

ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL OF SCIENCE
ENGINEERING AND TECHNOLOGY

**A THEORETICAL APPROACH TO THE MECHANISMS OF COPPER-
CATALYZED FUROFURAN AND 1,2,3-TRIAZOLE SYNTHESIS**

Ph.D. THESIS

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Department of Chemistry

Chemistry Programme

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İSTANBUL TEKNİK ÜNİVERSİTESİ ★ FEN BİLİMLERİ ENSTİTÜSÜ

**BAKIR KATALİZÖRLÜ FUROFURAN VE 1,2,3-TRIAZOL SENTEZ
MEKANİZMALARINA TEORİK BİR YAKLAŞIM**

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ABBREVIATIONS

B3LYP	: Becke-Lee-Yang-Parr Gradient Three Parameter Corrected Exchange-Correlation Functional
BLYP	: Becke-Lee-Yang-Parr Gradient Corrected Exchange-Correlation Functional
CuAAC	: Copper-Catalyzed Azide-Alkyne Cycloaddition
Cu(acac)₂	: Copper acetylacetonate
DFT	: Density Functional Theory
DMDM	: Dimethyldiazomalonate
DMSO	: Dimethyl Sulfoxide
ECP	: Effective Core Potential
GTO	: Gaussian Type Orbital
IEFPCM	: Integral Equation Formalism Polarizable Continuum Model
IRC	: Intrinsic Reaction Coordinate
LDA	: Local Density Approximation
LYP	: Lee-Yang-Parr Gradient Corrected Correlation Functional
NBO	: Natural Bond Orbital
PCM	: Polarizable Continuum Model
SCRf	: Self-Consistent Reaction Field
STO	: Slater Type Orbital

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A THEORETICAL APPROACH TO THE MECHANISMS OF COPPER-CATALYZED FUROFURAN AND 1,2,3-TRIAZOLE SYNTHESIS

SUMMARY

In this thesis different Cu catalyzed [3+2] cycloaddition reactions have been modelled to account on their reaction mechanisms. The [3+2] cycloaddition reactions are commonly employed in the literature. Basically, in a [3+2] cycloaddition reaction, two unsaturated bonds react with each other to produce a ring structure. 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition, can also occur in the presence of transition metals as catalyst.

The main aim of this study is to investigate the mechanisms of two copper-catalyzed Huisgen cycloaddition reactions. In the first one, copper catalyzed diazoester decomposition has been investigated with structurally similar dioxepine molecules as reactants, in which one of the dioxepines gives furofuran, a [3+2] cycloaddition product, while the other one gives a cyclopropanation product. The only difference between dioxepine species is the position of double bond. The possible mechanisms and the reasons behind the differences in product distribution have been investigated in the light of experimental and previous literature findings.

In the second part, the mechanism of a series of copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions which yield 1,2,3-triazole products, has been investigated. Although various mechanisms have been proposed kinetically and computationally on CuAAC, there are still unclear points. Recent studies contradict the initial studies. In this study, it is aimed to elucidate the mechanism and the unclear points about CuAAC reactions by considering all possibilities and the proposals, obtained in the literature.

In the first part of this thesis, the mechanism of copper-catalyzed furofuran synthesis has been investigated. Furofurans are important bicyclic rings particularly in pharmacology. Therefore, there are many experimental studies on the synthesis of furofurans. In this part of the thesis the reactions of two dioxepine with dimethyl diazomalonate in the presence Cuacac have been modelled with DFT at B3LYP/6-31G*. Two different dioxepine molecules react with diazoester in presence of copper-catalyst. While 4,5-dihydro-2-methyl-1,3-dioxepine gives [3+2] cycloaddition product, 4,7-dihydro-2-methyl-1,3-dioxepine reveals a cyclopropanation product. The difference in the position of double bond is the main factor that affects the product distribution. First, the mechanism that leads to [3+2] cycloaddition product, namely furan, has been investigated. The whole mechanism can be categorized into three sections which are copper-carbene, furan and furofuran formations. From the previous studies on cyclopropanation, it is known that the mechanism commence with copper-dioxepine coordination and it is the reference point for the energy profile of the mechanism. After that, diazoester approaches to the copper-dioxepine complex through its O and N atoms. This interaction weakens the copper dioxepine interaction whereby alkene is expelled from the copper catalyst.

κ -N-O copper-diazoester structure is transformed to copper-carbene via various intermediates and transition states.

When the copper-carbene formation is completed, it is reacted with the dioxepine to start furan formation as a next step. All the possible paths that lead to furan have been considered. In the preferred pathway, the double bond of the dioxepine interacts with carbene carbon enabling the double bond to attach to carbene-carbon. To constitute the five-membered ring, the carbonyl group in ester moiety, which will further attack to carbon atom, has to rotate. After attacking of the carbonyl group, the furan molecule is released from the copper-catalyst by the approach of a second dioxepine to the copper atom.

The hypothetically possible pathways that compete with the main pathway have also been examined. The first option is the [3+2] cycloaddition via metallacyclobutane intermediate. The copper-carbene structure is reacted with dioxepine molecule in proper geometry to produce metallacyclobutane and this highly reactive intermediate yields the desired products. The second option is the [3+2] cycloaddition via cyclopropane intermediate. The copper-carbene structure is reacted with furan molecule in proper geometry to produce cyclopropane associated copper-catalyst. After formation of cyclopropane associated copper-catalyst, a cyclopropane product or a less favorable [3+2] cycloaddition product can be obtained. Although these options hypothetically exist, energetically they are unfavorable over the main pathway by 10.5 and 3.1 kcal/mol, respectively. After conversion of dioxepine molecule to the furan intermediate, furofuran formation is initiated. The furan molecules react with copper-carbene to produce furofuran molecule to complete reaction. Geometrically, the mechanisms of furan and furofuran formations resemble each other. The barriers of furofuran mechanisms are higher than that of furan formation due to steric effects. Additionally, during investigation, the formation of a regioisomer of the furan has been taken into account and a similar mechanism has been devised. However; the formation of the regioisomer is energetically unfavorable by 11.8 kcal/mol as expected.

As mentioned before, when the double bond is shifted to the adjacent bond in dioxepine reactant, the route of reaction has changed from [3+2] cycloaddition to cyclopropanation. To understand the effect of shifting of the double bond on the dioxepine reactant, the mechanism of cyclopropanation has been probed. The mechanism of cyclopropanation consists of two sections which are copper-carbene formation and cyclopropanation. The position of the double bond enables different interactions with the copper-carbene species. Three different pathways have been devised for cyclopropanation. While two of them intersect at the metallacyclobutane intermediate, the third one directly leads to cyclopropane associated copper-catalyst complex. According to the calculations, the barriers of the rate-determining steps for the devised mechanisms of cyclopropanation are very close to each other. Hence, there is no distinctive pathway for cyclopropanation. Additionally, the possibility of [3+2] cycloaddition reaction of 4,7-dihydro-2-methyl-1,3-dioxepine is examined. The transition state for such an option is found to be energetically unfavorable by 3.2 kcal/mol as expected. The discrepancy in product distribution between two dioxepine molecules is stemming from the effect of double bond on the polarity of dioxepines. When the double bond comes closer to the O atom in dioxepine, the dioxepine molecule becomes more polar whereby it becomes more suitable for [3+2] cycloaddition.

In the second part of the thesis, the mechanisms of a series of copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions which yield 1,2,3-triazole derivatives have been investigated. 1,2,3-triazole derivatives show anti-HIV, anti-bacterial, anti-histamine and anti-tumor activity. CuAAC reactions are one of the most fruitful reactions of click chemistry. Click chemistry is a philosophy described by Nobel awarded K.B. Sharpless which generates substances by joining small modular units based on favorable carbon hetero atom connections. In CuAAC reactions, 1,2,3-triazole derivatives are obtained regioselectively and faster under benign reaction conditions contrary to uncatalyzed ones. However, only terminal alkynes are reactive species for CuAAC reactions. According to the literature, mechanism starts with the coordination of alkyne triple bond to the copper atom. Deprotonation is assumed to occur easily to form copper-acetylide due to highly acidic nature of the triple bond. Afterwards, azide attacks to copper-acetylide that gives rise to copper-triazolide formation. At the final step, protonation of copper-triazolide is released from copper.

Before investigating the mechanism, the structure of copper-acetylide species has to be ascertained because this structure could not be isolated and was assumed to form at the beginning of the reaction. To determine the structure, a series of copper-acetylides has been investigated which contain up to four copper atoms because higher number of copper has catastrophic effect in CuAAC reactions. Additionally, the solvents, acetonitrile and water which has been taken into account can act as ligand. According to calculations, four membered-copper copper-acetylide without ligand has the lowest free energy among the many possibilities, in accordance with literature findings.

The mechanism starts with Cu-azide interaction through the α -N which is found as rate-determining step. Then, terminal N atom of azide attacks to carbon atom to constitute a six-membered cyclic structure. Finally, formation of copper-triazolide intermediate takes place. Subsequently, the devised mechanism has been applied to the real world system which gave results consistent with the model system. Additionally, the protonation step has also been examined with the model system. The highest barrier has been found in this step.

In the second section, the mechanisms of copper-catalyzed diazide-alkyne and azide-dialkyne cycloaddition reactions have been investigated, respectively. According to the experiments, a diazide reacts with an alkyne to give a ditriazole product as major product even when excess diazide species are used over dialkyne while a dialkyne reacts with an azide to give both mono and di -triazole products as statistical mixture.

In the mechanism of diazide-alkyne reaction, two possibilities have been evaluated which have the same pathway until the formation of the first copper-triazolide: either a protonation can occur or unreacted azide moiety reacts with adjacent Cu-C-C group. The higher barrier for protonation makes this step unfavorable.

In the mechanism of azide-dialkyne reaction, there is a statistical mixture between mono and ditriazole products which is caused by the ligand functionality of monotriazole product for copper atom. The formation of monotriazole is inevitable in contrast to diazide-alkyne reaction.

On the other hand, the mechanisms for both diazide-alkyne and azide-dialkyne have great agreement with previous azide-alkyne reaction. Energy values are close to each other. Additionally, solvents have no important effect on the mechanisms.

BAKIR KATALİZÖRLÜ FUROFURAN VE 1,2,3-TRIAZOL SENTEZLERİNİN MEKANİZMASINA TEORİK BİR YAKLAŞIM

ÖZET

Bu çalışmada çeşitli [3+2] siklokatılma tepkime mekanizmaları kuantum mekanik yöntemlerle modellenmiştir. Siklokatılma tepkimeleri perisiklik tepkimelerden olup halka yapısına sahip ürünlerin sentezlenmesini sağlamaktadır. Literatürde birçok [3+2] siklokatılma tepkimesi raporlanmıştır.

Temel olarak, bu tip tepkimelerde iki doymamış bağ birbiri ile tepkimeye girerek halka ürünü oluşturur. 1,3-dipolar siklokatılma metodları, Huisgen siklokatılma ya da Huisgen tepkimesi olarak da bilinen, [3+2] siklokatılma tepkimelerinde kullanılan ana yöntemlerden birisidir. Diazoalkan 1,3-dipolar ve azit-alkin Huisgen siklokatılmaları 1,3-dipolar siklokatılmalara tipik örneklerdir. Bu tip tepkimelerde geçiş metalleri katalizör olarak da kullanılabilirler.

Bu tezin ana amacı bakır katalizörlü iki Huisgen tepkimesinin mekanizmalarını kuantum mekanik yöntemlerle detaylı bir şekilde incelemektir. İlk tepkime bakır katalizörlü diazoester bozulmasıdır. Diazoester molekülü bakır katalizör varlığında iki farklı dioksepin ile tepkimeye girerek ana ürün olarak [3+2] siklokatılma ürünü olan furofuranı ya da siklopropanasyon ürünü vermektedir. Dioksepin moleküllerindeki temel farklılık çift bağın yeridir. Olası mekanizmalar ve ürün dağılımındaki farklılığın nedenleri deneysel ve literatür çalışmalarına dayanılarak incelenmiştir.

İkinci bölümde, ürün olarak 1,2,3-triazol türevleri veren bir seri bakır katalizörlü azit-alkin siklokatılma (CuAAC) tepkimelerinin mekanizmaları incelenmiştir. CuAAC tepkimeleriyle ilgili olarak literatürde birçok çalışma bulunmasına rağmen, mekanizmada hala tam olarak aydınlatılamayan noktalar bulunmaktadır. Konuyla ilgili son çalışmalar ile ilk çalışmalar arasında çelişen noktalar mevcuttur. Bu çalışmada temel hedef olan CuAAC tepkime mekanizması tüm olasılıkları ile değerlendirilmiş ve hesaplamalı kimya yöntemleri ile incelenmiştir.

Bakır katalizörlü furofuran tepkime mekanizması tezin ilk bölümünü oluşturmaktadır. Furofuran farmakolojik açıdan önemli bisiklik halka yapıları içermektedir. Bu nedenle, furofuran türevlerinin sentezi ile ilgili bir çok deneysel çalışma bulunmaktadır. Tezin bu bölümünde iki farklı dioksepin bileşiğinin ve dimetildiazomalonatın bakır(II)asetilasetonat varlığında yaptığı tepkime Yoğunluk Fonksiyoneli Teorisi ile B3LYP/6-31G* baz seti kullanılarak incelenmiştir. 4,5-dihidro-2-metil-1,3-dioksepin bileşiği [3+2] siklokatılma ürünü verirken, 4,7-dihidro-2-metil-1,3-dioksepin bileşiği ana ürün olarak siklopropanasyon ürünü vermektedir. Dioksepin bileşiklerindeki tek fark çift bağın konumudur. Çift bağ oksijen atomuna yakın olan karbona kaydığında elde edilen ürün siklopropanandan furana değişmektedir. İlk olarak furan oluşum mekanizması incelenmiştir. Tüm mekanizma üç aşamadan oluşmaktadır. Bunlar sırasıyla bakır-karben, furan ve

furofuran oluşumlarıdır. Daha önce benzer bir dioksepin türevinin siklopropanasyon tepkime mekanizması tarafımızdan kuantum mekanik yöntemlerle incelenmiş ve bu çalışmadan elde edilmiş olan bilgiler ışığında, birinci aşamada gerçekleşen bakır karben oluşumu tez çalışmasına konu olan dioksepinler için de tekrarlanmıştır. Bakıra koordine olmuş dioksepin yapısının, bakır-karben oluşum mekanizması için başlangıç noktasını oluşturmuştur ve bu yapı tüm enerji profili için referans noktası olarak belirlenmiştir. Bu yapıya, diazoester bileşiği oksijen ve nitrojen atomlarıyla yaklaşarak bakıra koordine olur ve bu etkileşim dioksepinin bakır bağı zayıflatarak dioksepin molekülünün sistemden geçici olarak ayrılmasını sağlar. Daha sonrasında ise katalizör-diazoester yapısı çeşitli ara ve geçiş yapılarından geçerek bakır karbeni meydana getirir.

Bakır-karben oluşumunun arkasından [3+2] siklokatılma tepkimesi sonucu furan oluşumu gerçekleşmektedir. Bakır karben oluşumu esnasında sistemden ayrılan dioksepinin çift bağı bakır-karben ile tepkimeye girerek dioksepinin karben karbonuna bağlanmasını sağlar. Ancak, beş üyeli halka yapısını meydana getirebilmek için diazoester molekülündeki karbonil grubunun dönmesi gerekmektedir. Bu dönüşün sonucunda yapı furan oluşumu için uygun bir geometri kazanır. Karbonil grubunun karbon atomuna saldırmasından sonra, bu yapıya ikinci bir dioksepin yapısı bağlanarak meydana gelen furan halkasının serbest kalmasını sağlar.

Varsayımsal açıdan ana mekanizmaya alternatif olup furan ürünü verebilecek mekanizmalar da ayrıca dikkate alınıp incelenmiştir. İlk alternatif metalsiklobütan ara yapısı üzerinden furan sentezidir. Bakır-karben yapısı dioksepin bileşiği ile uygun bir şekilde tepkimeye girerek metalsiklobütanı meydana getirir. Bu oluşan oldukça aktif ara yapıdan furan elde edilir. İkinci alternatif, siklopropan ara yapısı üzerinden [3+2] siklokatılma ile furanın oluşmasıdır. Karben karbonu dioksepin bileşiği ile yine uygun bir geometri ile tepkimeye girerek siklopropan ara yapısını meydana getirir. Bu aşamadan sonra mekanizma iki kola ayrılmaktadır. Birinci yönde siklopropan enerji açısından daha düşük bir bariyer atlayarak bakır katalizörden ayrılır. İkinci yönde ise furan meydana gelmektedir. Teorik olarak alternatif yollar bulunmakla birlikte, bu alternatifler enerji açısından ana mekanizmanın hız-belirleyici adımından sırasıyla 10,5 ve 3,1 kkal/mol daha yüksek bariyerlere sahiptirler. Sistemdeki tüm dioksepin yapısı furana dönüştüğünde furofuran oluşum mekanizması başlar. Geometrik açıdan furan ve furofuran mekanizmaları birbirine benzer olup sterik etkilerden dolayı furofuran mekanizmasının enerji bariyerleri daha yüksektir. Ayrıca, araştırmamız sırasında tepkimeye giren iki molekülün birbirlerine göre duruş farklılıkları sonucu elde edilebilen izomerin oluşum ihtimali de dikkate alınmıştır. Bu izomere ait tepkime mekanizmasının modellenmesi sonucunda daha yüksek bir bariyere sahip olması nedeniyle (11,8 kkal/mol) ana ürüne alternatif olamayacağı doğrulanmıştır.

Daha önce de belirtildiği üzere, dioksepin molekülündeki çift bağı konumu değiştiğinde, elde edilen ürün de değişmektedir. [3+2] siklokatılma ürünü veren dioksepin yapısında çift bağ oksijen atomlarından birine yakın bulunurken, çift bağ oksijenlere eşit uzaklıktaki bağa kaydığında siklopropanasyon gerçekleşmektedir. Çift bağı neden böyle bir ürün dağılıma neden olduğunu anlamak için siklopropanasyon mekanizması da modellenmiştir. Siklopropanasyon mekanizması iki aşamadan oluşmaktadır; bakır-karben oluşumu ve siklopropanasyon aşaması. Bakır-karben oluşumu [3+2] siklokatılma bölümündeki mekanizmayla aynı şekilde ilerlemekte olup enerji açısından oldukça benzerdir. Bakır-karben yapısı çift bağı

kaymış dioksepin ile tepkimeye girdiğinde [3+2] siklokatılmadakinin daha farklı bir etkileşim elde edilmektedir. Siklopropanasyon için üç farklı mekanizma belirlenmiş olup enerji açısından birbirlerine oldukça yakın oldukları görülmüştür. Bu üç mekanizma içerisinde ikisi metallsiklobütan ara yapısını vermektedir. Üçüncü mekanizma ise doğrudan siklopropan meydana getirmektedir. Bu üç mekanizma için hız belirleyici adımların birbirlerine yakın oluşu herhangi bir mekanizmayı diğerleri arasından ön plana çıkarabilmeyi engellemektedir. Ayrıca, çift bağın kaymış olduğu dioksepin için de [3+2] siklokatılma ihtimali değerlendirilmiş ve bir geçiş yapısı bulunmuştur. Fakat bu geçiş yapısının bariyeri deneysel olarak gözlemlenmiş olan üçlü halkanın varlığını doğrulayacak şekilde siklopropanasyona göre oldukça yüksek olarak bulunmuştur. Çift bağın oksijene yaklaşmasından dolayı dioksepin molekülü daha polar olmaktadır. Artan polariteyle birlikte sistem 1,3-dipolar, bir başka deyişle [3+2] siklokatılma tepkimesi için daha uygun bir elektronik yapıya sahip olmaktadır.

Tezin ikinci bölümünde ise 1,2,3-triazol sentezi için kullanılan bakır katalizörlü azit-alkin siklokatılma (CuAAC) tepkimelerinin mekanizması incelenmiştir. 1,2,3-triazol bileşikler farmakolojide özellikle son yıllarda önemli bir yere sahip olmuşlardır. Yapılan araştırmalar sonucu bu bileşiklerin peptit bağlarını taklit edebilmeleri nedeniyle anti-HIV, anti-bakteriyel, anti-histaminik ve anti-tümör etkilerine sahip oldukları rapor edilmiştir. Ayrıca, farmakolojik özelliklerinin yanı sıra, literatürde agrokimyasal, korozyon önleyici ve boya özellikleri belirtilmiştir. Nobel ödüllü K.B Sharpless tarafından gerçekleştirilen klik kimyası çalışmalarında azit ve alkin molekülleri bakır katalizör varlığında tepkimeye sokulup yüksek verimle, çok basit tepkime koşullarında, oda sıcaklığında ve regioselektif olarak 1,2,3-triazol sentezi gerçekleştirilmiştir. “Klik-kimyası” yöntemi kimya literatürüne güçlü ve seçici bir yöntem getirmiştir. Bu yöntem sayesinde heteroatom linkleri basit deney koşulları altında başarıyla gerçekleştirilebilmektedir. Lakin bu yöntemle sadece uç alkinler tepkime verebilmektedir. Azit ve alkinin bakır varlığındaki klik tepkimesi bakır-asetilit oluşumu ile başlar. Başlangıç olarak alkin molekülü π -elektronlarını bakıra koordine eder. Üçlü bağın oldukça asidik olmasından dolayı sistem hızlıca deprotona olup bakır-asetilit meydana gelir sonrasında azit içindeki nitrojen atomuyla bakıra yaklaşır ve bir van der Waals yapısı oluşturur. Azit grubundaki uç nitrojen daha sonrasında karbonla bağ yaparak halka yapısını meydana getirir. Son aşamada bakır-triazolit yapısı protone olarak triazol mekanizması tamamlanır.

Öncelikli olarak bakır-asetilitin yapısının belirlenmesi gerekmekteydi çünkü tepkime çoklukla kullanılmasına rağmen bakır-asetilitte kaç bakırın bulunduğu, hangi ligandların bağlı olduğu ve bunun gibi benzeri noktalarda belirsizlikler mevcuttu. Başlangıçta sadece mekanizma üzerine odaklanmak için model bir sistem belirlenip sterik etkiler elimine edilmiştir. Daha sonrasında, bulunan mekanizma deneysel olarak 1,2,3-triazol veren bir sisteme uygulanmıştır. CuAAC mekanizması ile ilgili ilk çalışmalarda mekanizmanın tek bakır üzerinden ilerlediği düşünülmekteydi. Fakat daha sonra yapılan kinetik çalışmalar göstermiştir ki tepkime hız sabiti bakıra göre ikinci mertebededir. Bu sonuç çeşitli bakır-asetilit yapıları arasında dinamik bir dengenin varlığına işaret eder. Bizim çalışmamızda, model sistemdeki en kararlı bakır-asetiliti bulmak amacıyla bir, iki, üç ve dört bakırlı bakır-asetilit yapıları incelenmiştir. Daha yüksek sayıda bakır içeren yapılar mümkün olmasına rağmen bu yapıların CuAAC tepkimelerini durdurucu etkisi bulunduğu dikkate alınmamıştır. Ayrıca, bu tip tepkimelerde çözücü molekülleri ligant görevi görebilmektedir. Bu tez kapsamında yapılan hesaplamalara göre, dört-bakırlı bakır-

asetilit yapıları en düşük enerjiye sahiptirler ve bu yapılarda çözücü molekülleri bulunmamaktadır. Bu sonuç literatür bilgileri ile uyumludur.

CuAAC tepkime mekanizması literatürdeki öneriler ile uyumlu olarak azitin içindeki nitrojene koordine olması ile başlamaktadır. Bir sonraki aşamada ise uç nitrojen karbon atomu ile bağ yaparak altı üyeli halka yapısını meydana getirmektedir. En son aşama olarak bakır-triazolid yapısının protonasyonu gerçekleşerek, 1,2,3-triazol yapısı sistemden ayrılmaktadır. Geliştirdiğimiz model mekanizma bir adım ileriye götürülerek deneysel sisteme uygulanmıştır ve benzer sonuçlar elde edilmiştir. Yaptığımız literatür çalışmalarında protonasyon adımı ile ilgili herhangi bir çalışma bulunamamıştır. Bu amaçla model sistem tepkenleri kullanarak protonasyon aşaması ayrıca modellenmiştir. Elde edilen sonuçlara göre, en yüksek bariyer protonasyon aşamasında gözlemlenmiştir.

İkinci aşamada ise bakır katalizörlü diazit-alkin ve azit-dialkin tepkime mekanizmaları sırasıyla incelenmiştir. Deneysel sonuçlara göre, diazit-alkin tepkimesinde yüksek oranda diazit kullanılsa bile ditriazol ana ürün olarak elde edilmektedir. Diğer yandan azit-dialkin tepkimesinde tepkenlerin oranlarından bağımsız olarak daima mono- ve di-triazol karışımı elde edilmektedir.

Diazit-alkin mekanizması bakır-triazolit oluşumundan sonra iki farklı seçenek üzerinden gidebilmektedir. İlk seçenekte, bakır-triazolit protone olmaz ve kendisine bağlı diazitin tepkimeye girmemiş diğer uçtaki azit grubu Cu-C-C ile tepkimeye girerek bakır-ditriazoliti meydana getirmektedir. İkinci seçenekte ise bakır-triazolit protone olur ve sistemden monotriazollü azit ayrılır. Devamında ise monotriazollü azit bakır asetilit ile tekrar tepkimeye girmektedir. Protonasyon için bariyerin yüksek oluşu ve protone olabilsen bile devamında ikinci azitin tepkime mekanizmasının bariyerinin birinci seçeneğe göre daha yüksek olması tepkimenin yukarıda belirtilen ilk seçeneğini daha mümkün kılmaktadır. Bu da ne kadar azit kullanılırsa kullanılsın deneysel olarak ditriazol ürününün elde edilmesi ile uyumludur.

