans*-crotonaldehyde which may be attributed to the smaller size of the methyl group as compared to the phenyl or substituted phenyl group in other cases.

Theoretical studies reveal that the product resulting from the attack on the *Re* face is thermodynamically more stable than the product formed from the attack on the *Si* face. However, observed diastereoselectivity based on ^{1}H NMR cannot be rationalized on the basis of the relative thermodynamic stabilities of the two diastereomers determined theoretically.

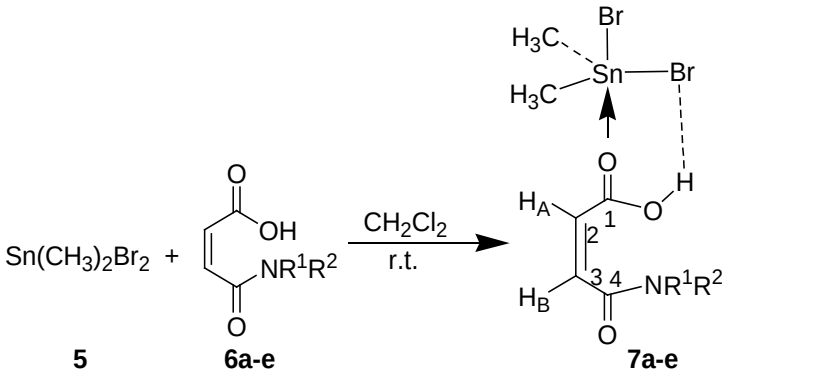
Chapter 5. Synthesis, Characterisation and Bioactivity of New Tin (IV) Complexes with Maleamic Acid Derivatives as Ligands

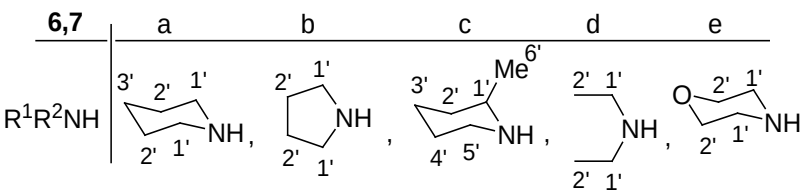
5.1 Introduction

A survey of the literature revealed that maleamic acids exhibit interesting bioactivity. Also, organotin (IV) complexes formed with N,O-ligands have been found to be effective anti-microbial, antifungal and antiviral agents. Recently, our research group also reported synthesis, characterization and bioactivity of tin(IV) complexes of imidazo[1,2-a]pyridines and related N-heterocycles.Since many new substituted maleamic acids from the reactions of secondary amines with maleic anhydride became available in good yields, we were tempted to use these compounds as ligands for the synthesis of new organotin (IV) complexes and screen these complexes for their bioactivity; the results are presented in this Chapter.

5.2. Experimental Results and Discussion

The reaction of dimethyltin dibromide (**5**) with maleamic acid derivatives (**6**) in dichloromethane afforded corresponding complexes (**7**).