Azit-dialkin tepkimesinde ise bakır-triazolit protone olması gerektiğinden sadece tek bir mekanizma üzerinden yürümektedir. Monotriazol ara ürünü bakır için ligant görevi görebildiğinden dolayı ditriazol oluşumunu etkileyerek mono- ve di-triazol karışımına neden olmaktadır.

Diğer taraftan, hem diazit-alkin hem de azit-dialkin mekanizmaları daha önce incelenen azit-alkin tepkime mekanizması ile uyumludur. Enerji değerleri ise birbirlerine oldukça yakındır. Ayrıca, çözücünün mekanizma üzerindeki etkisi incenmiş olup önemli bir değişiklik gözlemlenmemiştir.

1. INTRODUCTION

Since the beginning of the modern chemical synthesis, development of new economical and efficient synthetic processes is a major topic in organic and inorganic chemistry. Among the many versatile methods, transition metal catalyzed synthesis is one of the most convenient ones.

Substituted heterocycles are crucial constituents of a huge number of units or sub-units that are obtained in biologically active natural or non-natural compounds. Cycloaddition reactions are employed traditionally to produce heterocyclic structures. The [3+2] cycloaddition reaction is a powerful method to form five-membered heterocyclic structures that can be observed in both intra- and intermolecular modes. In the literature, there are numerous [3+2] cycloaddition reactions, where the various types of molecules react, either in the presence or in the absence of various metal catalysts [1-3]. Copper is one of the transition metals that is frequently used and there is an increasing interest on copper as catalyst or co-catalyst for the synthesis of paramount heterocycles. It may serve as an alternative instead of the more expensive transition metals such as rhodium and ruthenium because of its cheapness and abundance. In the literature, copper catalyzed reactions including [3+2] cycloadditions have been extensively reviewed [4-9]. Although the mechanism of uncatalyzed [3+2] cycloaddition reactions have been thoroughly studied, the transition metal catalyzed reactions in most of the cases have unknown reaction mechanisms and the metals as catalysts are used as black boxes. Therefore, the role of the metal and the product distribution in transition metal catalyzed reactions are not straightforward and explaining the observed selectivity is an important task.

Main focus of this thesis is to study the mechanism of two copper-catalyzed [3+2] cycloaddition reactions which yield five-membered heterocycles, namely furan and 1,2,3- triazole derivatives.

1.1 Furofuran Formation by Cu(I) Catalyzed Cycloaddition Reaction

In the first part of this thesis work, furofuran formation by the [3+2] cycloaddition reaction of dimethyldiazomalonate (**DMDM**) with dioxepine species (4,5-dihydro-2-methyl-1,3-dioxepine and 4,7-dihydro-2-methyl-1,3-dioxepine) in the presence of copper(II) acetylacetonate ($\text{Cu}(\text{acac})_2$) catalyst, reported by Talınlı *et al.*, have been studied [10]. The investigation of the reaction mechanism and product distribution have constituted the first part of this thesis (Figure 1.1)

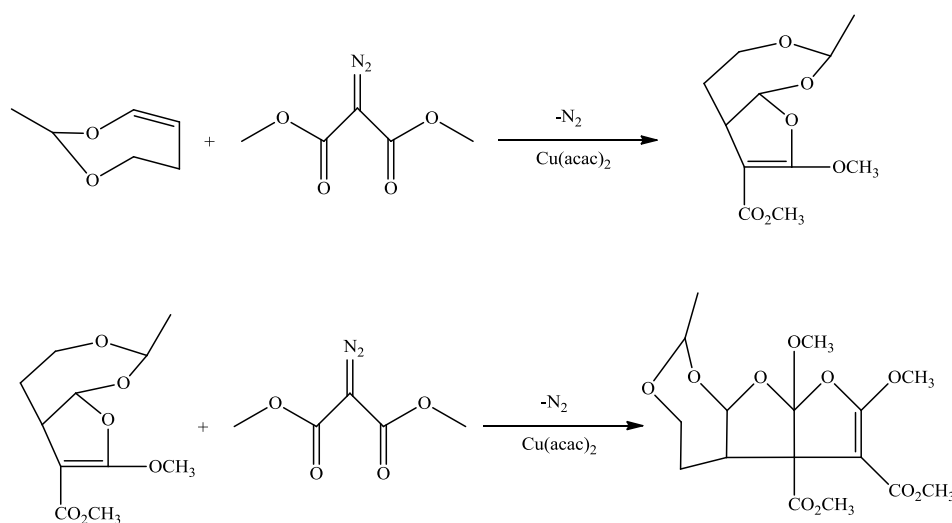


Figure 1.1 : The reaction scheme of copper-catalyzed furofuran synthesis.

Transition metals are effective catalysts for diazo decomposition since their complexes act as Lewis acid and then allow them to react as electrophiles with diazo compounds. In the generally accepted mechanism, the catalytic decomposition starts by the electrophilic addition and loss of dinitrogen to form a metal stabilized carbene species. The catalytic activity of the metal depends on the stability of the diazo compound and the electrophilicity of the transition metal. The forming metal carbene is electrophilic and eager to react with electron rich substrates [11].

Carbenes in general are highly reactive species in organic chemistry and they enable the synthesis of versatile products. Carbene complexes for almost all transition metals have been reported. Depending on the nature of the olefin species, metal-carbenes may take part in numerous paramount organic reactions such as cyclopropanation, cycloaddition and stevens re-arrangement [11-13]. Particularly, increasing attention on the cyclopropanation and cycloaddition reactions has given rise to both experimental and computational studies [11-16].

The coordinatively unsaturated transition metal compounds can effectively catalyze diazo decomposition reactions and stabilize the metal-bound carbenes. The "late" transition metals in the third and fourth period are generally selected for this purpose. In this respect, the Nozaki's synthesis of copper (II) complexes of chiral salicylaldehydes have opened a new era in asymmetric catalysis in metal carbene transformations [17]. Copper bronze and copper (II) sulfates are the oldest copper catalysts used for diazo decomposition. Formerly, it was assumed that both Cu(I) and Cu(II) are catalytically active species for this type of reactions. However; Kochi has shown that only Cu(I) is the catalytically active species and raised our understanding of copper in metal carbene reactions [18]. Copper-based catalysts are highly preferred in cyclopropanation and cycloaddition reactions due to their low cost and efficiency [19]. In the catalytic process, Cu(II) is reduced to Cu(I) by the diazo compound [18]. Today, generally Cu(I) is obtained via in situ reduction [20].

Starting from mid 60s, the copper (I) catalyzed cyclopropanation reaction came into prominence since many cyclopropane derivatives are found as subunits in antibiotics and biologically active substances or used as reagents in many organic reactions [21-24]. Among the various methods, diazo ester decomposition with olefins in the presence of transition metal catalysts is one of the most common methods to synthesize cyclopropanes [11,25]. Cyclopropanation via carbene transformation reactions provides achievement of high level of selectivity in addition to economical chemical synthesis.

[3+2] cycloaddition reaction is a powerful method to produce five membered cyclic structures which can be observed in both intra and intermolecular modes. In the literature, there are numerous [3+2] cycloaddition reactions, where the various types of molecules react, either in the presence or in the absence of various metal catalysts [4-9,13]. In the absence of metal catalyst, in thermal conditions, a variety of α -diazocarbonyl compounds can undergo 1,3-dipolar cycloaddition reactions with double bonds conjugated with carbonyl, amino or nitrile bonds without the loss of nitrogen. In the presence of metal catalyst, loss of dinitrogen is followed by formation of metal carbene or its metal bonded equivalent. The metal carbene acts as a 1,3-dipole and adds to double bonds to form five-membered heterocycles. The [3+2] cycloaddition reactions of methylene cyclopropanes with alkenes in the presence of nickel or palladium catalysts are also well known and theoretically

studied [26-31]. In the absence of a metal catalyst, 1,3-dipolar cycloaddition reactions have been shown to follow concerted path [32]. The concerted path can be either synchronous or asynchronous depending on the type of the molecules [33]. Cossio *et al.* have stated that in the presence of a metal catalyst such as chromium and tungsten, a highly asynchronous concerted mechanism in the limit of stepwise path was observed [34].

In the copper catalyzed carbene formation reaction mechanism, extrusion of N₂ has the highest Gibbs free energy value which is assigned as the rate determining step in literature [25,35,36]. Two mechanisms have been proposed for the formation of copper-carbene complex: olefin assisted [37] and olefin-nonassisted [35,36,38,39]. In the olefin-nonassisted mechanism, alkene leaves the catalyst before extrusion of N₂ where in olefin-assisted mechanism, alkene is bound to the catalyst until the formation of metal carbene. It is difficult to observe copper-carbenes spectroscopically due to their extremely high activity and it was only by ultra low temperature NMR that the first copper-carbene species could be detected [40]. Once the copper-carbene forms, it has got different alternatives.

In this study, a series of carbene transformation reactions reported by Talınlı *et al.* [10,41] has been modeled by means of computational chemistry methods (Figure 1.2). In the experiments, the diazo compound, dimethyldiazomalonate (**DMDM**), and the catalyst, copper(II) acetylacetonate Cu(acac)₂, have been reacted with a series of olefinic compounds. In the first part of the reaction, 4,5-dihydro-2-methyl-1,3-dioxepine used as substrate has revealed a furofuran product via [3+2] cycloaddition reaction. Pharmacologically, furofurans are used as antitumor, antimitotic, antiviral, antioxidant and antihypertensive agents [42]. Recently, many investigations have been made on the synthesis and modifications of furofurans [43] where most of these studies are experimental and the theoretical ones are rather scarce [44]. When the 4,7-dihydro-2-methyl-1,3-dioxepine was used as olefin under the same reaction conditions, a mixture of cyclopropanation and Stevens Rearrangement products was obtained with a ratio of 74:26, respectively.

The computational results discussed herein will allow one to understand the dynamics of catalytic [3+2] cycloaddition reaction in the presence of Cu(acac)₂. The modeling of cyclopropanation with 4,5-dihydro-2-methyl-1,3-dioxepine and 4,7-dihydro-2-methyl-1,3-dioxepine as substrate in addition to [3+2] cycloaddition will

enable us to explain the product distribution that was observed in their reaction with **DMDM** and Cu(I). In conjunction with our previous study, this work will shed a light on Cu(I) catalyzed carbene transformation reactions by considering possible competing reactions.

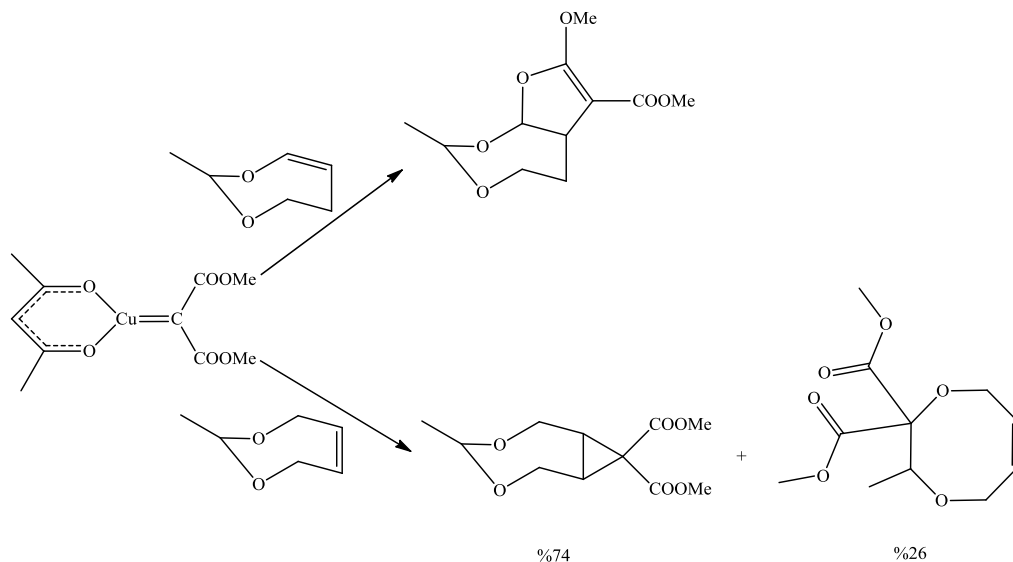


Figure 1.2 : The reactions of copper-carbene species with different dioxepine molecules.

1.2 1,2,3-Triazole Formation by Cu(I) Catalyzed Azide-Alkyne Cycloaddition Reaction

In the second part of the thesis, copper-catalyzed 1,2,3-triazole synthesis via the reaction of azides with alkynes has been modeled. Recently, a great deal of research has concentrated on the pharmacologically very important five-membered 1,2,3-triazole derivatives. According to investigations, due to their ability to mimic peptide bonds, 1,2,3-triazole derivatives show anti-HIV [45,46], anti-bacteriel [47], anti-histamine [48-50] and anti-tumor activity [51-53]. Besides their pharmacological features, they are used in agrochemistry, dye industry and as anti-corrosion agent [54].

The triazoles are generally obtained via 1,3-dipolar cycloaddition reactions of azides and alkynes (Figure 1.3). The reaction by heat has three disadvantages:

- i) Requires high temperature
- ii) The reaction has a slow rate
- iii) Shows poor regioselectivity

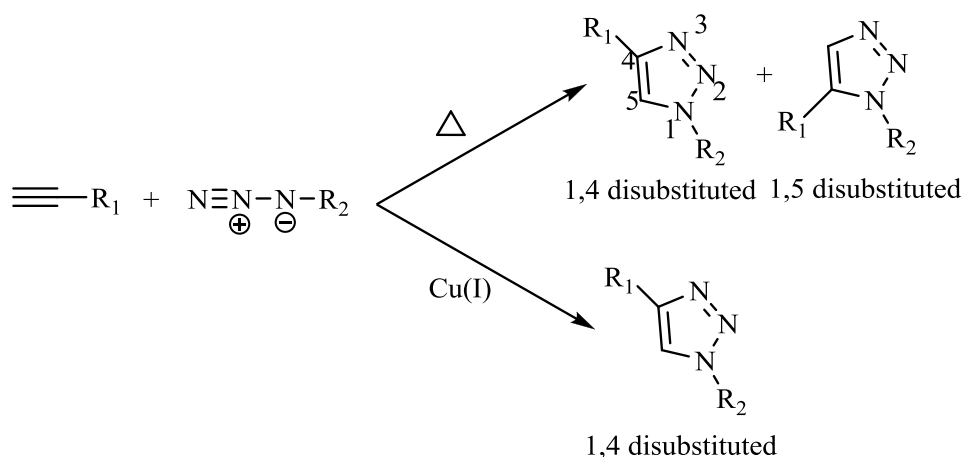


Figure 1.3 : The product distributions of catalyzed and uncatalyzed azide-alkyne cycloaddition reactions.

In 2001, M. Meldal [55] and Nobel awarded K.B Sharpless [56] reacted azide and alkyne in the presence of copper-catalyst in accordance with a protocol which is termed as “click chemistry”. By this reaction, triazoles could be obtained regioselectively. This reaction is 10^7 times faster as compared to the uncatalyzed one and required benign reaction conditions [57]. In copper-catalyzed azide-alkyne cycloaddition reactions (CuAAC), generally copper salts are used as catalyst and the copper at +1 oxidation state is required. Metal at +1 oxidation state is obtained either by oxidizing the metal or from a copper salt at +1 or +2 oxidation state.

Even if CuAAC may have ligand-free conditions for azide-alkyne cycloaddition reactions, solvent molecules and base used in the reaction may act as ligand. Besides, heterocyclic chelates are used to speed up the rate. These chelates protect the copper-catalyst against oxidation and it has been reported that they are enantioselective [58].

The uncatalyzed 1,3-dipolar cycloaddition reactions have been studied extensively by both experiments and quantum mechanical calculations [59,60]. For the thermal cycloaddition two pathways, concerted and stepwise, are possible where for azide-alkyne reactions concerted pathway has been stated to be more favorable [61].

The first mechanistic study on the catalytic process, done by K.B. Sharpless and his group showed that a stepwise addition reaction is more favorable than the concerted mode [61]. Experimental studies reported that internal alkynes do not undergo this catalytic cycloaddition reaction and only terminal alkynes reacted [55,56]. In the light of this experimental finding, the scientists proposed that the catalytic cycle starts with copper-acetylide formation. Entire mechanism has not been discovered

completely but some mechanistic proposals are presented in the literature [61-66]. In all the proposals, the reaction starts with coordination of Cu(I) to π -electrons of acetylene and thereby accounts for the experimentally observed pK_a value decrease. Therefore, only terminal alkynes are reactive compounds for CuAAC reactions. Subsequently, exothermal copper-acetylide formation is proposed to take place, followed by coordination of azide to the copper-acetylide species and then metallocyclic structure is formed. Through the re-organization of this cyclic structure, 1,2,3-triazole molecule is obtained (Figure 1.4).

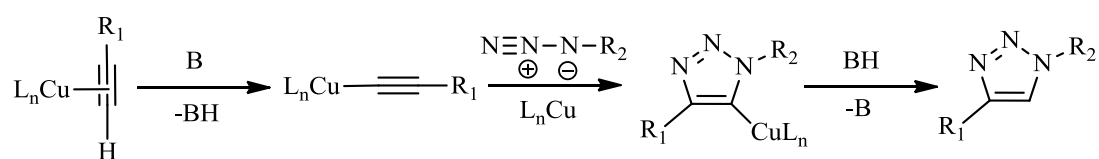


Figure 1.4 : The steps of copper-catalyzed azide-alkyne cycloaddition reactions.

In the study of Sharpless group, the reaction mechanism was modeled with one single copper atom. However; the kinetic studies which were done later by the same group indicated that the reaction is second order with respect to the concentrations of catalyst and alkyne [66]. In other words, instead of one single copper, the mechanism should advance with two copper atoms. Depending on the conditions, different copper-acetylide structures may be formed. There is limited knowledge about the nature of copper-acetylide species [62]. It is assumed that a second copper atom is required for activation of azide molecule but there is a possibility of binding of acetylene to the second copper atom to attain a proper position to facilitate the cycloaddition reaction. However, these were all uncertain at the present state. Another question about the mechanism is that whether one or two alkyne molecules are required. In the high copper concentration, rate was found between 1 and 2 with respect to alkyne.

As of 2001, although kinetic [66,67] and computational studies have been published, the role of catalytically active species in π complexation was still uncertain. The results of the kinetic work led to other computational studies where the mechanism has been modeled via various copper-acetylide species. In those mechanistic studies, the presence of dinuclear and tetranuclear copper acetylide complexes has been considered in model reactions where copper has been mostly treated by the LACVP basis at the B3LYP level of theory. In the work of Straub [64], tetranuclear copper acetylides have been proposed to be the catalyst resting states while Cantillo *et al.*

have proposed two-metal centered species based on their computed reaction barriers [65].

In the second part of this thesis, the copper-catalyzed azide alkyne cycloaddition reaction in the presence of copper has been modeled. Initially, a model study has been conducted in which copper-alkyne π complex and copper-acetylide species were analyzed elaborately. The number of copper species involved, the role of alkyne and the effect of solvent have been searched. After the model work, a real case has been tested. In this scope, the experimental results of Wu *et al.* were utilized [68] (Figure 1.5).

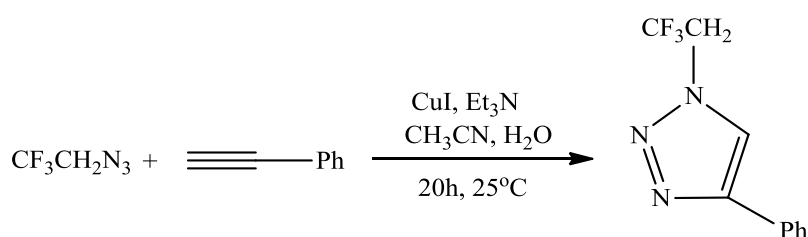


Figure 1.5 : Copper-catalyzed azide-alkyne cycloaddition reactions by Wu *et al.* [68]

Lastly, substrates involving double alkyne and double azide have been investigated. Calculations were based on the experimental results of Finn and his group [66]. In the experimental findings of Finn *et al.* a diazide reacts with an alkyne to give a ditriazole product **b** as major product even when excess diazide species are used over dialkyne while a dialkyne reacts with an azide to give both mono and di-triazole products **c** and **d** as statistical mixture. The authors proposed that while in the diazide-alkyne reaction, the ditriazole product is synthesized directly, in the azide-dialkyne reaction, the ditriazole product is synthesized through mono-triazole intermediate. In this part of the study, the reasons behind the differences in product distribution in accordance with the previous experimental and computational studies have been sought (Figures 1.6 and 1.7).

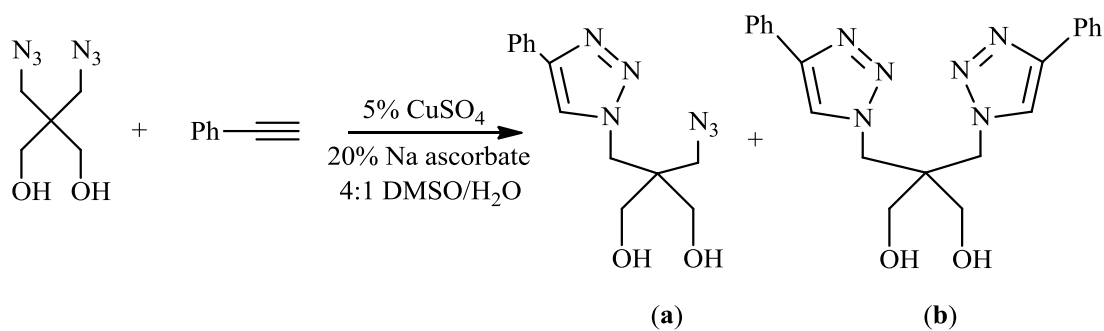


Figure 1.6 : Copper-catalyzed diazide-alkyne cycloaddition reactions which were done by Finn *et al.*[66]

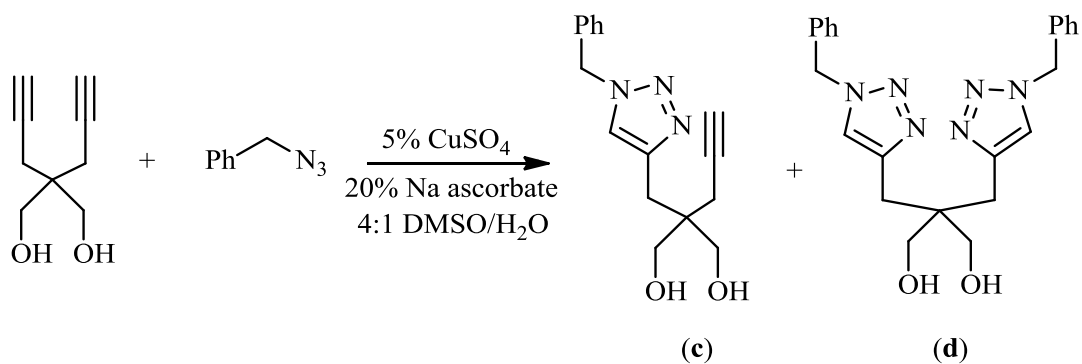


Figure 1.7 : Copper-catalyzed azide-dialkyne cycloaddition reactions which were done by Finn *et al.*[66]

2. THEORY

2.1 Calculation Methods

All computational procedures are based on electronic structure methods which utilize Schrödinger equation for describing the energy of a system

$$H\psi = E\psi \quad (2.1)$$

where, Ψ is a wavefunction describing the x, y and z spatial coordinates of the particles in the system, E is the energy of the system at that state and $\mathbf{H}$ is the Hamiltonian operator to derive the kinetic and potential energy of a system. Calculating the exact solution of Schrödinger equation is almost impossible and computationally impractical. Therefore, in electronic structure methods, some approximations are used. The mostly encountered three major classes of electronic structure methods are:

- Semi-empirical methods, they use parameters derived from experimental data. Different semi-empirical methods are characterized by their different parameters.
- Ab initio methods, use no experimental parameters.
- Density functional methods, the total energy of the system only depends on the electron density [69].

2.1.1 Ab-initio methods

In ab initio method, the Hamiltonian and the wavefunction (Ψ) have been defined, the effective electronic energy can be found by use of the variational method. In the variational method, the best wavefunction can be found by minimizing the effective electronic energy with respect to parameters in the wavefunctions [69].

The accuracy of this method depends on chosen wavefunction. However, with increasing molecule size and complexity of wavefunction, ab initio calculations become more expensive computationally [70].

2.1.2 Density functional theory

Density Functional Theory (DFT) [71-74] is a theory in which ground state energy is expressed in terms of electron density. This method was proposed by P. Hohenberg and W. Kohn in 1964 but it contained only virtual functionals. In 1965, Kohn and Sham brought formal functionals based on total electron density. Contrary to Hartree-Fock method [75-77], DFT has smaller computational cost with high accuracy. Although both methods account for the instantaneous interactions of pairs of electrons with opposite spin, DFT methods include the effects of electron correlation (electrons in a molecular system react to one another's motion and attempt to keep out of another's way) while Hartree-Fock calculations see this effect in an average sense (each electron sees and reacts to an averaged electron density).

Density functional methods partition the electronic energy into several terms and compute them separately.

$$E = E_T + E_V + E_J + E_{XC} \quad (2.2)$$

E_T is the kinetic energy term, E_V is the potential energy of the nuclear-electron attraction and nuclear-nuclear repulsion term, E_J is the electron-electron repulsion term (also called Coulomb energy), E_{XC} is the exchange-correlation term that includes the remaining part of the electron-electron interactions and it is not known how to calculate exactly.

All the terms except the nuclear-nuclear repulsion, are functions of electron density, $\rho(r)$. E_{XC} can be categorized into exchange and correlation functionals. E_{XC} accounts for the exchange energy arising from the antisymmetry of the quantum mechanical wavefunction and the dynamic correlation in the motions of the individual electrons.

The variational principle determines the ground state energy and electron density in terms of the electron density. Further, the ground state electron density $\rho(r)$ determines the external potential, $v(r)$ and variationally determines the ground state properties of the system of interest.

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

$$E[\rho] = \int v(r)\rho(r)dr + T[\rho] + V_{ee}[\rho] \quad (2.3)$$

where $T[\rho]$ is the kinetic energy of interacting electrons and $V_{ee}[\rho]$ is the interelectronic interactions. The electronic energy may be written in the form of Kohn-Sham approach.

$$E[\rho] = \int v(r)\rho(r)dr + T_s[\rho] + J[\rho] + E_{xc}[\rho] \quad (2.4)$$

This is based upon an orbital density description that removes the necessity of knowing the exact form of $T[\rho]$. Kohn-Sham proposed focusing on the kinetic energy of non-interacting system of electrons $T_s[\rho]$, as a functional of a set of single particle orbitals that give exact density.

$$T_s[\rho] = \sum_{i=1}^N \langle \Psi_i | -\frac{1}{2} \nabla^2 | \Psi_i \rangle \quad (2.5)$$

$J[\rho]$ represents the electron-electron repulsion (Coulomb energy), and $E_{xc}[\rho]$ is the exchange-correlation energy functional with its functional derivative called the exchange-correlation potential, $v_{xc}(r)$.

$$E_{xc}[\rho] = T[\rho] - T_s[\rho] + V_{ee}[\rho] - J[\rho] \quad (2.6)$$

$$v_{xc}(r) = \frac{\delta E_{xc}[\rho]}{\delta \rho(r)} \quad (2.7)$$

$E_{xc}[\rho]$ is divided into two parts, namely an exchange functional, $E_x[\rho]$ and a correlation functional, $E_c[\rho]$.

$$E_{xc}[\rho] = E_x[\rho] + E_c[\rho] \quad (2.8)$$

and functionals can be both local and gradient-corrected functionals. Local or gradient-corrected functionals are called traditional functionals. Local functionals depend only on electron density ρ , while gradient-corrected functionals depend on both ρ and its gradient, $\Delta\rho$.

A system of non-interacting electrons moving in an external effective potential is shown as;

$$v_{eff}(r) = v(r) + \frac{\partial J[\rho]}{\partial \rho(r)} + \frac{\partial E_{xc}[\rho]}{\partial \rho(r)} = v(r) + \int \frac{\rho(r')}{|r-r'|} dr' + v_{xc}(r) \quad (2.9)$$

Now, an equation very similar to the Schrödinger Equation exists.

$$\left[-\frac{1}{2} \nabla^2 + v_{eff}(r) \right] \Psi_i = \varepsilon_i \Psi_i \quad (2.10)$$

(2.4), (2.5), (2.6), (2.7), (2.8), (2.9) are Kohn-Sham Equations.

In order to evaluate the exchange-correlation functional some approximations are made. The first one is the local density approximation (LDA). It is based upon a model of uniform electron gas. In the uniform electron gas model, a large number of electrons uniformly spread out in a cube where there is a uniform distribution of the positive charge to make the system neutral. It assumes that the charge density varies slowly throughout the molecule so that a localized region of the molecule behaves like a uniform electron gas. The energy expression is:

$$E[\rho] = T_s[\rho] + \int \rho(r)v(r)dr + J[\rho] + E_{xc}[\rho] + E_b \quad (2.11)$$

where E_b is the electrostatic energy of the positive background. Since the positive charge density is the negative to the electron density, the equation reduces to:

$$E[\rho] = T_s[\rho] + E_{xc}[\rho] = T_s[\rho] + E_x[\rho] + E_c[\rho] \quad (2.12)$$

The exchange functional is given by:

$$E_x[\rho] = -C_x \int \rho(r)^{4/3} dr \quad (2.13)$$

where $C_x=0.7386$, this form was developed to reproduce the exchange energy of a uniform electron gas.

DFT methods are defined by pairing an exchange functional with a correlation functional and can be named as traditional or hybrid functionals. Hybrid functionals include exact term in the exchange functional, whereas traditional functionals do not. BLYP (Becke's gradient-corrected exchange functional with Lee-Yang-Parr's gradient-corrected correlation functional) method is a traditional functional whereas,

B3LYP (Becke style three parameter functional in combination with the Lee-Yang-Parr correlation functional) method [78,79], the linear combination of LDA, B88, exact and LYP functionals, is a hybrid functional:

$$E_{xc} = E_{xc}^{LDA} + a_0(E_x^{exact} - E_x^{LDA}) + a_x \Delta E_x^{B88} + a_c \Delta E_c^{non-local} \quad (2.14)$$

where ΔE_x^{B88} is the Becke's gradient correction, i.e. the second term at the right hand side of the equation (2.14) and the correction to the correlation ($\Delta E_c^{non-local}$) is provided by the Lee-Yang-Parr functional but, LYP includes both local and non-local terms. Then the correlation functional used is actually: $a_c E_c^{LYP} + (1-a_c) E_c^{VWN}$ where E_c^{VWN} is the Vosko-Wilk-Nusair correlation energy. The parameters are specified by Becke by fitting the atomization energies, ionization potentials, proton affinities and first row atomic energies in the molecule set, $a_0=0.20$, $a_x=0.72$ and $a_c=0.81$. Hybrid functionals have proven to be superior to the traditional functionals [69].

2.1.3 Basis sets

A basis function is a mathematical function which describes atomic orbitals. A basis set is a series of basis functions to describe molecular orbitals in which molecular orbitals are constructed as linear combination of atomic orbitals. The basis functions are categorized into two classes, Slater Type Orbitals (STO) and Gaussian Type Orbitals (GTO). Slater Type Orbitals have the functional form,

$$\Theta_{abc}(x,y,z) = N x^a y^b z^c e^{-\zeta r} \quad (2.15)$$

N is the normalization constant, a, b and c are angular momentum ($L=a+b+c$). Gaussian type orbitals can be written as

$$\Theta_{abc}(x,y,z) = N x^a y^b z^c e^{-\zeta^2 r^2} \quad (2.16)$$

GTOs are preferable over STOs because of the computational efficiency although STOs are more accurate. The split valence basis set which is developed by Pople and coworkers is the most popular one among the various types of the basis sets (minimal basis sets, split valence basis sets, polarized basis sets, high angular momentum basis

sets). Pople type basis sets are termed as 3-21G, 4-31G, 6-31G. The first number symbolizes the number of primitive GTO for core orbitals, the second number symbolizes the number of primitive GTO for inner valence and third number symbolizes the number of primitive GTO for outer valence.

Split valence basis sets allow orbitals to change size not the shape. Polarized basis sets remove this limitation by adding orbitals with angular momentum beyond the ground state configuration for each atom.

2.1.4 Intrinsic reaction coordinate

Intrinsic Reaction Coordinate (IRC) [80,81] is a minimum energy reaction path on a potential energy surface in mass-weighted coordinates, connecting reactants to products via the transition state [82]. When a transition state is optimized with an imaginary frequency, it must be confirmed that it is the correct transition state by making IRC calculations.

The simplest method of following a reaction path is to solve the differential equation for the intrinsic reaction path:

$$dx(s)/ds = t \quad (2.17)$$

Here x are the (mass-weighted) coordinates, s is the path length and t is the (negative) normalized gradient. Determining the IRC requires solving equation 2.17 starting from a geometry slightly displaced from the TS along the normal coordinate for the imaginary frequency.

The simplest method for integrating equation 2.17 is the Euler method. A series of steps are taken in the opposite direction of the normalized gradient at the current geometry x_n .

$$x_{n+1} = x_n - \Delta s t(x_n) \quad (2.18)$$

This corresponds to a steepest descent minimization with a fixed step size Δs . Unless very small steps are taken, this approach tends to oscillate about the true IRC [83].

2.1.5 Natural bond orbital

Natural Bond Orbital (NBO) [84-91] analysis is the diagonalization of the first-order density matrix which is used to define character of bonds and orbitals. The density matrix can be written in terms of blocks of basis functions belonging to a specific centre as

$$D = \begin{pmatrix} D^{AA} & D^{AB} & D^{AC} & \dots \\ D^{AB} & D^{BB} & D^{BC} & \dots \\ D^{AC} & D^{BC} & D^{CC} & \dots \\ \dots & \dots & \dots & \dots \end{pmatrix} \quad (2.19)$$

Where A, B and C are the atoms of a molecule. NBO for A can be defined as diagonalization of the D^{AA} block. The same process is valid for B by D^{BB} block and C by D^{CC} block. NBOs are not orthogonal and orbital occupation numbers are not the total number of electrons [83].

In an initial step, orbitals that are associated almost entirely with a single atom, e.g., core orbitals and lone pairs, are localized as so-called natural atomic orbitals (NAOs). Next, orbitals involving bonding (or antibonding) between pairs of atoms are localized by using only the basis set AOs of those atoms. Finally, the remaining Rydberg-like orbitals are identified, and all orbitals are made orthogonal to one another. The result is that, except for very small contributions from other AOs to ensure orthogonality, all NAOs and Rydberg orbitals are described using the basis-set AOs of a single atom and all NBOs are described using the basis-set AOs of two atoms (in cases where resonance or other delocalization effects require orbitals delocalized over more than two atoms, additional work is required). Thus, NBO analysis provides an orbital picture that is as close as possible to a classical Lewis structure for a molecule [92].

2.1.6 Solvation Model

Solvation is an important aspect in computational chemistry. There are two types of method for considering solvent effect: i) individual solvent molecules and ii) treat the solvent as a continuous medium.

In continuum model, [93] the solvent is regarded as a uniform polarizable medium with a dielectric constant, and with the solute **M** located in a properly shaped hole in the medium (Figure 2.1) [94].

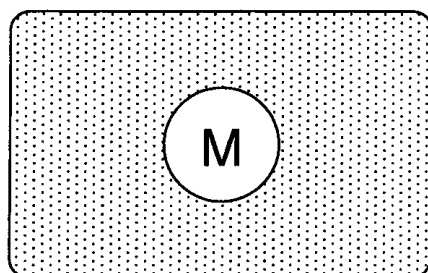


Figure 2.1 : Reaction field model (picture is taken from reference 83).

A destabilization is produced due to the creation of a hole in the medium (ΔG_{cavity}). In contrast, dispersion interactions between the solvent and solute add a stabilization. Additionally, it is possible to obtain repulsive component which is termed as dispersion/repulsion ($\Delta G_{\text{dispersion}}$). Electrostatic stabilization is created by the polarization of the medium by **M** (ΔG_{elec}). The solvation free energy ($\Delta G_{\text{solvation}}$) is written as in equation 2.20.

$$\Delta G_{\text{solvation}} = \Delta G_{\text{cavity}} + \Delta G_{\text{dispersion}} + \Delta G_{\text{elec}} \quad (2.20)$$

When a quantum description of **M** is employed, the interaction with the solvent model must thus be calculated by an iterative procedure, leading to various Self-Consistent Reaction Field (SCRF) models.

The Polarizable Continuum Model (PCM) employs a van der Waals cavity formed by interlocking atomic van der Waals radii scaled by an empirical factor, a detailed description of the electrostatic potential, and parameterizes the cavity/dispersion contributions based on the surface area [91,95].

The integral equation formalism PCM (IEF-PCM) is a recent method addressed to solve the electrostatic solvation problem at the quantum mechanical level with the aid of apparent surface charges. IEF uses a new formalism of this problem, based on integral operators never used before in the chemical community and it manages to treat on the same footing linear isotropic solvent models, as well as anisotropic liquid crystals and ionic solutions [96,97].

3. MECHANISTIC STUDY ON [3+2] CYCLOADDITION AND CYCLOPROPANATION REACTIONS OF 1,3-DIOXEPINE DERIVATIVES IN THE PRESENCE OF COPPER(I) CATALYST

3.1 The Mechanism of Copper-catalyzed Furofuran Synthesis

In this part of this thesis study, a series of carbene transformation reactions reported by Talinli *et al.* [10,41] has been modeled by means of computational chemistry methods (Figure 1.2). In the experiments, the diazo compound, dimethyldiazomalonate (**DMDM**), and the catalyst, copper(II) acetylacetonate $\text{Cu}(\text{acac})_2$, have been reacted with a series olefinic compounds. In the first part of the reaction, 4,5-dihydro-2-methyl-1,3-dioxepine used as substrate has revealed first a furan then a furofuran product via [3+2] cycloaddition reaction. When the 4,7-dihydro-2-methyl-1,3-dioxepine was used as olefin under the same reaction conditions, rather than [3+2] cycloaddition, a mixture of cyclopropanation and Stevens Rearrangement products were obtained with a ratio of 74:26, respectively (Figure 1.2).

According to the proposed mechanism (Figure 3.1) for furan species, first copper carbene formation takes place. The mechanism for furan and then for furofuran formation have been completed in this study. Cyclopropanation as the major side reaction has also been considered and the product distribution depending on the substrate bond has been evaluated in the following chapter. This has complemented our previous study on dioxepine derivatives where cyclopropanation and carbene formation have been modeled in detail [39].

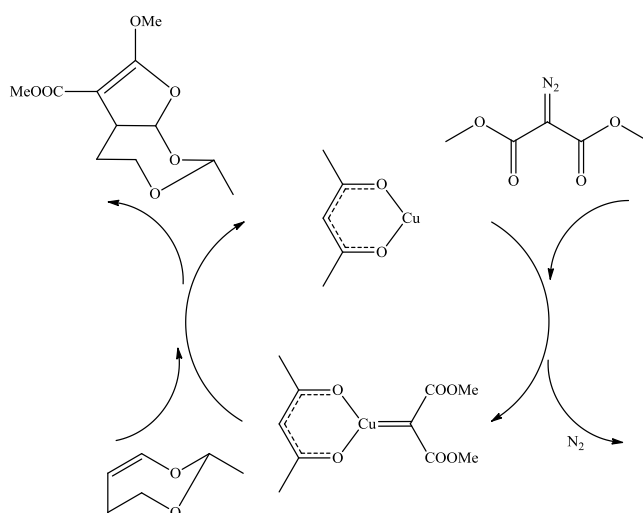


Figure 3.1 : The proposed mechanism of [3+2] cycloaddition reaction of dioxepine and diazo compounds in the presence of $\text{Cu}(\text{acac})_2$.

The transformation of catalyst-ethylene species to catalyst-diazo compound can occur via two pathways; associative and dissociative displacements [35,36]. In the dissociative displacement, naked catalyst binds to the diazo compound whereas in the associative displacement, it is the catalyst-ethylene complex that binds to the diazo compound. In this system, the calculations indicate that the dissociative displacement requires a higher energy (38.8 kcal/mol [39]) than the associative path. Thus, it is expected that the associative path is favored over the dissociative.

Copper-carbene formation through the diazoester decomposition in presence of copper-catalyst can occur via two possible pathways. The first option is the olefin assisted copper-carben formation in which the alkene is attached to the copper center until copper-carbene formation. Otherwise, it is named as olefin-non-assisted copper carbene formation. Based on previous findings [39], it is known that olefin-non-assisted copper carbene formation is favorable.

3.1.1 Computational method

In this part of study, all the possible reaction mechanisms, including intermediates and transition states, have been modeled and discussed in terms of relative energies obtained from quantum-mechanical calculations. The DFT method employing the B3LYP functional [78,79] with the 6-31G* basis set has been used to carry out the full optimization of the compounds of interest in the gas phase with the G03 package [98]. The DFT methodology with B3LYP functional has been shown to give reliable results in transition metals, including copper-catalyzed cyclopropanations [99-102].

Single-point B3LYP/6-311+G(d,p) calculations have been performed on B3LYP/6-31G* geometries to investigate the effect of higher basis set. The barriers from electronic energies of higher basis are consistent with those of B3LYP/6-31G* results for the competitive mechanisms of [3+2] cycloaddition.

The stationary points were analyzed by vibrational frequency calculations. All transition states were verified to be saddle points by one imaginary frequency belonging to the reaction coordinate. For all transition state structures the intrinsic reaction coordinate (IRC) was followed to validate the expected reactants and products [80,81]. The energies discussed in the text are Gibbs free energies calculated at 298 K, unless otherwise stated. Natural Bond Orbital (NBO) analysis has been carried out on some structures in order to investigate the stabilizing donor-acceptor interactions and the nature of the Cu-C bonds in some selected structures [84-91].

The effect of solvent was considered for the reactions by single-point SCRF calculations with the IEF-PCM [96,97] method at the B3LYP/6-31G(d) level. The free energies in benzene were obtained by using the frequencies from the gas-phase results. These observations are in accordance with the literature findings where it was stated that the uncharged copper complexes minimize solvation artifacts when comparing computed gas-phase energies with experimental results in hydrocarbon solutions [36,103].

In the figures critical bond lengths are shown (in Å) and hydrogens have been omitted for clarity. The charges that are shown on figures are obtained from NBO calculations. The acetylacetonate is depicted as L in all figures.

3.1.2 Results and discussions

3.1.2.1 Reactants' geometries

In the copper carbene transformation reaction, the active form of copper, Cu(I) (**1**) (Figure 3.1), is prepared by in situ reduction of Cu(acac)₂. Copper(I) alkene complexes have been stated as the resting states of the catalytic cycle of copper-catalyzed cyclopropanation [104-107]. The initial step of cyclopropanation and [3+2] cycloaddition reactions start with the interaction of copper(I) alkene complex and **DMDM** (**2**) (Figure 3.2), leading to copper carbene.

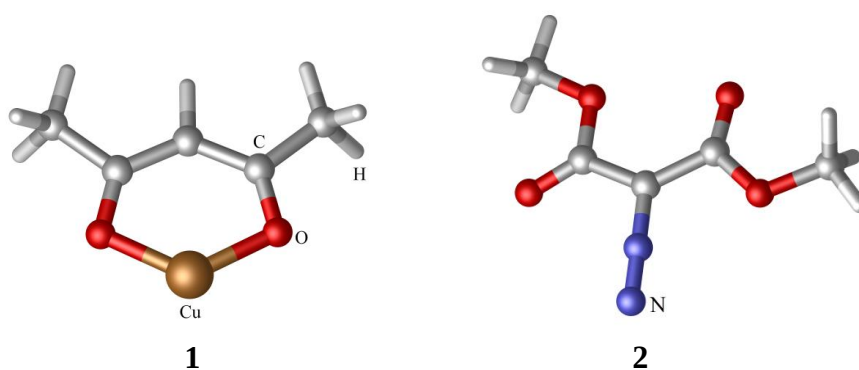


Figure 3.2 : 3D representations of copper-catalyst Cu(acac) **1** and diazo compound DMDM **2**, respectively.

For (Z)-2-methyl-4,5-dihydro-1,3-dioxepine four different conformers; two chair (**3a**, **3b**) and two twisted-boat (**3c**, **3d**) with methyl substitution at the equatorial and axial positions of C2 have been optimized. The chair conformer (**3a**) with the methyl group on the equatorial position has the lowest Gibbs free energy where the next lowest conformer, **3c**, is 3.6 kcal/mol higher than **3a** (Figure 3.3).

For (Z)-2-methyl-4,7-dihydro-1,3-dioxepine substrate; three different conformers (**4a**, **4b**, **4c**); one twisted-boat (**4a**) and two chair (**4b**, **4c**) have been optimized. While **4a** and **4b** have quite similar free energy values ($\Delta G_{4a-4b} = 0.1$ kcal/mol), **4c** is 4.6 kcal/mol higher than **4a**. The lowest energy conformers, **3a** and **4a** (Figure 3.3), were chosen as reactants for the paths modeled. The reaction starts with the formation of the copper carbene complex (**19**) and is followed either by [3+2] cycloaddition or cyclopropanation reactions depending on the type of the dioxepine.

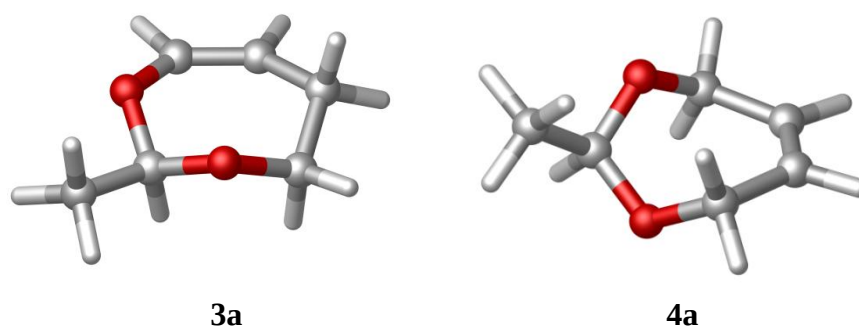


Figure 3.3 : 3D representations of dioxepine compounds **3a** and **4a**, respectively.

3.1.2.2 Metal-carbene formation

Following the formation of catalyst alkene complex, direct dinitrogen extrusion can take place in the presence of alkene or after the olefin is lost from the catalyst. Based on the results of the previous work where copper-carbene formation has been

considered in detail with a different dioxepine molecule [39], the more plausible copper-carbene formation via olefin non-assisted mechanism is modeled with **3a** and **4a** as substrates (Figure 3.3) in this work. The copper-carbene formation initiates with the reaction of **5** (Figure 3.4) and **DMDM** through transition structure **6** where an adduct intermediate is formed in which copper coordinates with oxygen and nitrogen atoms simultaneously (Structure **7**). Then, the dioxepine leaves the copper center with a small energy barrier (1.2 kcal/mol) to produce the catalyst-diazo complex (Structure **9** in Figure 3.4). X-ray crystallography on an analogous Cu(I) catalyst with diazophenanthrone has been reported by Straub *et al.* [108]. The analogous structures of the intermediates **9** and **11** have been identified in carbene transformation experiments which support the preference for this mechanism [109-111].

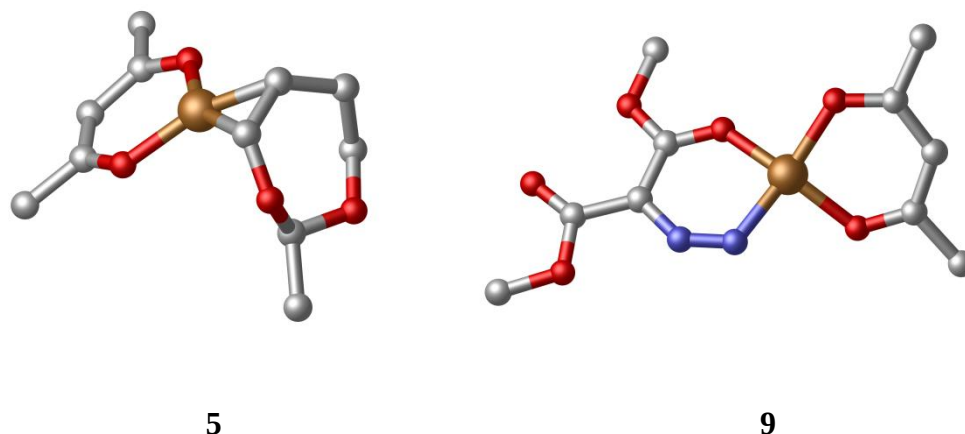
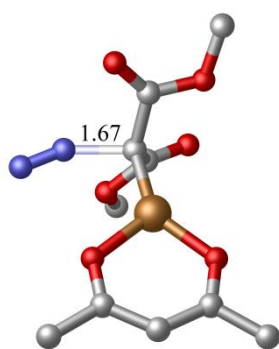
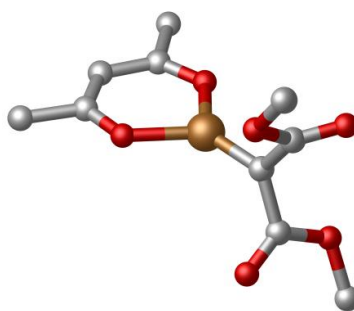


Figure 3.4 : 3D representations of structures **5** and **9**, respectively.

The paths followed both by **3a** and **4a** molecules are exergonic and the obtained free energy values are in harmony with the previously derived results [39]. It is noteworthy to state that the pathway advances without the dioxepine molecules so that the structural differences on dioxepine derivatives have no effect on the copper-carbene formation thereafter (Structure **8**). The N₂ extrusion step **18** (Figure 3.5) has the highest overall Gibbs free energy (28.5 kcal/mol) and enthalpy (29.5 kcal/mol) which can be considered as the rate-limiting step for the copper carbene **19** (Figure 3.5) formation [39]. The mechanism and whole energy profile for the copper-carbene formation are depicted in Figure 3.6.



18



19

Figure 3.5 : 3D representations of structures **18** and **19**, respectively.