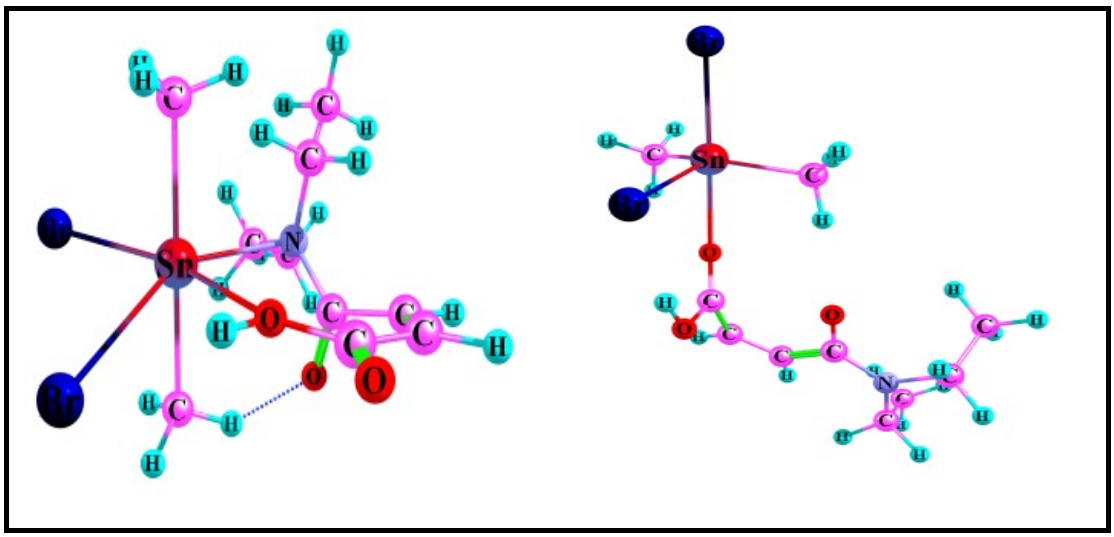
Complexes **7a, 7b** and **7d** are colourless crystalline solids having high melting points and are readily soluble in polar solvents like dichloromethane, ethanol but sparingly soluble in nonpolar solvents such as hexane and toluene. However, other two complexes **7c, 7e** were obtained as viscous mass which did not form crystals in spite of repeated efforts using different solvents. Structures of the resulting complexes have been established on the basis of spectroscopic techniques (IR, ^{1}H, ^{13}C, ^{119}Sn NMR) and HRMS.

5.2.1. Characterization of the products

Although it has not been possible to obtain suitable single crystals of any of the complexes for X-ray crystal structure analysis, good inferences could be drawn about the mode of co-ordination of the ligands on the basis of a comparison of the IR and ^{1}H NMR spectra of the ligands (given in Chapter 2) and the corresponding tin complexes. A peak in the range of -49 to -115 ppm confirms the formation of a single complex in each case.

Possible geometry of the tin (IV) complexes

As it has not been possible to do X-ray crystal structure analysis of the complexes, we decided to look into the possible geometry by carrying out DFT calculations. DFT calculations of some tin complexes have been reported in the past. We expected that maleamic acid would act as a chelating ligand co-ordinnating through N and O atoms giving an hexa-coordinated tin complex. We optimized the possible geometry having hexa- coordinated tin species at the B3LYP/lanl2dz level. The starting point (A) and the optimized geometry as the minimum (B) of the complex formed with N,N-diethylmaleimic acid are shown in Figure 5.8.



A B

Figure 5.8. The starting points and the optimized geometry of **7d**.

It may be noted that after optimization, global minimum of the complex has a penta co-ordinated tin species, maleamic acid co-ordinating to the tin atom through the carbonyl oxygen of the acidic group. Thus it may be assumed that the resulting complexes have distortrd trigonal bipyrimidal geometry having two methyl groups in the equatorial positions.

5.2.2. Results of the bioactivity of organotin(IV) complexes

Antibacterial activity

All the synthesised organotin(IV) complexes were screened for the antibacterial activity. The test organisms included the 3 Gram negative and 3 Gram positive bacteria procured from MTCC, Chandigarh. The Gram positive bacteria included *Micrococcus luteus* (MTCC 106)*Bacillussubtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 737) while the Gram negative bacteria included *Escherichia coli* (MTCC 40), *Proteus vulgaris* (MTCC 426) and *Pseudomonas aeruginosa* (MTCC 424).

5.3. Experimental Details

Reaction procedure and experimental techniques used during the synthesis of maleimic acid derivatives and its purification is given in this section.

5.3. 4. Material and methods for the antibacterial activity

Model Organisms, sources of organisms, maintenance and culture of the bacteria strain etc. are included in this section and in its subsections.

5.3.5. Minimum inhibition concentration determination

Calculated values and data related to the minimum inhibition concentration (MIC) are given in this section.

5.4. Conclusions

Maleimic acid derivatives act as mono-dantate ligands and form 1:1 complexes with dimethyltin dibrommide, co-ordination taking place through the carbonyl oxygen of the acidic group. Computational energy minimization indicates that the complexes possibly have a distorted trigonalbipyramidal geometry having both methyl groups in the equatorial position.

The synthesised complexes are found to be active against both gram positive and gram negative bacteria. Organotin(IV) complex formed with *N*-(piperidino)maleamic acid is found to be the most potent antibacterial agent. Also these complexes can be further studied for their other application in medical sciences.