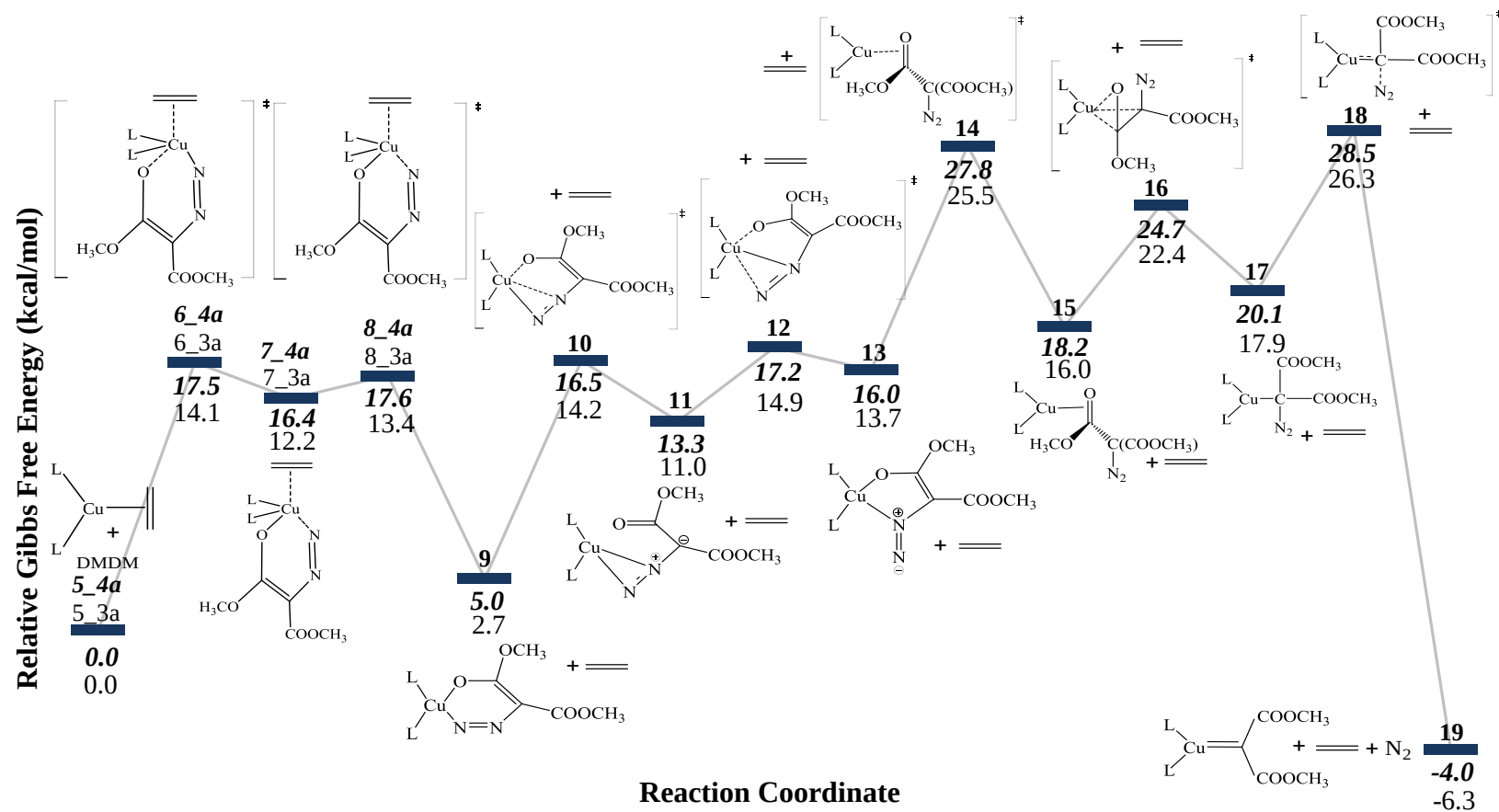


Figure 3.6 : The energetics and mechanism of the Copper-carbene formation from dioxepines **3a** (plain text) and **4a** (bold and italic). Gibbs free energies refer to B3LYP/6-31G*(= refers to **3a** and **4a**).

3.1.2.3 [3+2] cycloaddition reaction of **3a**

After copper-carbene formation, the [3+2] cycloaddition reaction of **3a** is modeled. The whole free energy profile and the schematic representation of cycloaddition path are depicted in Figure 3.9. The reaction starts with the approach of the copper carbene complex to **3a** leading to the formation of transition state structure **20** (Figure 3.7). In transition state **20**, while the double bond of dioxepine approaches to the carbene carbon, the Cu-C_{carbene} distance extends to 1.82 Å from 1.77 Å. The obtained product is shown as **21A**. In order to obtain five-membered cycloaddition product, the carbonyl group has to rotate about its axis to adopt a conformer which promotes the formation of a σ bond between the olefinic carbon atom of the dioxepine molecule and the carbonyl oxygen. Therefore, a rotation around the axis of carbonyl group has been modeled via **21_TS_AB** (Figure 3.7) and the obtained product **21B** has a lower energy than its conformer **21A**. On the other hand, the Cu center increases its interaction with the carbonyl group of **DMDM** and forms a bond with a carbonyl carbon to compensate its coordination deficiency. This rotation enables **DMDM**'s oxygen to adopt a proper conformation to complete the [3+2] cycloaddition reaction.

In transition structure **22** (Figure 3.7), the distance between the carbonyl oxygen and carbon is 2.47 Å. Formation of the cyclic structure is energetically highly favorable ($\Delta G_{23-19} = -27.5$ kcal/mol). To disconnect the catalyst from the cyclic structure for regeneration, a second dioxepine molecule is needed to assist this cleavage. In the previous study, it is found that the detachment of the catalyst without the assistance of a second dioxepine is highly endergonic which makes this step impossible to occur [39].

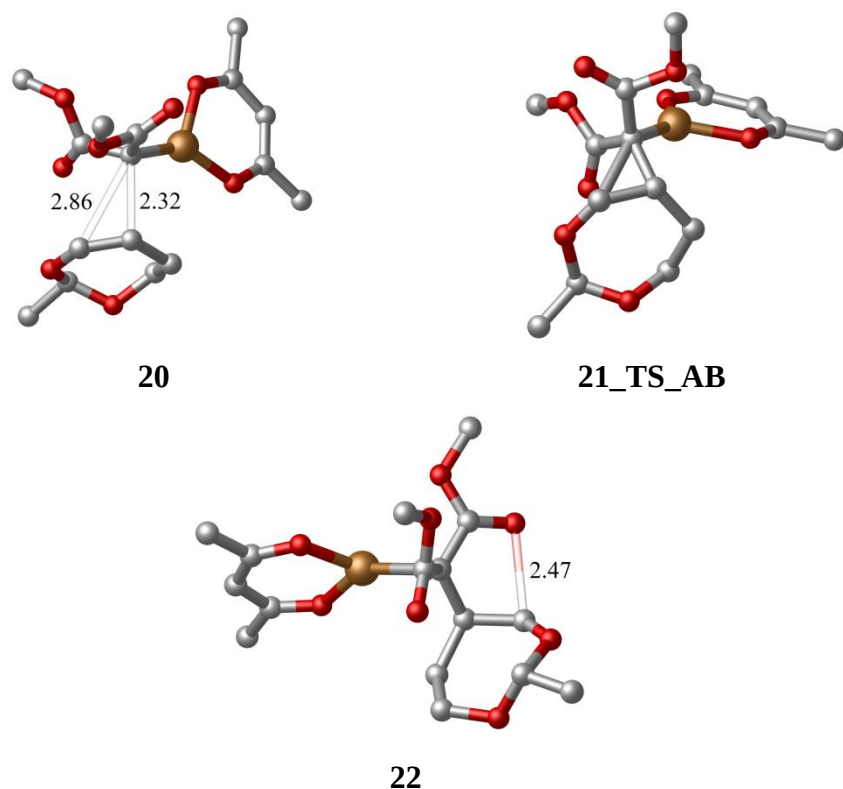


Figure 3.7 : 3D representations of structures **20**, **21_TS_AB** and **22**, respectively.

In the last step, the double bond of a second dioxepine approaches to the copper center of the catalyst through transition state **24** and the forming product (**25**), namely (2R,5aS,8aR)-methyl 7-methoxy-2-methyl-4,5,5a,8a-tetrahydrofuro[2,3-d][1,3]dioxepine-6-carboxylate, leaves the copper center and the catalytic cycle is completed (Figure 3.8).

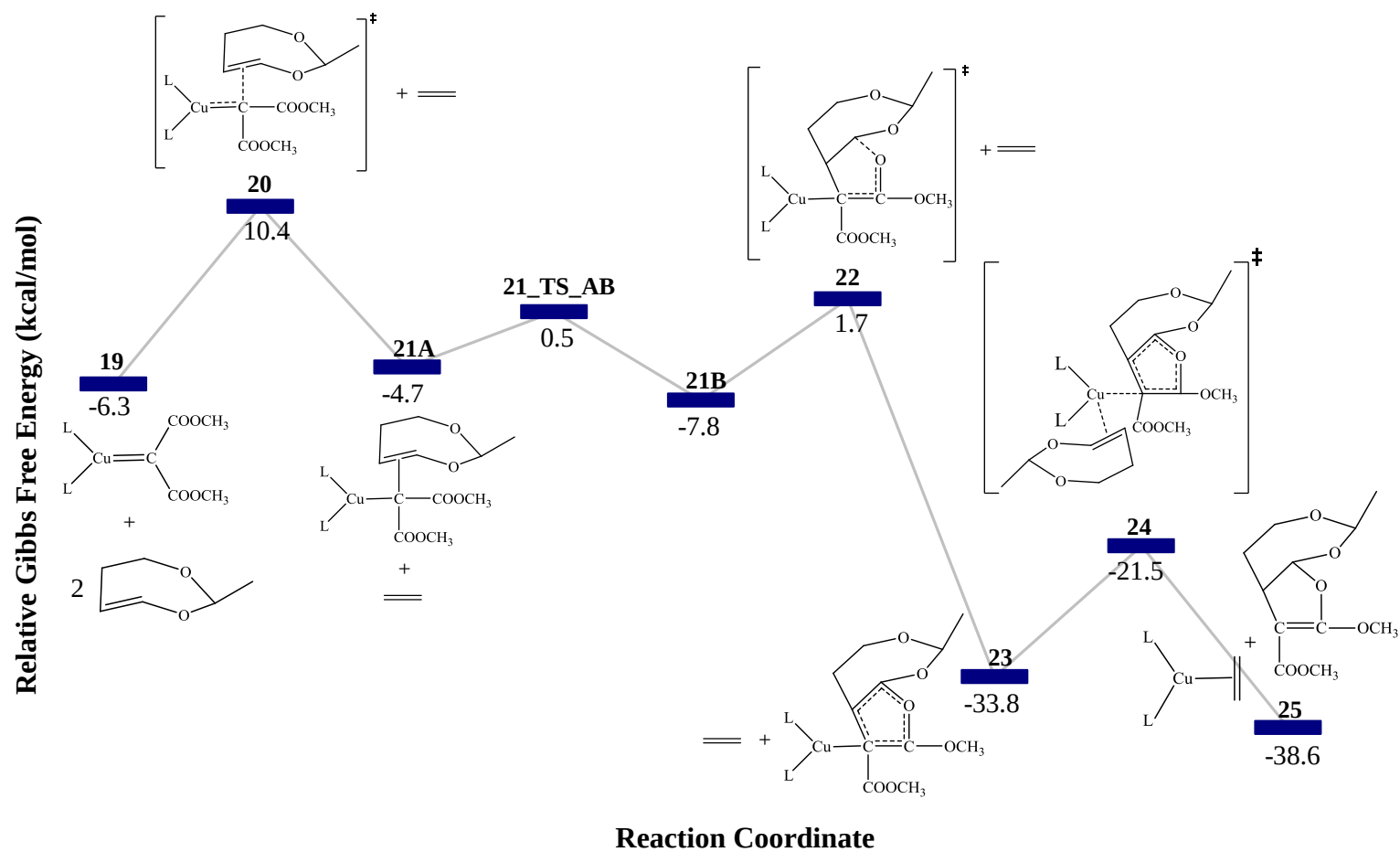


Figure 3.8 : The energetics and mechanism of the [3+2] cycloaddition reaction of dioxepine (**3a**). Gibbs free energies refer to B3LYP/6-31G* (= refers to **3a**).

When copper carbene approaches to the dioxepine (**3a**) molecule from the opposite direction with respect to the position of copper carbene complex in the transition state **20**, the regioisomer of the product **25** (Figure 3.8) can be obtained. The new path is found to be energetically unfavorable relative to the stepwise path by 11.8 kcal/mol. The highest free energy values are 10.4 and 22.2 kcal/mol for the experimentally obtained and regioisomer products paths, respectively (Figures 3.9 and 3.10).

Surprisingly, while the experimental product is obtained via stepwise pathway, the regioisomer is obtained in a concerted manner. Severe structural differences in two transition states (**20** vs **26**) are observed. In structure **26** (Figure 3.9), the distance between $C_{olefinic1}-O_{carbonyl}$ is 2.60 Å and $C_{carbene}-C_{olefinic2}$ is 2.08 Å, where the same distances are 3.05 Å and 2.32 Å, respectively in structure **20**. Additionally, according to second order stabilization energy results from NBO analysis, in the concerted transition state, there is a stabilizing interaction of 5.1 kcal/mol between $C_{olefinic1}-O_{carbonyl}$ atoms but the same interaction is 0.12 kcal/mol for transition state in the stepwise path. Moreover; NBO charges indicate a charge separation on the double bond of substrate (-0.33 and 0.24) in the stepwise transition state (**20**). The interaction of the lone pairs of the substrate's oxygen with the double bond carbon can facilitate stabilization of transition state structure **20** with respect to **26**. The value of the stabilizing interaction is 50.1 kcal/mol in the stepwise process whereas no such stabilizing interaction is present in the concerted transition state in which the double bond is almost neutral. It is known that the metal coordination plays the key role in such reactions [34]. As the metal catalyst is more effectively involved in the active site of the reaction, the reaction becomes more asynchronous and even a change from concerted to stepwise mechanism is observed. According to NBO analysis, the second order stabilization energy points out extra stabilization energy of 24.8 kcal/mol from the antibonding orbitals of the Cu-C bond towards carbonyl group but the same interaction reduces to 7.6 kcal/mol in the concerted transition state. It can be deduced that copper catalyst actively plays a dominant role in the formation of experimental product.

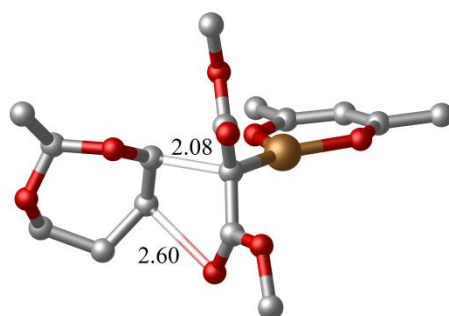


Figure 3.9 : 3D representation of structure **26**.

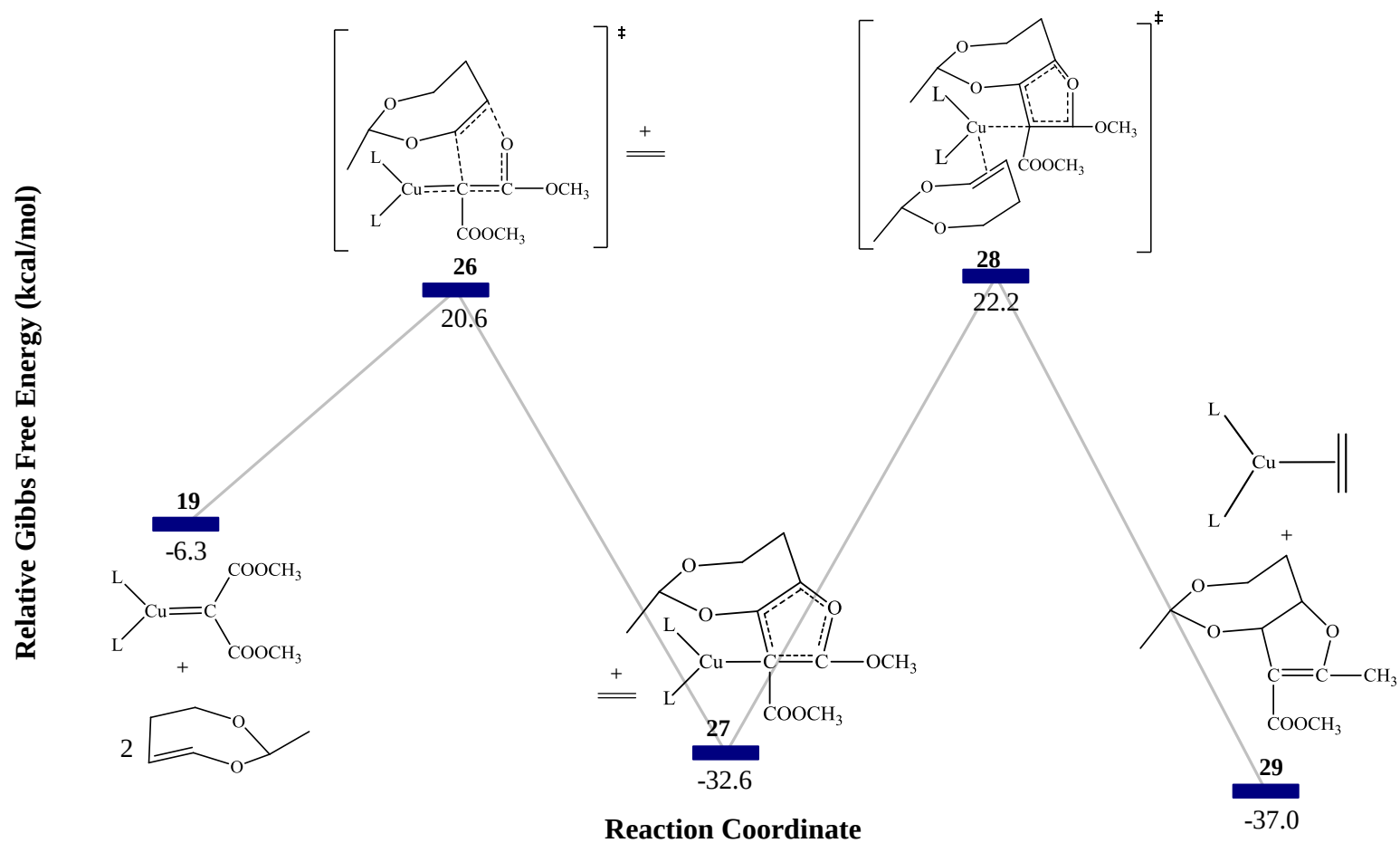


Figure 3.10 : The energetics and mechanism of the regiomers obtained via concerted path. Gibbs free energies refer to B3LYP/6-31G* (= refers to **3a**).

Alternative pathways of [3+2] cycloaddition reaction

In this study, the probability of competing mechanisms for the [3+2] cycloaddition reaction has been also investigated. Two different mechanisms have been modeled where five-membered ring is obtained either via a metallacyclobutane or a cyclopropane intermediate.

[3+2] cycloaddition via metallacyclobutane intermediate

When the double bond of **3a** reacts with copper-carbene **30** (Figure 3.11) where the oxygen atom of dioxepine and copper-carbene are located on the same side, the metallacyclobutane intermediate is obtained with a free energy barrier of 23.6 kcal/mol (Figure 3.12). The formation of metallacyclobutane intermediate is highly exergonic. Once the intermediate is formed, the reaction proceeds with the formation of five-membered ring. The dissociation of copper catalyst is no longer modeled since the path is not a favorable process with 51.0 kcal/mol of activation barrier (ΔG_{23-19}).

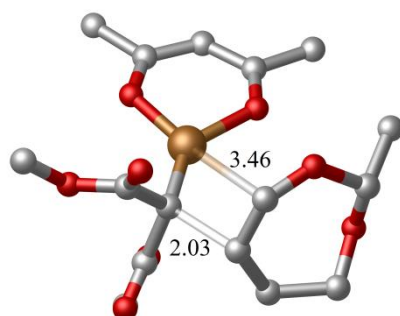


Figure 3.11 : 3D representation of structure **30**.

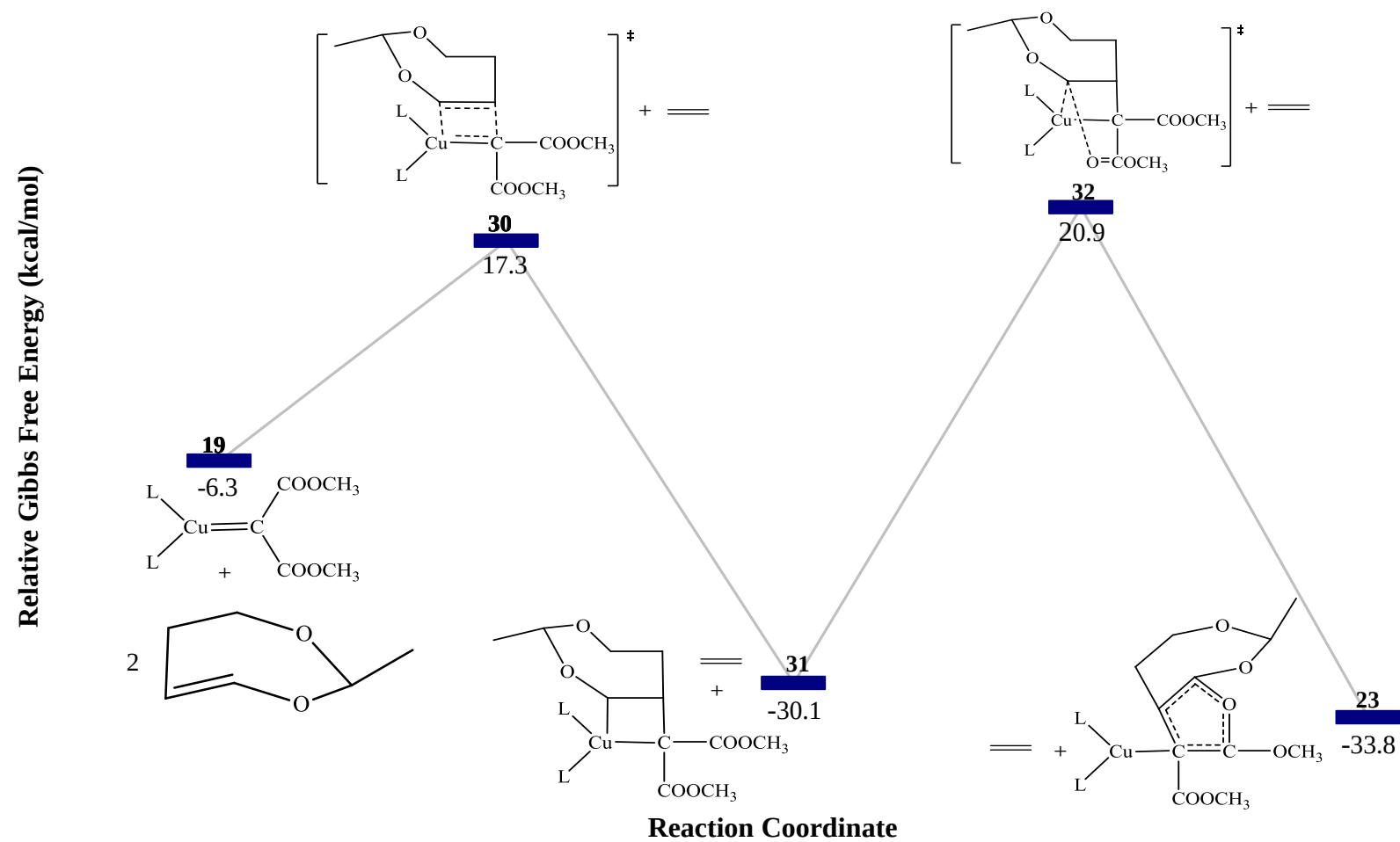


Figure 3.12 : The energetics and mechanism of [3+2] cycloaddition via metallacyclobutane intermediate. Gibbs free energies refer to B3LYP/6-31G* (= refers to **3a**).

Cycloaddition via cyclopropane intermediate

The olefinic carbons of the dioxepine can react with copper carbene (Structure **33**, Figure 3.13), in another mode of attack in which the dioxepine substrate is inverted as compared to transition structure **30** (Figure 3.12). Contrary to the metallacyclobutane intermediate, a cyclopropane structure is formed in which carbon and oxygen atoms of the carbonyl group associate with the metal-center through 1.96 and 1.87 Å distances, respectively. From the cyclopropane intermediate (Structure **34**, Figure 3.13), either cyclopropanation or experimental [3+2] cycloaddition product can be obtained. While transition state **35** leads to structure **23**, energetically more favorable transition state **36** leads to cyclopropane product **37** (Figure 3.14). The higher exergonicity and the lower activation barrier of the cyclopropane path hinder the formation of five-membered ring via cyclopropane intermediate.

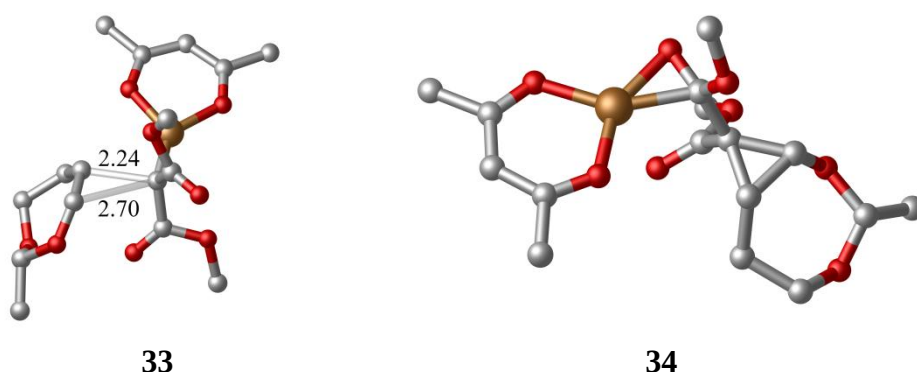


Figure 3.13 : 3D representations of structures **33** and **34**, respectively.

According to the theoretical results, the formation of [3+2] cycloaddition product from (Z)-2-methyl-4,5-dihydro-1,3-dioxepine (**3a**) in the presence of copper catalyst and **DMDM** is thermodynamically and kinetically favorable as compared to the formation of the cyclopropane and the regioisomer products. The results of calculations are in harmony with the experimental findings.

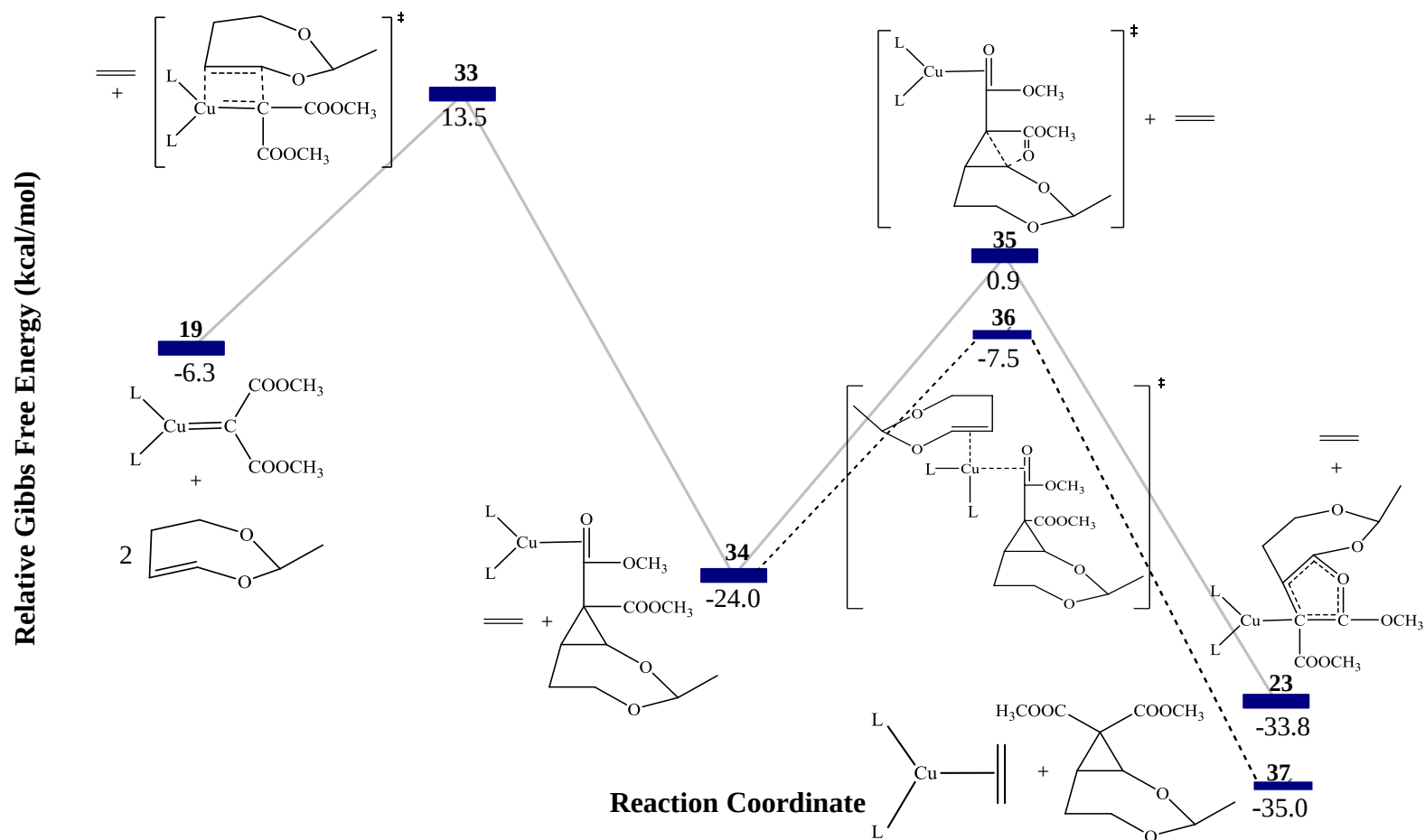


Figure 3.14 : The energetics and mechanism of [3+2] cycloaddition and cyclopropanation reaction via intermediate **34**. Gibbs free energies refer to B3LYP/6-31G* (= refers to **3a**).

3.1.2.4 Cyclopropanation of 4a

The experimental study on the reaction of (Z)-2-methyl-4,7-dihydro-1,3-dioxepine substrate **4a** with **DMDM** in the presence of Cu(I) catalyst has resulted with the formation of mainly cyclopropane product. In this study, both the 3-centered and 4-centered pathways of cyclopropanation are modeled with the boat conformer of (**4a**) by considering the possible stepwise and concerted mechanisms. Three centered pathway starts either with transition state **38_C1** (Figure 3.15) which gives a metallacyclobutane intermediate **39** or with transition state **38_C2** (Figure 3.15) which goes in concerted manner to structure **41**. The activation energy barrier difference between two transition states is 1.6 kcal/mol where the formation ratio is found to be 1:15 on behalf of the stepwise path. The copper-carbene complex approaches to the dioxepine ring from the top in **38_C1** and from bottom in **38_C2**. The small energy difference between the two transition states has led us to investigate the effect of basis set on the energetics. The calculation at the B3LYP/6-311+G** level of theory have discriminated between the stepwise and concerted paths more clearly by yielding a higher free energy difference ($\Delta E=2.0$ kcal/mol) between **38_C1** and **38_C2**. Thus, the formation of structure **41** via stepwise path is more plausible. A second dioxepine molecule (**4a**) reacts with the copper center in structure **42** to release the product. Finally, dimethyl 4-methyl-3,5-dioxabicyclo[5.1.0]octane-8,8-dicarboxylate product **43** is obtained (Figure 3.16).

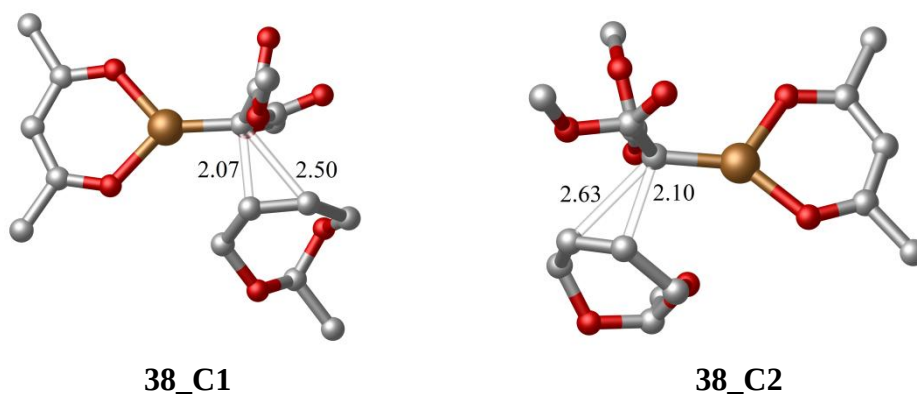


Figure 3.15 : 3D representations of structures **38_C1** and **38_C2**, respectively.

In the four centered pathway (Figure 3.17), the carboxyl group of copper-carbene structure rotates by overcoming a free energy barrier of 8.9 kcal/mol in order to make an intramolecular bond between the copper and the carbonyl oxygen. Following rotation, the olefinic bond of dioxepine attacks the copper center (**46**). In transition

state **48**, while one of the olefinic carbon atoms of the dioxepine is bonding to the copper center, the other one is bonding to carbene carbon through a four-centered geometrical structure. As a result, a metallacyclobutane intermediate (**39**) is formed exergonically.

Considering the overall barriers (17.4 and 17.9 kcal/mol) of two competing pathways, the preference for the mechanism of cyclopropanation reaction of (Z)-2-methyl-4,7-dihydro-1,3-dioxepine cannot be deduced. It is known from the literature that the substituents at the C-2 position alter the chair and twist-boat preference of the dioxepine ring. Thus, the transition state structures that discriminate between the 3-centered and 4-centered pathways (**38** vs **48**, respectively) have been modeled with chair conformation of **4a**. The barriers for the two paths are 2.8 kcal/mol apart from each other on behalf of 4-centered pathway. Earlier calculations on the cyclopropanation reaction of 2,2-dimethyl-4,7-dihydro-1,3-dioxepine with Cu(acac)₂ have also shown the same trend [39]. The barriers indicate that cyclopropanation of both conformers of dioxepine are facile via different pathways. The calculations are qualitatively in agreement with the experimental results of Talinli *et al.* where the ratio of chair:twist-boat product is 1.2:2.2 [10].

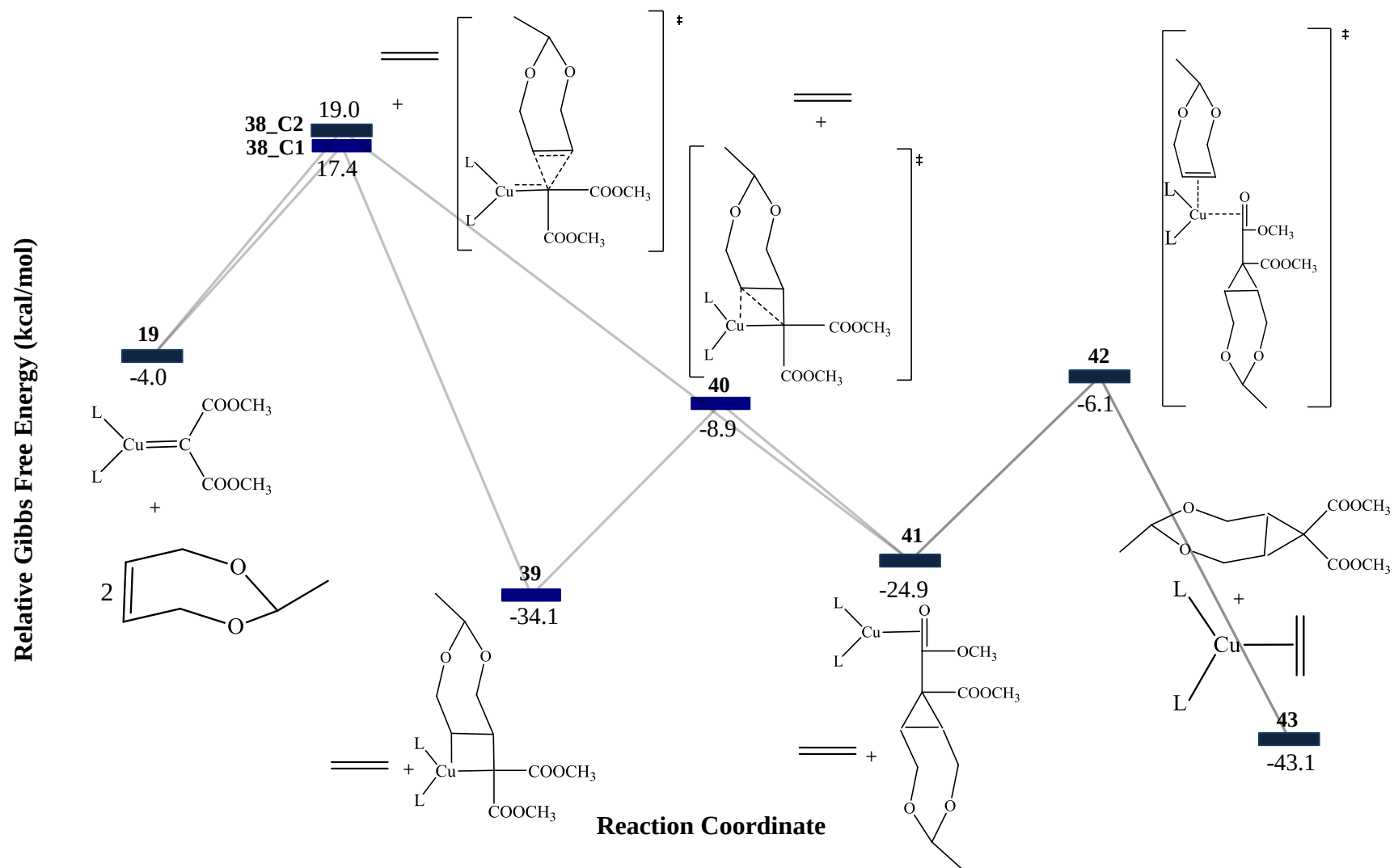


Figure 3.16 : The energetics and mechanism of the cyclopropanation reaction of **4a** via 3-centered path. Gibbs free energies refer to B3LYP/6-31G* (= refers to **4a**).

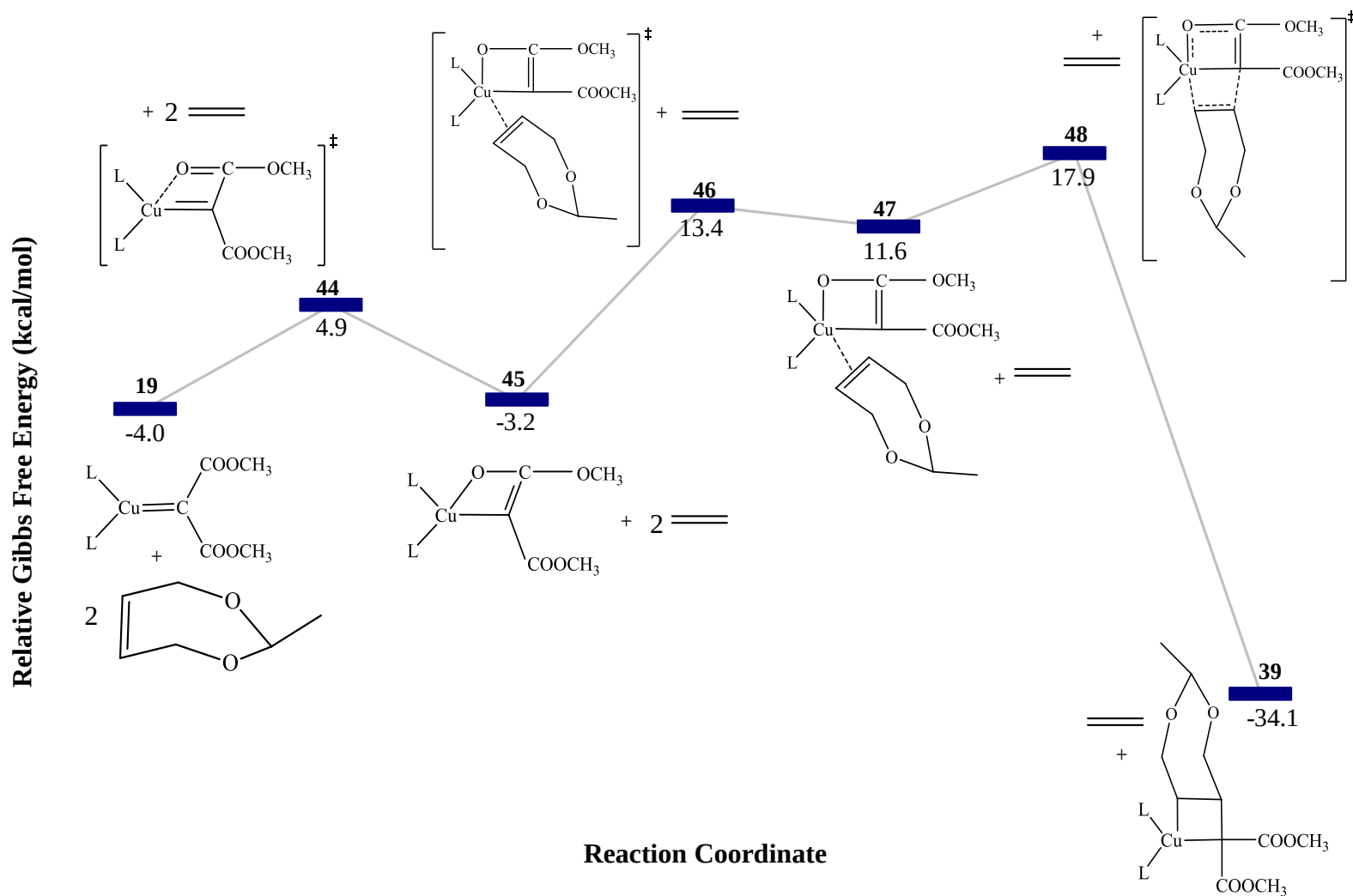


Figure 3.17 : The energetics and mechanism of the cyclopropanation reaction of **4a** via 4-centered path. Gibbs free energies refer to B3LYP/6-31G* (= refers to **4a**).

3.1.2.5 [3+2] Cycloaddition reaction of **4a**

The shift of the double bond on the ring, which is the only structural difference between the two isomers, created an unexpected reactivity difference between **3a** and **4a**. The reaction of **3a** with **DMDM** in the presence of copper(I) catalyst resulted with the formation of [3+2] cycloaddition product where the reaction under the same experimental conditions with **4a** gave mainly cyclopropane product [10]. In order to elucidate this preference, the [3+2] cycloaddition reaction of **4a** has been modeled both for chair and twisted-boat conformers of the substrate. The attempts for the calculation of the [3+2] cycloaddition reaction via stepwise path resulted with the concerted mechanism. The transition state structure **49** (Figure 3.18) (twisted-boat) has 20.6 kcal/mol of free energy value with respect to **5_4a**. It is also noteworthy to state that the contribution of oxygen to carbon-carbon double bond is not present in the transition state structure **49** which enables the charge separation over the olefinic carbon atoms facilitating the stepwise pathway. The cyclopropanation reaction either via 3-centered (17.4 kcal/mol) or 4-centered pathway (17.9 kcal/mol) has free energy values lower than the relative free energy of transition state **49** (analogous of **26** with **3a**). This higher energy barrier of **49** as compared to that of cyclopropanation reaction is good enough to state that [3+2] cycloaddition of **4a** will not be favored over cyclopropanation. Our calculations are in harmony with the experimental product distribution [10,41].

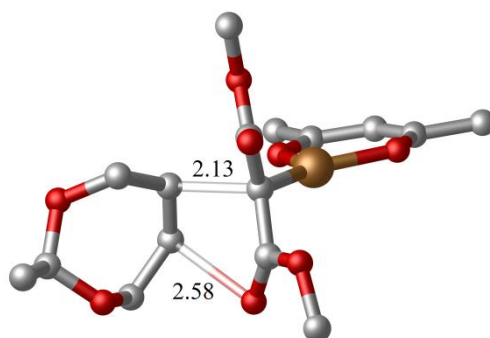


Figure 3.18 : 3D representation of **49**.

3.1.2.6 The mechanism of furofuran formation

The third stage of mechanism follows after the formation of furan molecule. In transition state **50** (Figure 3.19), the furan intermediate **25** reacts with copper-carbene **19** to in a similar way of structure **20** (Figure 3.20). Energetically, this step requires 21.1 kcal/mol Gibbs free energy for activation. While C-C distance is 2.22 Å, C-O distance is 2.70 Å. Although a rotation of CO moiety takes place for furan formation, furofuran product **53** is formed directly. To complete the catalytic cycle a second furan molecule attacks to the copper center to release the furofuran **53** (Figure 3.19).

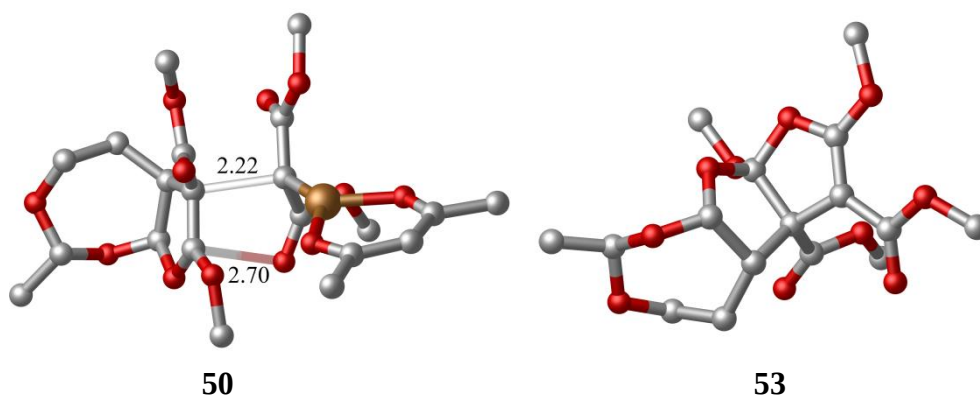


Figure 3.19 : 3D representations of structures **50** and **53**, respectively.

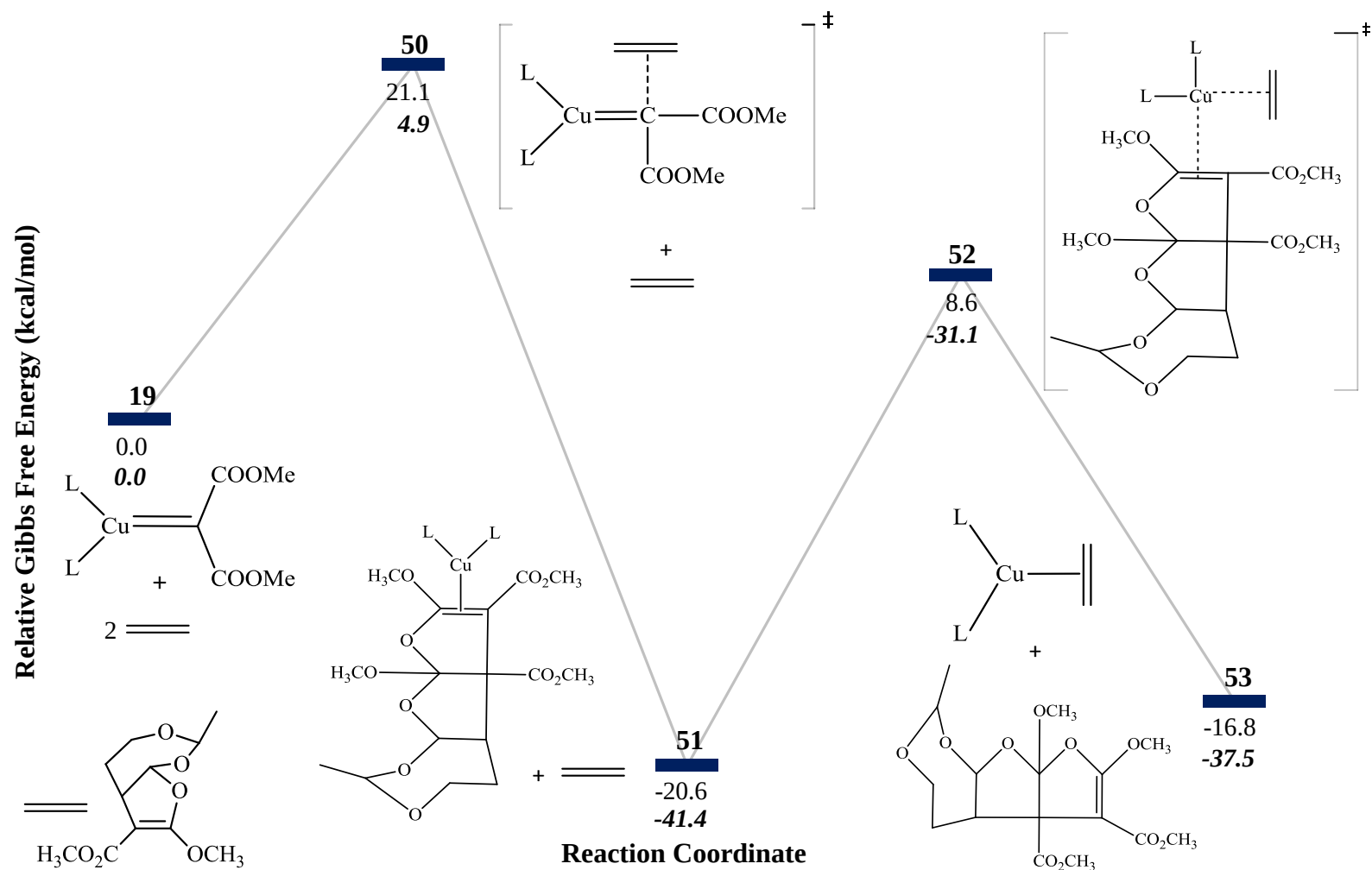


Figure 3.20 : The energetics and mechanism of furofuran formation. Gibbs free (plain text) and electronic (Bold and italic) energies refer to B3LYP/6-31G*.

The proposed mechanism for the [3+2] cycloaddition reaction accounts for the key experimental observations with the 4,5-dihydro-2-methyl-1,3-dioxepine (**3a**) molecule. The formation of the experimental [3+2] cycloaddition product via a stepwise path is more favorable relative to the concerted one for **3a**. The copper catalyst is responsible for the charge separation on the olefinic bond, which enables the reaction mechanism to proceed via a stepwise path rather than a concerted one. The stepwise [3+2] cycloaddition reaction is more plausible relative to the cycloaddition via metallocyclobutane or cyclopropane intermediates in terms of free energy barriers (Table 3.1). Thus, the formation of furan rather than the cyclopropane product is supported both kinetically and thermodynamically for **3a**. The furan product further undergoes a facile cycloaddition reaction to form the furofuran product. Although furan formation was step-wise, furofuran formation took place via concerted path. The barriers to furofuran formation are higher than that of furan mainly due to steric effects and the observed concerted nature of bicyclic ring formation

It is reported that under the same experimental conditions, (Z)-2-methyl-4,7-dihydro-1,3-dioxepine (**4a**) gave mainly cyclopropane product. The calculations based on the hypothetical [3+2] cycloaddition and cyclopropanation of **4a** have shown that formation of a cyclopropane product is favored over a furan derivative (Table 3.1). Possible cyclopropanation mechanisms of **4a** have been modeled by considering both the chair and the twist-boat conformers of the dioxepine ring due to their comparable energies. Although the twist-boat conformer could not distinguish between the three- and four-centered pathways, the barriers for the two paths differ significantly from each other in favor of the four-centered pathway with a chair conformation of **4a**. The details of [3+2] cycloaddition and the role of the copper center in the mechanism have been elucidated by the results of the study.

The experimental study investigated herein was conducted in benzene, thus significant solvent effects are not expected. In our earlier study, copper-carbene formation and cyclopropanation mechanisms of 2,2-dimethyl-4,7-dihydro-1,3-dioxepine have been analyzed by single-point IEF-PCM [96,97] calculations in dichloromethane at the B3LYP/6-31G* level [39]. Free energy values were calculated by using the entropic contribution from the gas-phase results. No significant change in the preference of reaction paths has been observed. The same

methodology has been applied to the competing pathways in this study (Figure 3.21 and 3.22).

Table 3.1 : Summary of the highest relative Gibbs Free Energy and Enthalpy values (values in paranthesis) in [3+2] Cycloaddition and Cyclopropanation reactions of **3a** and **4a** in kcal/mol.

Reaction Type \ Molecule	3a				4a	
[3+2] Cycloaddition	10.4 ^a (8.5)	22.2 ^b (6.2)	20.9 ^c (17.2)	13.5 ^d (12.4)	20.6 (18.2)	
Cyclopropanation	13.5 (12.4)				17.4 ^e (14.3)	17.9 ^f (14.3)

a: Relative free energy of the transition state of the experimental product obtained via stepwise [3+2] Cycloaddition reaction, b: Relative free energy of the transition state of the regioisomer product obtained via concerted [3+2] Cycloaddition reaction, c: Relative free energy of the transition state of the experimental product obtained via metallacyclobutane, d: Relative free energy of the transition state of the experimental product obtained via cyclopropane, e: Relative free energy of the transition state of cyclopropanation reaction via 3-center pathway, f: Relative free energy of the transition state of cyclopropanation reaction via 4-center pathway.

In order to test the effect of basis set, single point calculations at the B3LYP/6-311+G** level have been performed on [3+2] cycloaddition via step-wise pathway which was chosen as the preferred mechanism in gas phase and two other competing paths ([3+2] via cyclopropane intermediate and cyclopropanation). The high level calculations have made changes on the relative energies to the reference point, however the barriers have not changed significantly. Thus, the same preference for [3+2] cycloaddition was observed. Relying on this data, it can be said that the methodology used is good enough for the system that have been investigated (Figure 3.23).

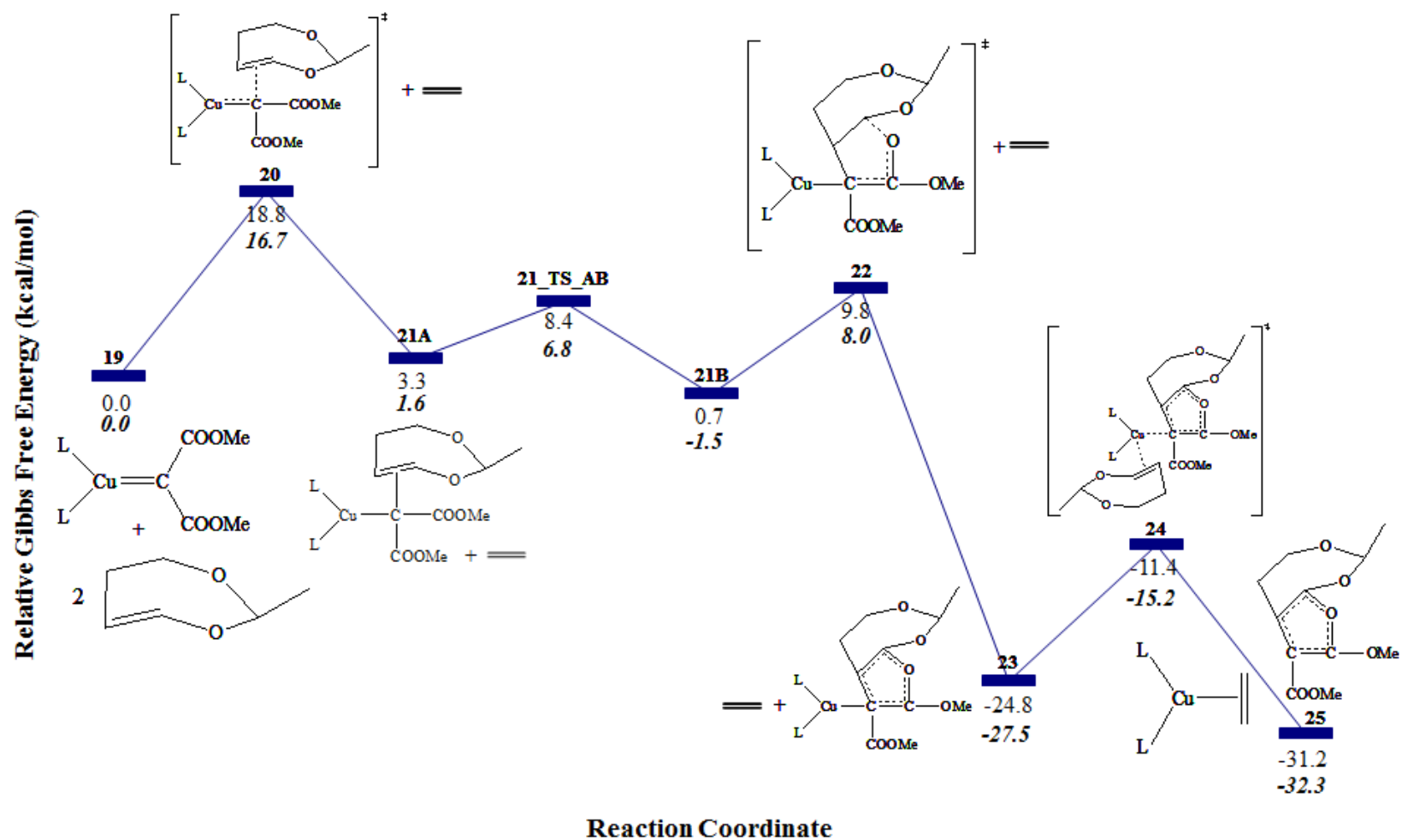


Figure 3.21 : The energetics and mechanism of the [3+2] cycloaddition reaction of dioxepine (**3a**) in benzene (text plain) and gas phase (bold and italic) (= refers to **3a**).

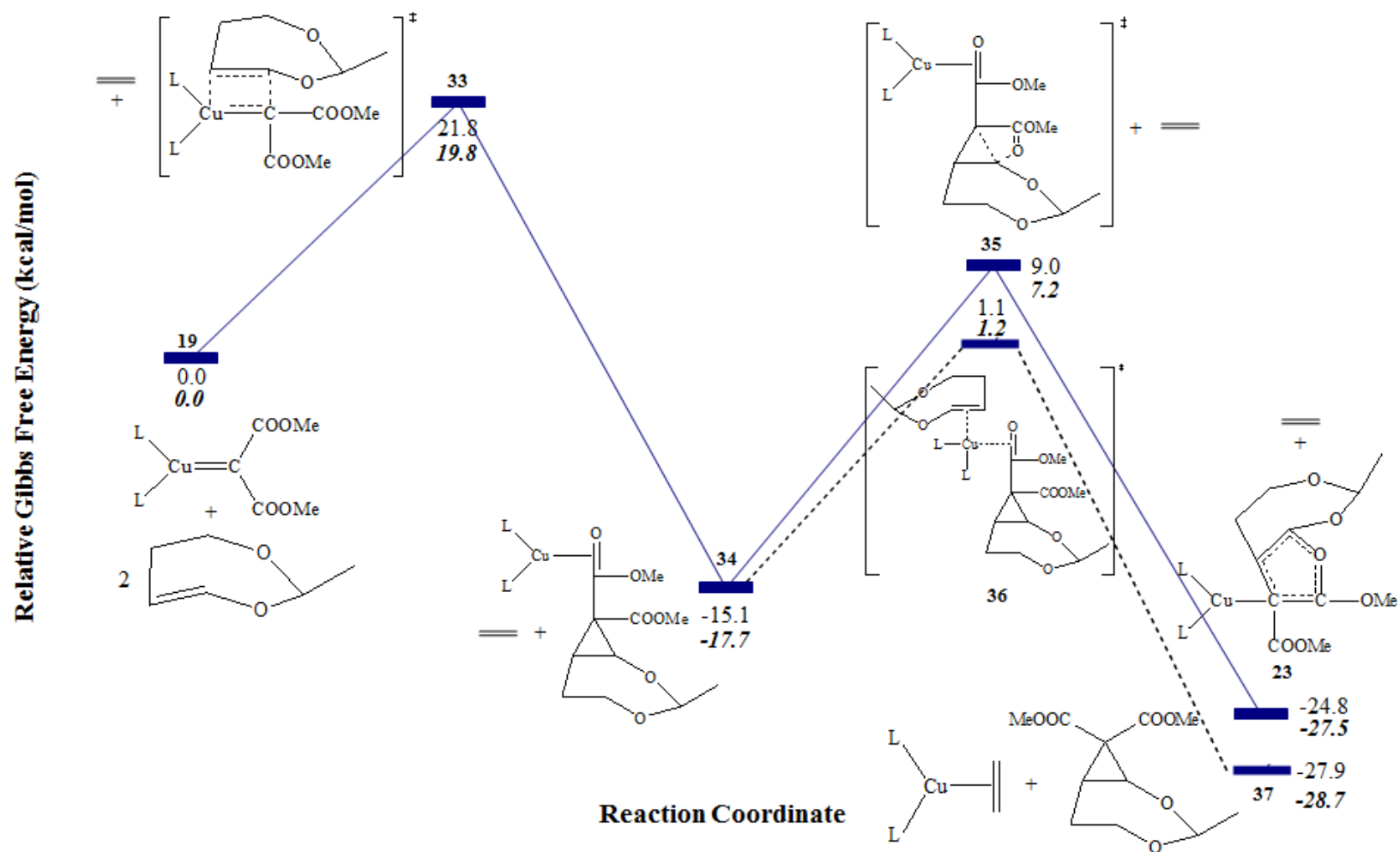


Figure 3.22 : The energetics and mechanism of [3+2] cycloaddition and cyclopropanation reaction via intermediate **34** in benzene (text plain) and gas pahse (bold and italic) (= refers to **3a**).

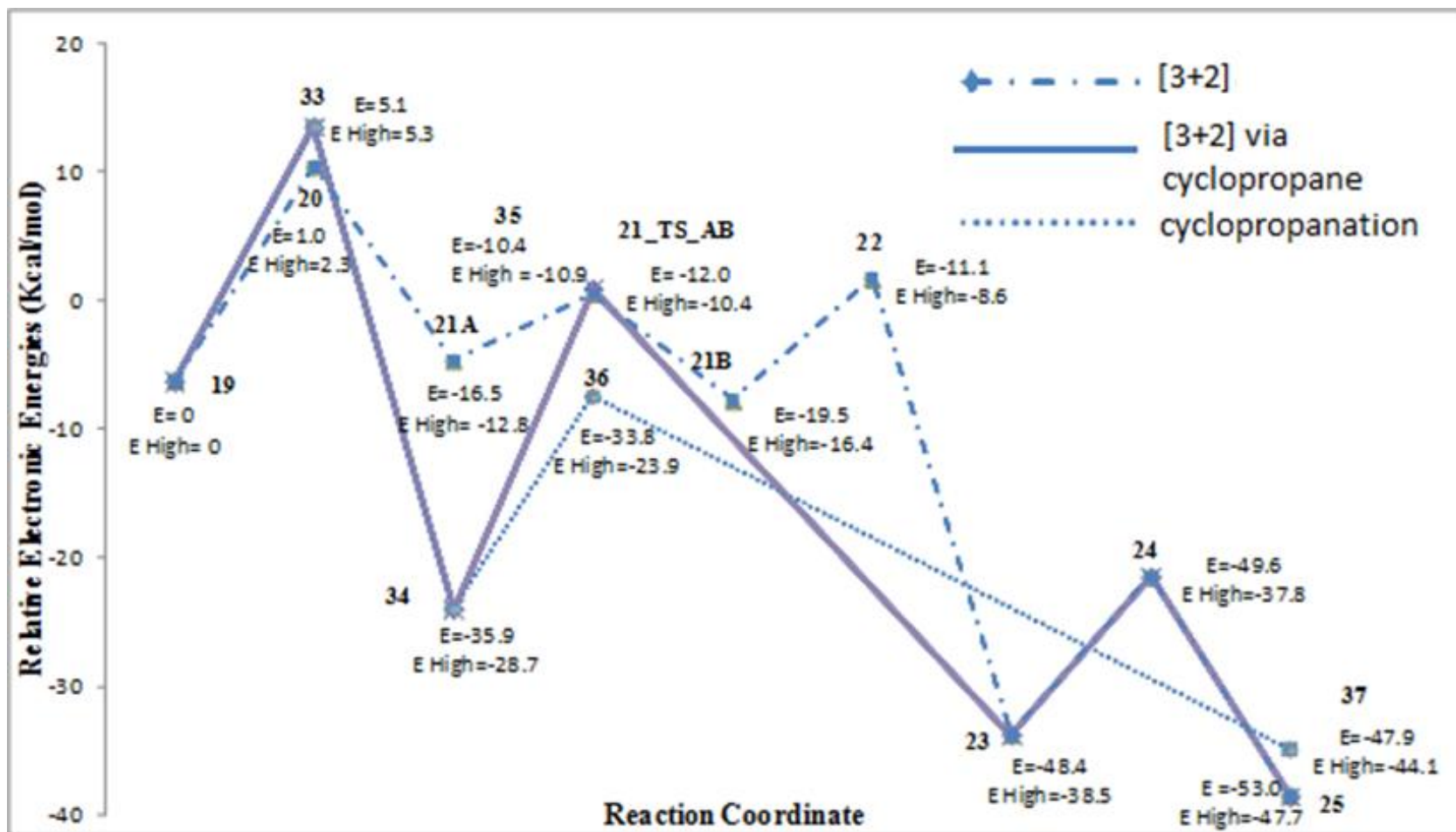


Figure 3.23 : The energetics and mechanism of [3+2] cycloadditions and cyclopropanation reaction via intermediate **34** with electronic energies (E High refers to B3LYP/6-311+G** and E refers to B3LYP/6-31G*).

4. THE MECHANISM OF COPPER-CATALYZED AZIDE-ALKYNE CYCLOADDITION REACTION

In the second part of this thesis, the mechanism of CuAAC reaction has been investigated in detail by the quantum mechanical calculations to account on the differences observed in earlier studies [61-66]. The nature of copper acetylide and how it participates in the reaction has been elucidated by considering the possible types of multinuclear copper-acetylide species with full basis set for copper, in contrast to some earlier computational studies. Although the history of the copper-acetylide species is very old, their nature is not well known due to their tendency to form polymeric structures [112]. Understanding the interaction of copper and alkynes is the key factor to explain the copper-acetylides. The reaction with a representative simple alkyne and a simple azide has been modeled first with full basis set to concentrate solely on the electronic effects of the mechanism. Later, the devised mechanism has been applied to an experimentally worked system [68], namely to the reaction of 2-azido-1,1,1-trifluoroethane and ethynylbenzene in the presence of copper.

4.1 Computational Method

In most of the previous computational studies about CuAAC mentioned so far, effective core potential has been used. In a previous computational study on the copper-acetylide complexes, it is stated that the LACVP calculations did not reproduce the cuprophilic interactions [64,113], which are reported to be important interactions for dimeric and tetrameric Cu (I) complexes [114]. The DFT methodology with B3LYP [78,79] hybrid functional and 6-311+G(d,p) basis set has been carried out for optimizations of all atoms in gaseous phase at 298 K to provide sufficient accuracy and to refine the energetics. So far, mechanistic studies about CuAAC have been generally carried out with LACVP pseudopotential, however; it is known that this ECP overestimates cuprophilic interactions and Cu-N bond [112,113]. B3LYP has been reported to give accurate results with transition metals

[98-101] and in our previous studies on copper [39-115], it had shown satisfactory performance. Additionally, in the literature, this functional has been successfully used for the mechanisms of copper catalyzed azide-alkyne cycloaddition reactions [61,64,65,116]. The stationary points were analyzed by vibrational frequency calculations. All transition states were verified to be saddle points by one imaginary frequency belonging to the reaction coordinate. For all transition state structures, the intrinsic reaction coordinate (IRC) [80,81] was followed to validate the expected reactants and products. Charge analysis has been performed with Natural Bond Orbital (NBO) [84-91] calculations. Throughout the investigation, all structures and mechanisms have been interpreted by means of relative Gibbs free energy, unless otherwise stated. The effect of solvent was considered for the reactions in real world system by single-point SCRF calculations with the IEF-PCM [96,97] method at the B3LYP/6-311+G(d,p) level. The free energies in acetonitrile and water were obtained by using the frequencies from the gas-phase results. Gaussian 03 computational chemistry software has utilized for all calculations [98].

4.2 Results and Discussions

4.2.1 Model system

The reaction of azide with alkyne is assumed to start with π coordination of the alkyne to copper, followed by deprotonation of the alkyne and formation of a copper-acetylide species. To understand the nature of copper acetylides first a model system, then an experimentally worked system has been modeled with full basis set calculations. For this purpose one, two, three and four-copper-membered possibilities of copper-acetylide species for model reaction have been evaluated computationally (Tables 4.1, 4.2 and 4.3) (Figures 4.1, 4.2 and 4.3). Even though polynuclear copper-acetylide structures may form, it is not possible in CuAAC reactions since it will be hindered by both azide and amine ligands [112]. Although three-copper-membered acetylide species have been proposed [63], it was later reported to be unfavourable and additionally no experimental evidence existed [112]. Solvent molecules are known to act as ligand and high alkyne concentration was reported to affect the binding of azide in CuAAC reactions [61]. The presence of ligands increases the rate of reaction however, they are not mandatory for the fate of the reaction and as stated by Finn *et al.*, the ligand-free process is a good starting point for mechanistic studies

[66]. In our effort to rationalize the structure of copper-acetylide species, besides the number of copper, the number of alkyne has been modified and the possibility of binding one or more acetonitrile and water molecules has been considered (Tables 4.1 and 4.2). The calculations have showed that while acetonitrile molecules can bind to copper in two- and three copper-membered copper-acetylide species, no four-copper-membered copper-acetylide structure could be optimized with acetonitrile or water (Figure 4.1 and 4.2). Moreover, in our calculations, many copper-acetylide structures with acetonitrile as ligand could be located, in contrast to the ones with water. This is in accordance with the literature findings that acetonitrile is a more effective ligand than water [117,118]. According to our results, four-copper-membered structures are much more stable than the others, consistent with the literature [64]. The copper-acetylide with two copper atoms and acetonitrile (**M1C**) as ligand has been found to be the lowest energy dicopper species.

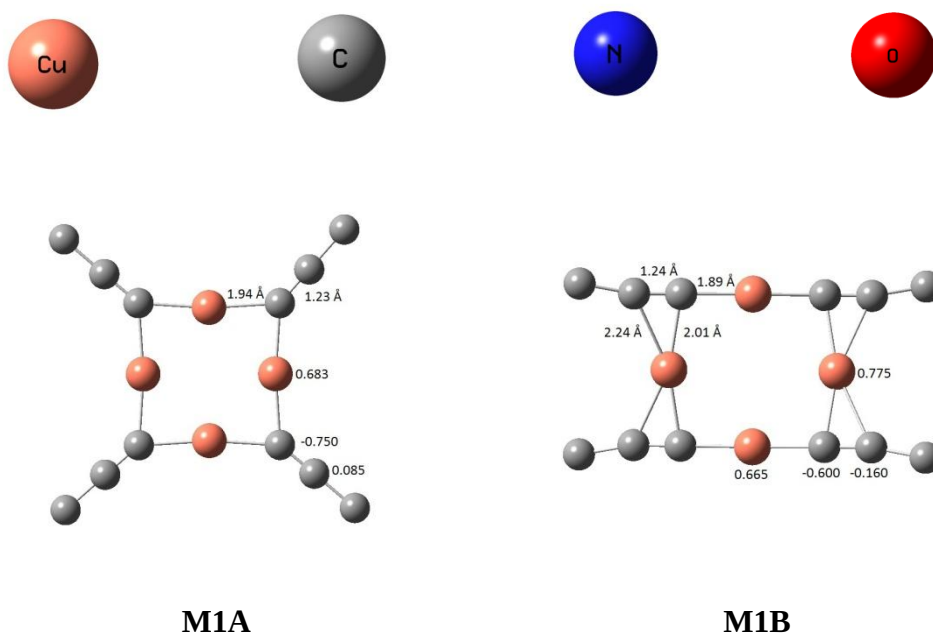
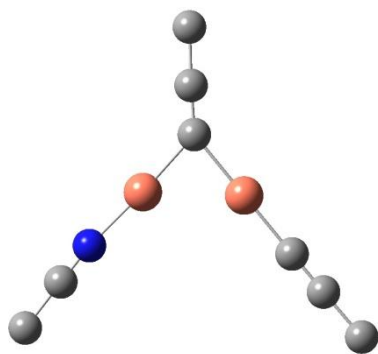
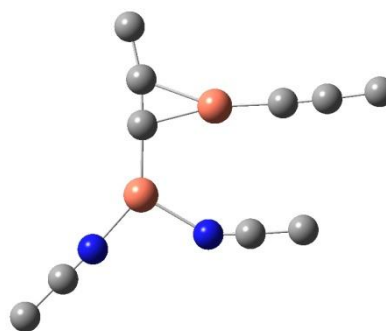


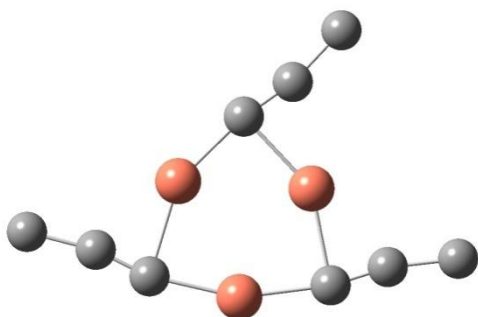
Figure 4.1 : Copper-acetylide species with acetonitrile ligand (H atoms are omitted for clarity).



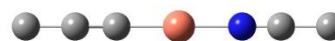
M1C



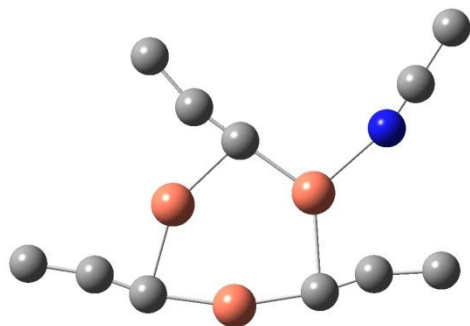
M1D



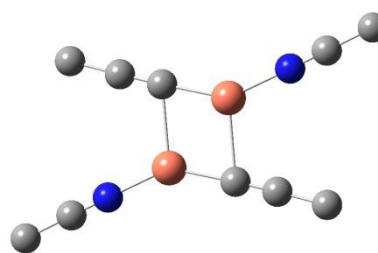
M1E



M1F

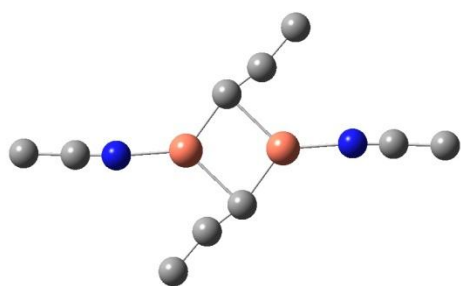


M1G

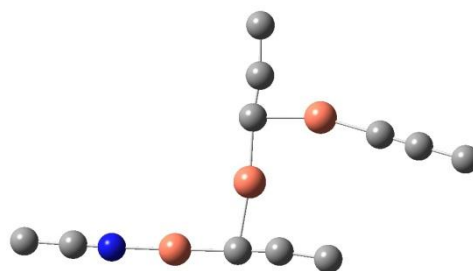


M1H

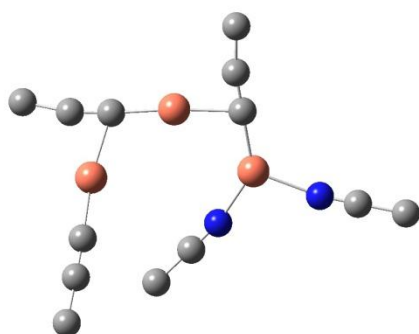
Figure 4.1 (continued): Copper-acetylide species with acetonitrile ligand (H atoms are omitted for clarity).



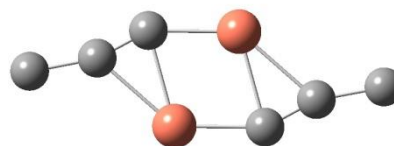
M1I



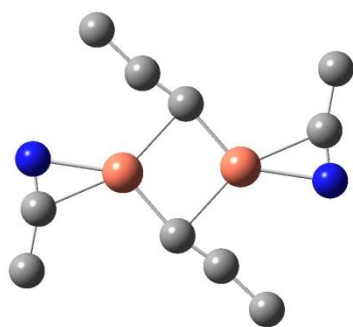
M1J



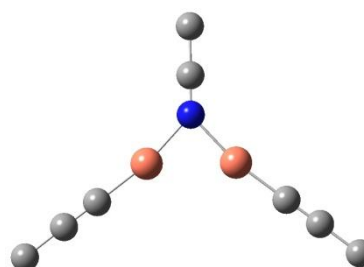
M1K



M1L



M1M

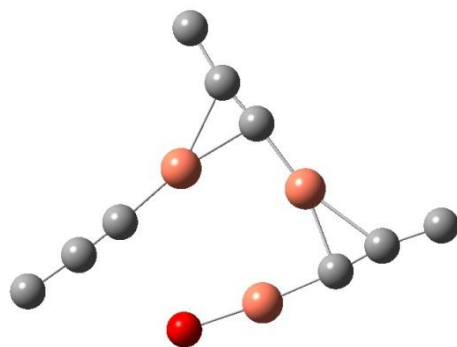


M1N

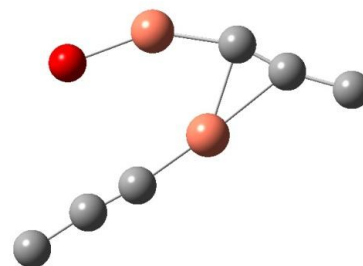
Figure 4.1 (continued): Copper-acetylide species with acetonitrile ligand (H atoms are omitted for clarity).

Table 4.1 : The relative Gibbs free energy values of the copper-acetylide species with solvent acetonitrile as ligand. (The relative energies are calculated by adding the energy of smaller units so as to keep the number of atoms equal).

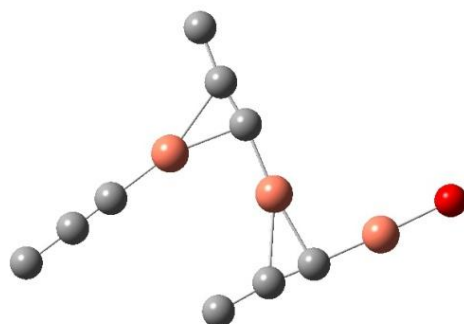
Structure	Relative Gibbs Free Energy (kcal/mol)
M1A (4 Cu)	0.0
M1B (4 Cu)	4.0
M1C (2 Cu)	35.4
M1D (2 Cu)	42.7
M1E (3 Cu)	45.1
M1F (1 Cu)	46.7
M1G (3 Cu)	51.6
M1H (2 Cu)	53.4
M1I (2 Cu)	56.0
M1J (3 Cu)	57.0
M1K (3 Cu)	58.0
M1L (2 Cu)	72.0
M1M (2 Cu)	75.0
M1N (2 Cu)	84.5



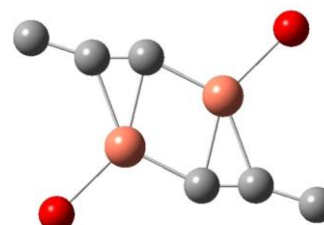
LW_A



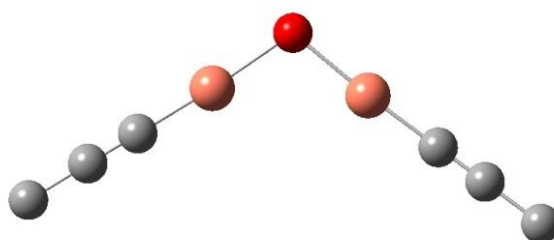
LW_B



LW_C



LW_D



LW_E

Figure 4.2 : Copper acetylide species with water ligand (H atoms are omitted for clarity).

Table 4.2 : The relative Gibbs free energy values of the copper-acetylide species with solvent water as ligand. (The relative energies are calculated by adding the energy of smaller units so as to keep the number of atoms equal).

Structure	Relative Gibbs Free Energy (kcal/mol)
M1A(4 Cu)	0.0
LW_A(3 Cu)	36.6
LW_B(2 Cu)	50.8
LW_C(2 Cu)	51.7
LW_D(3 Cu)	74.4
LW_E(1 Cu)	76.3

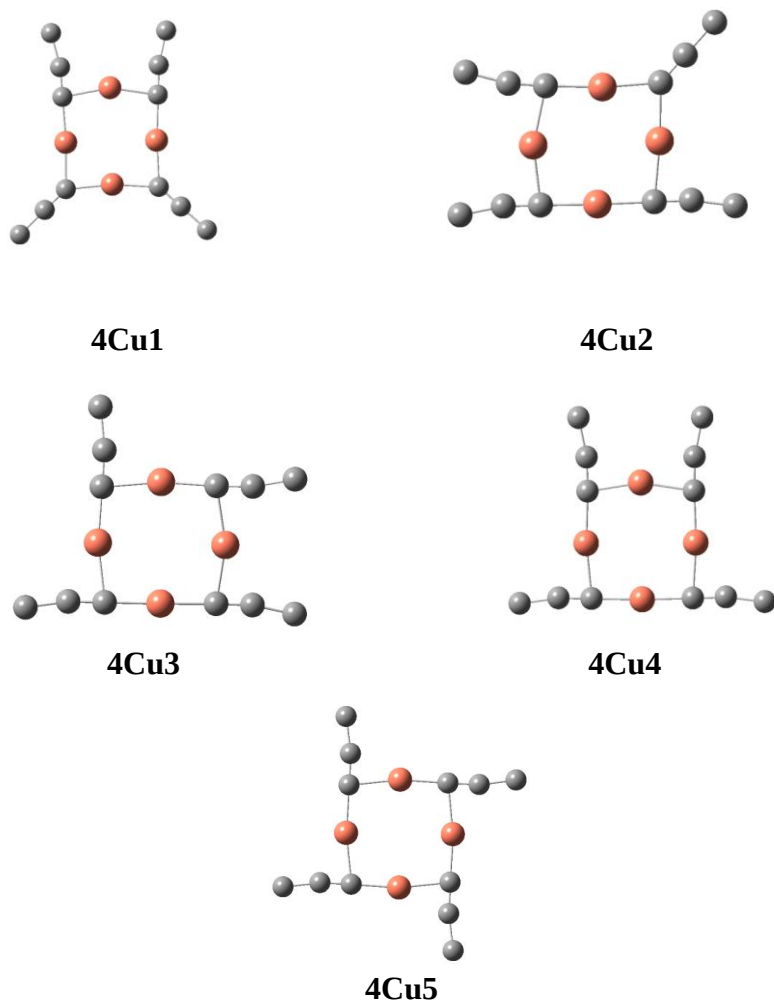


Figure 4.3 : Four copper-member copper-acetylide species (H atoms are omitted for clarity).

Table 4.3 : The relative Gibbs free energy values of the four-copper-member copper-acetylide species.

Structure	Relative Gibbs Free Energy (kcal/mol)
M1A	0.0
M1B	4.0
4Cu1	1.6
4Cu2	2.4
4Cu3	3.0
4Cu4	4.1
4Cu5	4.3

In Figure 4.4, the most stable structures of the four membered copper species are shown. For four membered copper-acetylide species, two different structures, **M1A** and **M1B** will be considered. Coordination of copper to π electrons in **M1B** has distorted the planarity by 30° although **M1A** has a perfectly planar structure. The electronic and Gibbs free energies show the opposite trends, such that the free energy of **M1A** is lower than **M1B** by 4.0 kcal/mol and the electronic energy of **M1B** is lower than **M1A** by 4.0 kcal/mol. Cataldo *et al.* reported similar Cu-polynide structures based on their FT-IR spectra, which may serve as an experimental basis for the modeled **M1B** structure [119]. **M1B** is also similar to the propeller-like structure of the 2,4,6-triisopropylphenylcopper compound, a tetranuclear organocopper species with unsymmetrical bridging of σ - π bonded aryl ligands in the solid state [120]. The tetranuclear species **M1A** and **M1B** also resemble the X-ray structures of organocopper compounds of the type $[\text{Cu}_4\text{R}_4]$ [114].

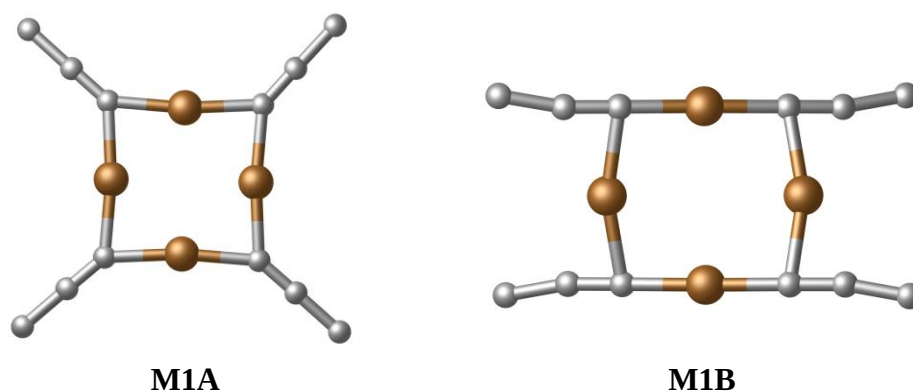


Figure 4.4 : 3D representations of structures **M1A** and **M1B**, respectively.

After formation of copper-acetylide, azide molecule attacks to the copper atom in **M1A**. The approach of azide forces the **M1A** conformer to turn into **M1B** structure in the forming van der Waals complex, **M2**. Energetically, the coordination of α -nitrogen to copper is considerably endergonic. The terminal nitrogen in **M2** attacks to the alkyne carbon atom to constitute the six-membered metallocyclic structure. According to NBO charges, π interaction with alkynes causes a small increase in the charge of the two copper atoms in **M1B** structure compared to that of **M1A**. When the azide molecule approaches to the copper through α -N, the charge of interacted copper is increased from 0.66 to 0.71. As the reactants engage to undergo cyclization reaction, a small electronic interaction between copper and α -N takes place to enable 1,4-product to form. The azide coordination brings the substrates to proper position and suitable electronic states for cyclization to take place through transition state **M3** (Figure 4.5) which requires a barrier of 16.6 kcal/mol. After formation of six-membered metallocyclic structure **M4** with a relative 24.0 kcal/mol free energy, α -N starts to detach from copper atom to bind to carbon atom, leading to 1,4-triazole molecule with a small barrier of 1.7 kcal/mol (**M5**). The catalyst associated 1,4-triazole structure **M6** (Figure 4.5) is formed as a result of the exergonic process. In the literature, a similar structure of **M6**, with steric substituents and single-copper as catalyst was isolated and identified by NMR [121]. The forming triazole can be regenerated by protonation of **M6** structure.

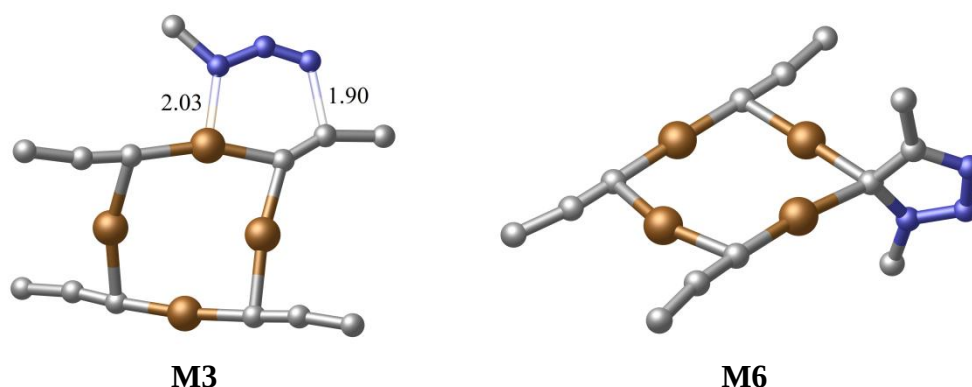


Figure 4.5 : 3D representations of structures **M3** and **M6**, respectively.

In this mechanism, formation of **M3**, is the rate-determining step and the highest point on the Gibbs free energy diagram. This result is in accordance with a recent IR study which states that the rate-determining step is the preproduct formation from the azide-alkyne complex [122]. The B3LYP/6-311+G(d,p) calculations in this study predict a stepwise reaction contrary to computational studies in the literature, all

performed at the B3LYP level of theory with LANL2DZ on copper. The second transition state, **M5** from a short-lived complex **M4**, takes place via a very small energy barrier but at a relatively high energy point on the reaction profile. Analogous metallacyclic intermediate **M4** has been suggested for dinuclear paths in the literature, but not for the tetranuclear path [64,65].

The possibility of 1,5-disubstituted triazole formation has also been investigated in the context of this study. It was found to undergo a concerted mechanism contrary to 1,4-disubstituted triazole formation. The transition state for 1,5-product, **M7** (Figure 4.6), is 9.0 kcal/mol higher in energy than **M3**, as expected. The bigger barrier for 1,5-triazole formation is stemming from the unfavorable electronic interaction between the terminal nitrogen and the positively charged copper atom. Additionally, while in **M6** two copper atoms coordinate to the triazole's carbon atom, in **M8** (Figure 4.6), the product of **M7**, one copper atom coordinates to nitrogen and the other one coordinates to the carbon atom, which makes it harder for the triazole molecule to detach and regenerate the catalyst.

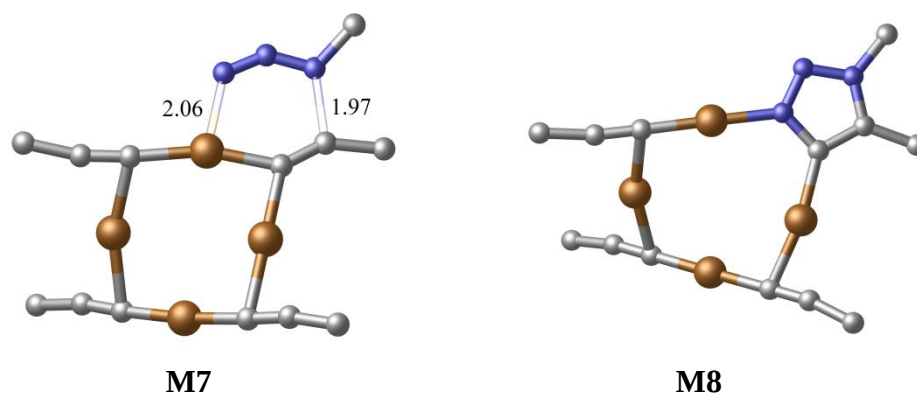


Figure 4.6 : 3D representations of structures **M7** and **M8**, respectively.

4.2.2 Real system

At this stage of the study, the model mechanism has tested with an experimentally reported system. For this purpose, a convenient example in terms of computational cost has been searched among the many CuAAC reactions that have been reported in literature. The experimental results of Wu *et al.* have been chosen in which 2-azido-1,1,1-trifluoroethane (Figure 4.7) reacts with ethynylbenzene in the presence of copper catalyst [68]. Among the vast of triazole derivatives, CF₃ containing scaffolds have increasing attention due to their biological features [123-125]. As for copper-acetylide, **R1A** (Figure 4.7) has been obtained due to the ethynylbenzene.

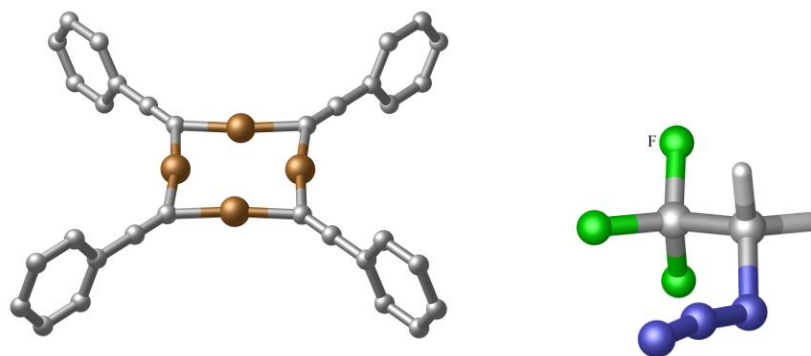


Figure 4.7 : 3D representations of structures **R1A** and 2-azido-1,1,1-trifluoroethane, respectively.

The substituents on the real system did not show a change in the reaction mechanism of the model (Figure 4.8) in production of the triazole product **R6**. The barriers are slightly lower than the model system. The electron-withdrawing substituent on the alkyne has enabled easier complexation of the copper-acetylide with the azide as compared to the model compound (12.1 kcal/mol for **M2** and 8.5 kcal/mol for **R2**). This is consistent with the experiments where electron-withdrawing groups on the alkyne were reported to accelerate the CuAAC reaction rate [56,126].

While the energy barrier for transition from **M4** to **M5** is 1.7 kcal/mol, this value is increased to 5.2 kcal/mol in the real system, although other barriers have decreased slightly as compared to the model system. Thus, depending on the substituents, the second transition state may become more distinctive and reach to a relative energy comparable to the highest point on the free energy diagram.

The effect of solvent has been investigated for the real system with two solvents that are most frequently used: acetonitrile and water (Figure 4.9). It has been observed that solvents increase the barriers by 0.4-3.7 kcal/mol. The barrier of the rate determining step has increased by 3.7 kcal/mol in acetonitrile (3.4 kcal/mol in water) since the stabilization in the bimolecular starting step of reaction is higher than in the unimolecular **R3** step.

The calculated energy barrier for the uncatalyzed process of 1,4-disubstituted triazole formation is 34.0 kcal/mol in the gas phase (36.0 kcal/mol in acetonitrile). The difference in barriers of catalyzed and uncatalyzed reactions (8.8 kcal/mol in the gas phase and 7.4 kcal/mol in acetonitrile) has exhibited great acceleration of the reaction in the presence of copper catalyst.

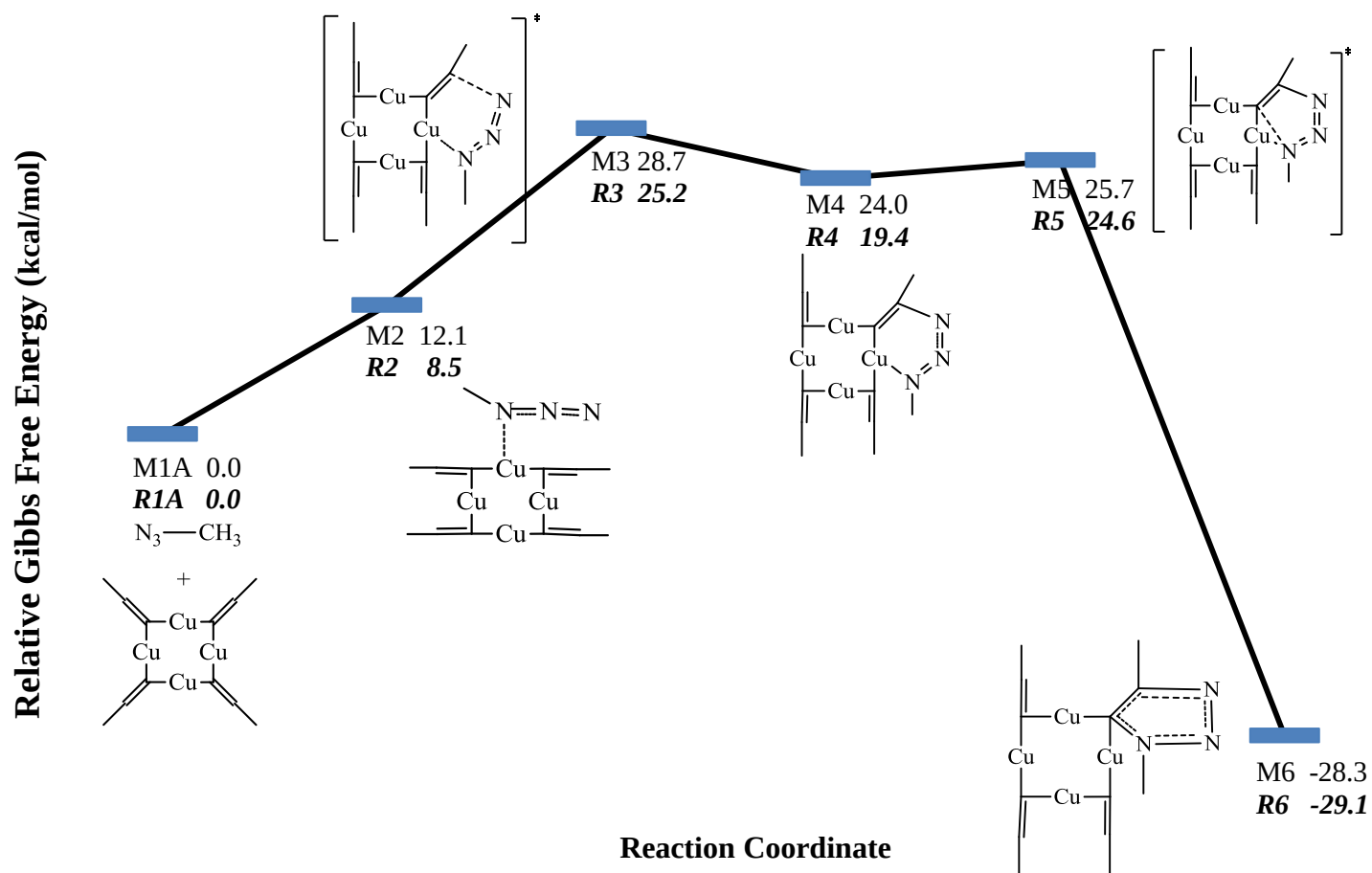


Figure 4.8 : Reaction mechanism of CuAAC in gas phase (M refers to model system, R refers to real system).

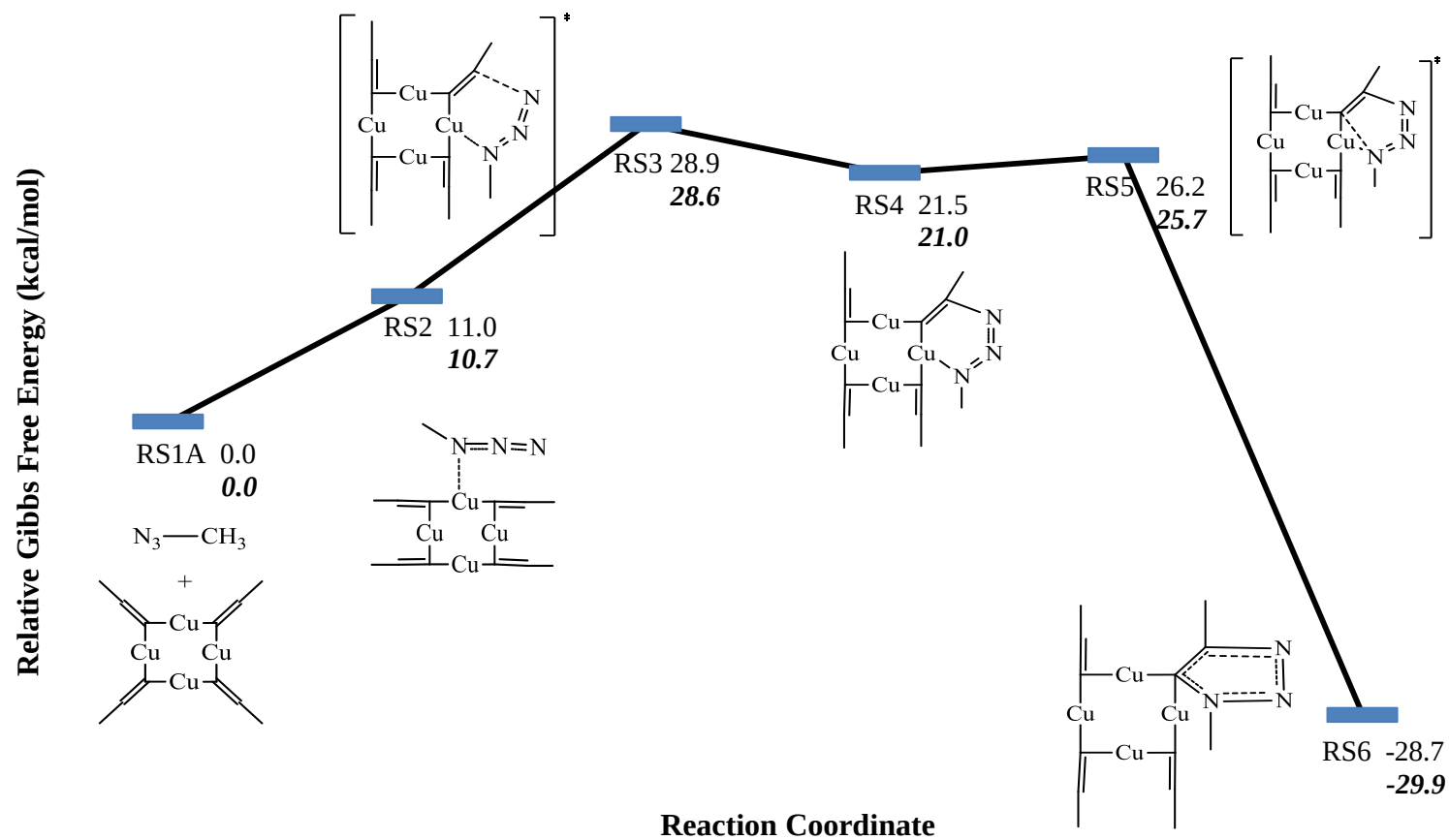


Figure 4.9 : The mechanism of CuAAC in acetonitrile (plain text) and water (bold and italic values) solvents with IEFPCM method at B3LYP/6-311+G(d,p) level of theory.

In a recent paper on CuAAC reaction mechanism, the authors consider the reaction barrier from the polynuclear copper species without considering the stability of these copper-acetylides and conclude that the CuAAC reaction proceeds via di-copper acetylide structures, based on their calculated barriers [65]. Our calculations show that formation of a 4-membered acetylide is much more facile as compared to that of dicopper acetylide species both in the gas phase and in solvent (35.4 kcal/mol in the gas phase and 18.2 kcal/mol in acetonitrile). Following the reaction from **M1C** (Figure 4.10) and azide, the highest point on the energy path corresponds to the first transition structure (**M3**) at a relative free energy of 23.6 kcal/mol and the azide coordinated complex is 8.0 kcal/mol higher than the uncoordinated reactants. A direct comparison of the reaction barriers of four and two centered species shows that once the azide-copper acetylide complex is formed, the reaction through the dicopper species **M1C** is slightly more facile than the tetracopper species (16.6 kcal/mol for tetracopper and 15.6 kcal/mol for the dicopper acetylides, in the gas phase, and 17.9 kcal/mol for tetracopper and 16.1 kcal/mol for dicopper in acetonitrile). The corresponding barriers in the aforementioned study were 18.0 kcal/mol and 16.0 kcal/mol for the tetracopper and dicopper acetylides, respectively and the dicopper species involved odd number of electrons, indicating that the species had a charged nature [65]. Additionally, the IRC calculations following the dicopper transition state structure with full basis set in this study predict a complex and separated reactants contrary to the results of Cantillo *et al.* [65].

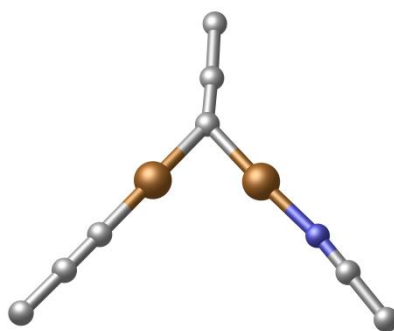


Figure 4.10 : 3D representation of structure **M1C**.

4.3 Mechanism of Protonation of Copper-triazolide

Protonation is a distinctive and final part in CuAAC reactions in which copper-triazolide molecule is protonated by a proton source or an alkyne reactant. Depending on the reaction conditions, protonation could be faster or vice versa [127]. Straub has isolated a copper-triazolide species using water as a weak proton source and bulk substituents to retard protonation [121]. Hu *et al.* promoted this step using carboxylic acid [127]. In the context of this thesis, the mechanism of protonation of copper-triazolide was also investigated with model reactants. Generally the bases used in CuAAC reactions are computationally very expensive, thus, prop-1-yne reactant was utilized as a proton source to simplify the mechanism. To the best of our knowledge, there is no mechanistic study on protonation of copper-triazolide in CuAAC reactions in the literature.

4.3.1 Computational method

The DFT method employing the B3LYP functional [78,79] has been used to carry out the full optimization of the compounds of interest in the gas phase with the G09 package [128]. For copper and nitrogen atoms B3LYP/6-31+G* and for the rest B3LYP/6-31G* basis sets have been used.

The stationary points were analyzed by vibrational frequency calculations. All transition states were verified to be saddle points by one imaginary frequency belonging to the reaction coordinate. For all transition state structures the intrinsic reaction coordinate (IRC) was followed to validate the expected reactants and products [80,81]. The energies discussed in the text are Gibbs free energies calculated at 298 K, unless otherwise stated.

4.3.2 Results and discussions

The protonation starts with the coordination of π -electrons of alkyne molecule to the copper atom of **M6** to form intermediate **M9** (Figure 4.11) In **M9**, the Cu-C distances are 2.25 and 2.40 Å, respectively. **M9** leads to **M10** intermediate in which copper interacts more strongly with the olefinic bond, such that the Cu-C_{alkyne} distances have shrunk to 2.10 and 2.18 Å. (Cu-C_{acetylide} 1.89→1.94 Å, Cu-C_{triazolide} 1.98→2.23 Å). The last step is the proton transfer from the alkyne to the carbon atom triazolide part of **M10**. The C_{alkyne}-H and C_{triazolide} distances are 1.38 and 1.41 Å, respectively. In section 4.2.1, formation of copper-triazolide has been modeled with

B3LYP/6-311+G(d,p) level of theory. The highest barrier in **4.2.1** is between **M2-M3** (16.6 kcal/mol). In this section the highest barrier is 19.9 kcal/mol (**M10-M11**) (Figure 4.12) indicating that depending on reaction conditions, protonation may be affective in accelerating or decelarating reaction [127].

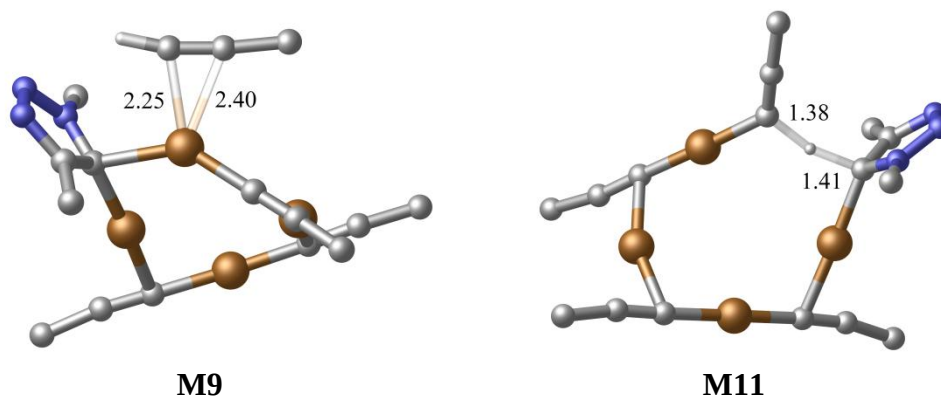


Figure 4.11 : 3D representations of structures **M9** and **M11**.

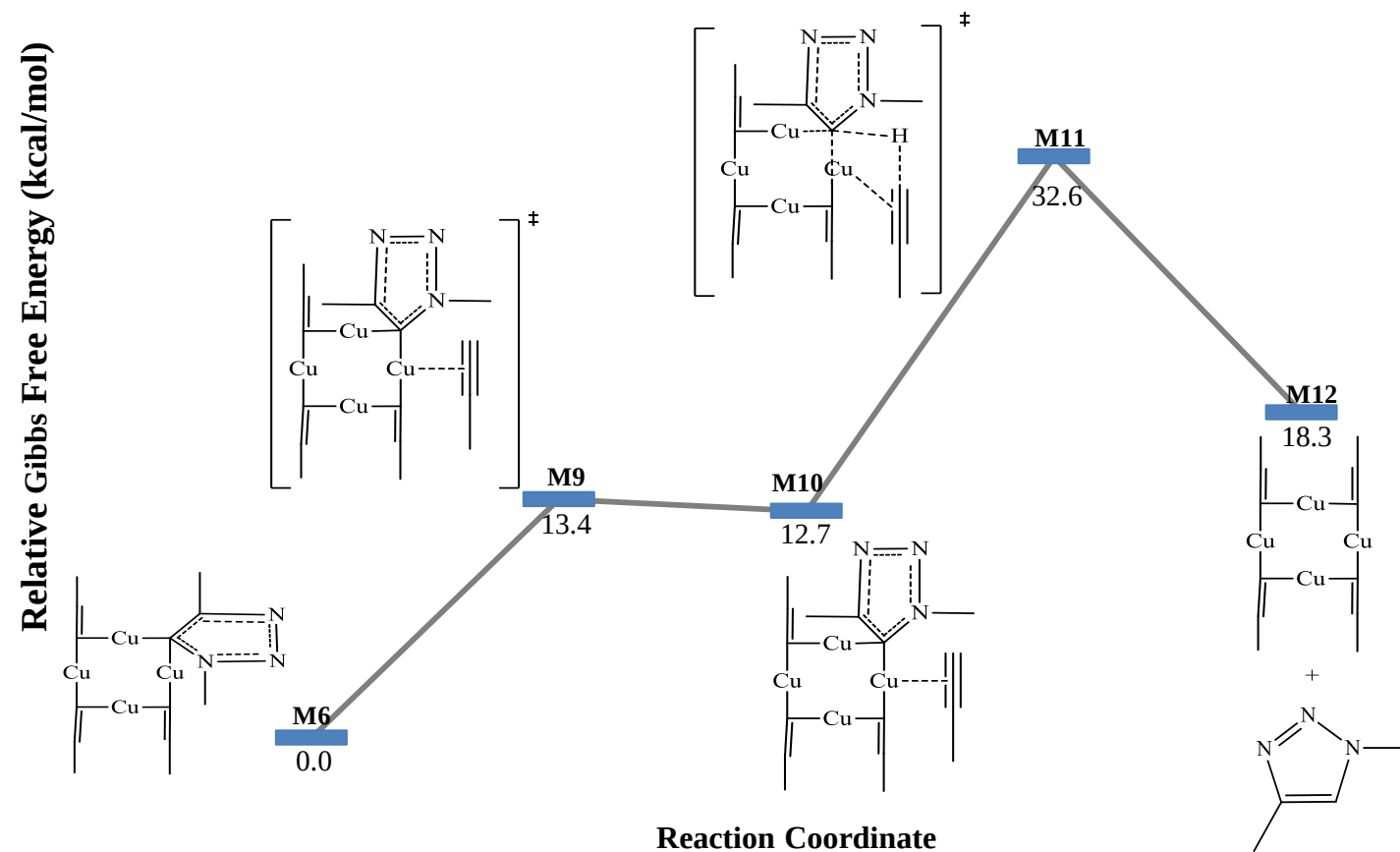


Figure 4.12 : The mechanism of protonation of copper-triazolide. Relative energy values refer to B3LYP/6-31+G(d) for Cu and N and B3LYP/6-31g(d) for C and H.

5. THE MECHANISM OF COPPER-CATALYZED DIAZIDE-ALKYNE AND AZIDE-DIALKYNE CYCLOADDITION REACTIONS

In this part of the study, the mechanisms of copper-catalyzed diazide-alkyne and azide-dialkyne cycloaddition reactions have been investigated using quantum mechanical methods. The experimental findings of Finn *et al.* [66] have been utilised in which a diazide reacts with an alkyne to give a ditriazole product **b** as major product even excess diazide species are used over dialkyne while a dialkyne reacts with an azide to give both mono and di-triazole products **c** and **d** as statistical mixture in Figures 1.6 and 1.7. The authors proposed that while in the diazide-alkyne reaction the ditriazole product is synthesized directly, in the azide-dialkyne reaction, the ditriazole product is synthesized through mono-triazole intermediate. The reasons behind the differences in product distribution have been sought in this chapter in accordance with the previous experimental and computational studies.

As explained in the first part of this chapter, the CuAAC reaction is assumed to start by copper-acetylide structure formation. A series of possible copper-acetylide species which contain up to four copper atoms and solvent molecules as ligand has been evaluated and a four-copper containing copper-acetylide, **DA_1** (Figure 5.1), was proposed more likely to form based on its thermodynamic stability. In the difunctional part, the results from the general mechanism of triazole formation and the copper-acetylide structure from the first part of the study will be utilized. Although a ligand effect has been shown to be effective, it has not been considered in this study since the ligands are not essential for CuAAC reactions [63,64,66], and they increase the expense of calculations when included.

5.1 Computational Method

In the context of this study, all the possible reaction mechanisms, including intermediates and transition states, have been modeled and discussed in terms of relative energies obtained from quantum-mechanical calculations. The DFT method employing the B3LYP functional [78,79] has been used to carry out the full

optimization of the compounds of interest in the gas phase with the G09 package [124]. For copper and nitrogen atoms B3LYP/6-31+G* and for the rest B3LYP/6-31G* basis sets have been used. In most of the previous computational studies mentioned so far, effective core potential has been used. In a previous computational study on the copper-acetylide complexes, it is stated that the LACVP calculations did not reproduce and overestimate the cuprophilic interactions [113], which are reported to be important interactions for dimeric and tetrameric Cu (I) complexes [114].

The stationary points were analyzed by vibrational frequency calculations. All transition states were verified to be saddle points by one imaginary frequency belonging to the reaction coordinate. For all transition state structures the intrinsic reaction coordinate (IRC) [80,81] was followed to validate the expected reactants and products. The energies discussed in the text are Gibbs free energies calculated at 298 K, unless otherwise stated. Natural Bond Orbital (NBO) [84-91] analysis has been carried out on some structures in order to investigate the stabilizing donor-acceptor interactions.

The effect of solvent was considered for the reactions in real world system by single-point SCRF calculations with the IEF-PCM [97,98] method at the B3LYP/6-311+G(d,p) level. The free energies in DMSO were obtained by using the frequencies from the gas-phase results. In the figures only critical bond lengths are shown (in Å) and hydrogens have been omitted for clarity.

5.2 The Mechanism of Copper-catalyzed Diazide-Alkyne Cycloaddition Reaction

In the ligand free experiment conducted by Finn *et al.*, the reaction of phenylacetylene and 2,2-bis(azidomethyl)propane-1,3-diol, provided ditriazole 2,2-bis((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)propane-1,3-diol (**b**) as the major product, even when 10 equivalents of diazide over alkyne were used [66]. The diazide-alkyne cycloaddition reaction can be divided into two parts. In the first part, monotriazole formation takes place. In this mechanism, the copper-acetylide is formed from phenylacetylene (**DA_1**, Figure 5.1) as in Section 4 (Real system) and same geometry has been optimized by the basis set employed in this section. Among the four conformers of 2,2-bis(azidomethyl)propane-1,3-diol, structure **DA_2** has been obtained as global minimum (Figure 5.1).

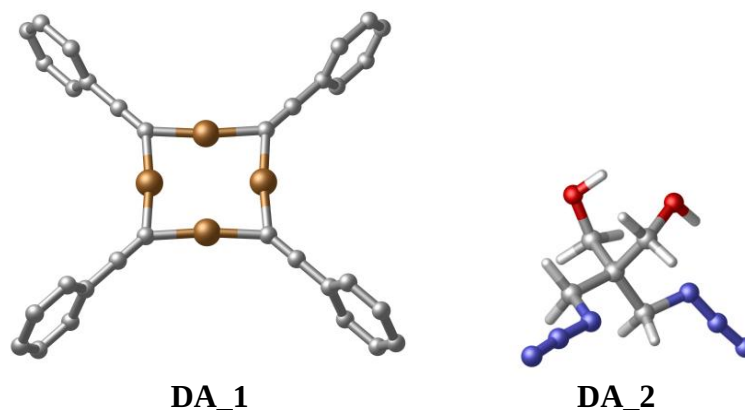


Figure 5.1 : 3D representations of structures **DA_1** and **DA_2**.

The reaction mechanism starts with the interaction of α -N to copper atom (**DA_3**) at a distance of 2.46 Å. This interaction is important in determining the regioselectivity. The partial negative charge of α -N (-0.41 and same for unreacted azide moiety in **DA_2**) enables a more efficient interaction with copper than the relatively neutral terminal nitrogen (-0.06 and same for unreacted azide moiety in **DA_2**) atom whereby the possibility of formation of 1,5-disubstituted triazol is hindered. The two phenyl groups are bended for diazide molecule to attack copper atom. Energetically, formation of this van der Waals molecule is endergonic. Subsequently, the terminal nitrogen makes bond with carbon atom in acetylide moiety in structure **DA_4** (Figure 5.2). While the Cu-N distance is decreased from 2.46 Å to 2.03 Å, C-N distance becomes 1.91 Å. This molecule is located as the highest point (24.2 kcal/mol) on the energy profile and thus it is the rate-determining step as in section 4.2.2 calculations on copper catalyzed 2-azido-1,1,1-trifluoroethane-ethynylbenzene cycloaddition system (25.2 kcal/mol).

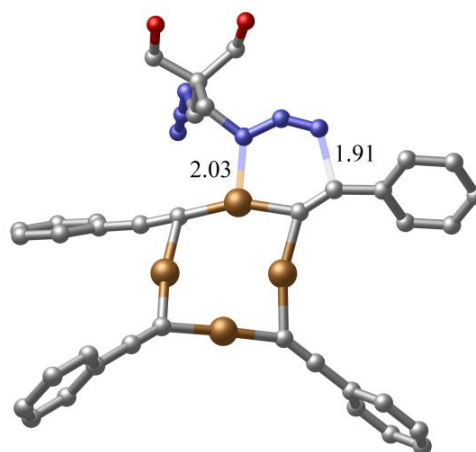


Figure 5.2 : 3D representation of structure **DA_4**.

After the first transition state, six-membered ring forms (Structure **DA_5**) which further turns into copper-triazolide very easily via a second transition state **DA_6** (Figure 5.3). In structure **DA_6**, N is detached from Cu (2.03 Å) and makes bond with C (2.35 Å) to produce the first triazole ring via a relatively small (3.1 kcal/mol) energy barrier.

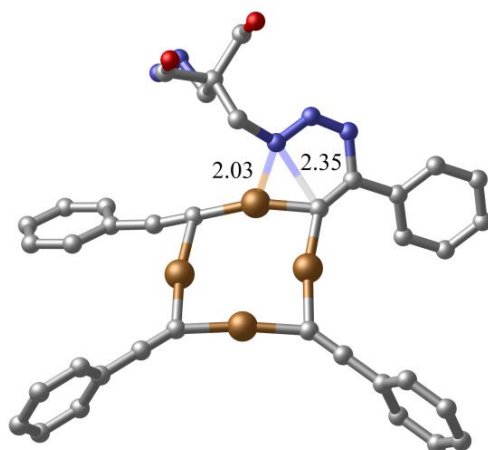


Figure 5.3 : 3D representation of structure **DA_6**.

In copper-triazolide **DA_7** structure, the entropically favored μ bonding between copper and carbon atoms dominate just as in structure **DA_2** and throughout the mechanism this type of bonding is not effective only in copper-acetylides but carried out in all structures. This step is extremely exergonic ($\Delta G=56.7$ kcal/mol). The cycloaddition reaction at this point have two possible paths: the mechanism may continue without protonation of C (**i** path) or the copper-triazolide **DA_7** might be detached from copper atoms by protonation of C as monotriazole azide which further reacts with another copper-acetylide to produce ditriazole (**ii** path) (Figure 5.4).

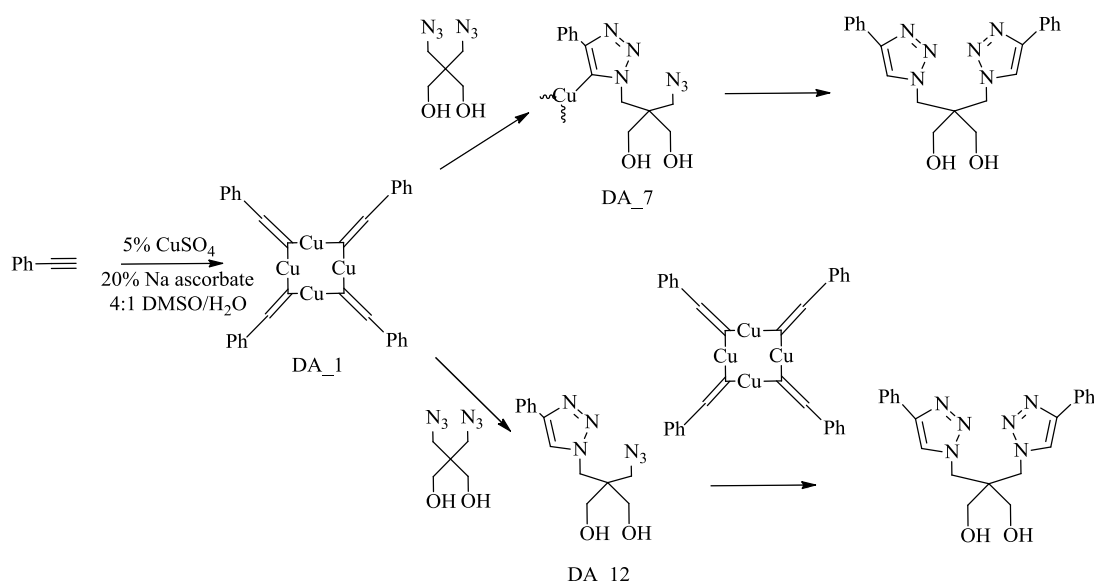


Figure 5.4 : The possible pathways for copper-catalyzed diazide-alkyne cycloaddition reaction mechanism.

In the first alternative, the unreacted azide moiety in **DA_7** will attack the other alkyne in close proximity to form the second triazole ring via transition state (**DA_8**) (Figure 5.5). In this transition state structure the triazole ring keeps unreacted N atoms in the second azide moiety close to the Cu-C-C plane, without encountering steric or geometric obstacles for the second attack to take place. In transition states of diazide-alkyne cycloaddition pathway (**DA_4**, **DA_6** and **DA_8**), almost all Cu-αN distances are the same (2.03 Å). A 14.9 kcal/mol of energy is required for the cyclization, which is 1.5 kcal/mol easier than the first triazole formation (**DA_3**→**DA_4**).

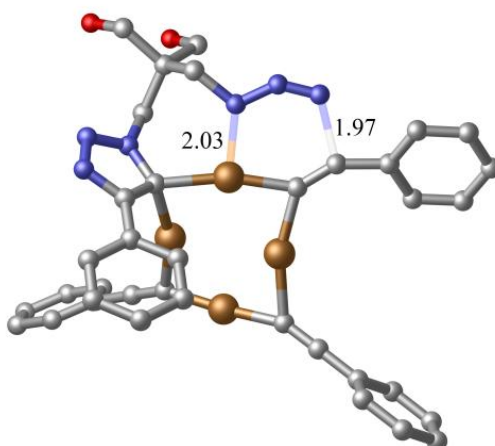


Figure 5.5 : 3D representation of structure **DA_8**.

The second ring formation continues with the detaching of α -N from the copper and bonding to carbon. In the end, the ditriazole structure is released from system by protonation of the carbon atoms (Figure 5.6).

In the second possible pathway (Figure 5.7), the copper-triazolide (**DA_7**) is protonated and the obtained structure involving unreacted azide (**DA_12**) further reacts with copper-acetylide (**DA_1**). Protonation is known to depend on the efficiency of the proton source. It is known that in some experimental conditions protonation can occur easily or it can hardly take place, e.g. in the absence of electrophiles in aprotic solvents [117]. In another study, the yield and the time of copper-catalyzed azide-alkyne cycloaddition could be improved in the presence of CH₃COOH which has been attributed to the ease of protonation. Thus, protonation step is important for the efficiency of this reaction. The mechanism starts with the same copper-acetylide (**DA_1**) and mono-triazole-azide molecule (**DA_12**). Although a van der Waals complex has been observed in the first pathway, no such molecule could be found before the first transition state (**DA_13**) which may be stemming from the steric effects. The relative energy of the first transition state is 24.8 kcal/mol, which is almost the same with that of **DA_4**. The remaining mechanism proceeds in an identical way in terms of geometries and relative energy values (Figure 4.8 and 4.9). According to experiments, monotriazole-azide structure (**DA_12**) is obtained as trace even when 1 to 10 amount of diazide over alkyne is reacted [66]. This result indicates that the protonation does not occur in structure **DA_7**. However; this conclusion might be altered by the efficiency of proton source [127]. Additionally, from thermodynamic viewpoint, structure **DA_16** is located at -34.0 kcal/mol, whereas **DA_11** is located at -68.3 kcal/mol on the energy profile.

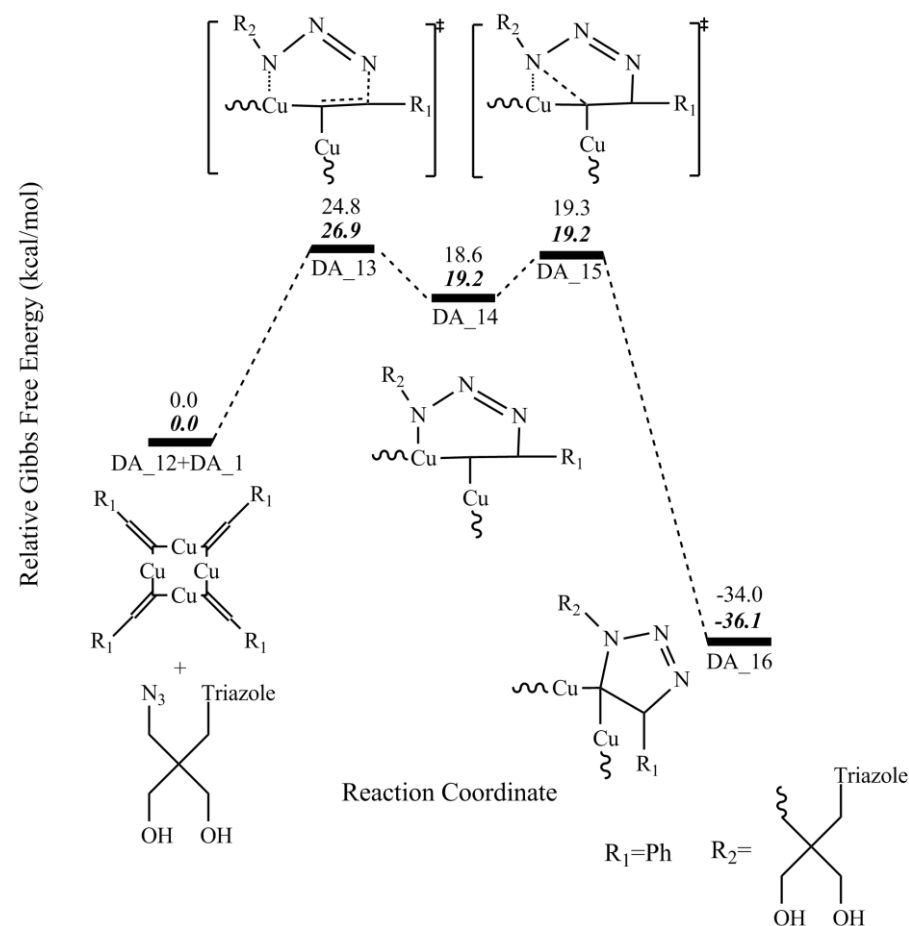


Figure 5.7 : The reaction mechanism of copper-catalyzed diazide-alkyne cycloaddition reaction for protonation of **DA_7** (Bold and italic values refer to solvent with DMSO) (Energy values are not to scale).

5.3 The Mechanism of Copper-catalyzed Azide-Dialkyne Cycloaddition Reaction

In the second part of this study, the reaction of 2,2-di(prop-2-yn-1-yl)propane-1,3-diol and (azidomethyl)benzene (**AD_18**) has been modeled. The modeled copper-catalyzed azide-dialkyne reaction has the same experimental conditions of diazide-alkyne but both mono- and di-triazole species are yielded as statistical mixtures contrary to diazide-alkyne reaction.

The reaction starts by the formation of van der Waals complex between **AD_18** and the copper acetylide complex. The copper-acetylide complex now will have difunctional alkyne groups. The structure, in which H-bondings dominate, has been located as the global minimum after performing conformer search (**AD_17**, Figure 5.8). The general azide-alkyne cycloaddition is followed for the reaction of first functional group, in accordance with the mechanism of copper-catalyzed azide-alkyne reaction (Figure 5.9) and a copper-triazole complex with one unreacted alkyne group is formed (**AD_23**).

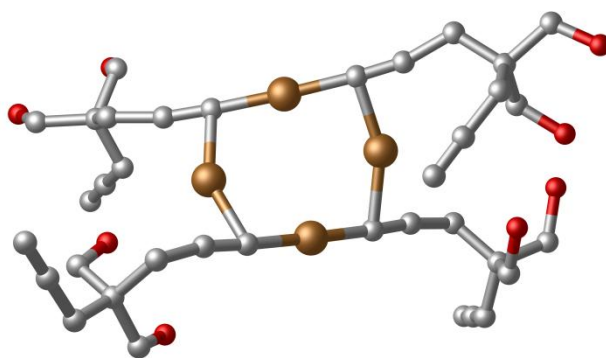


Figure 5.8 : 3D representation of structure **AD_17**.

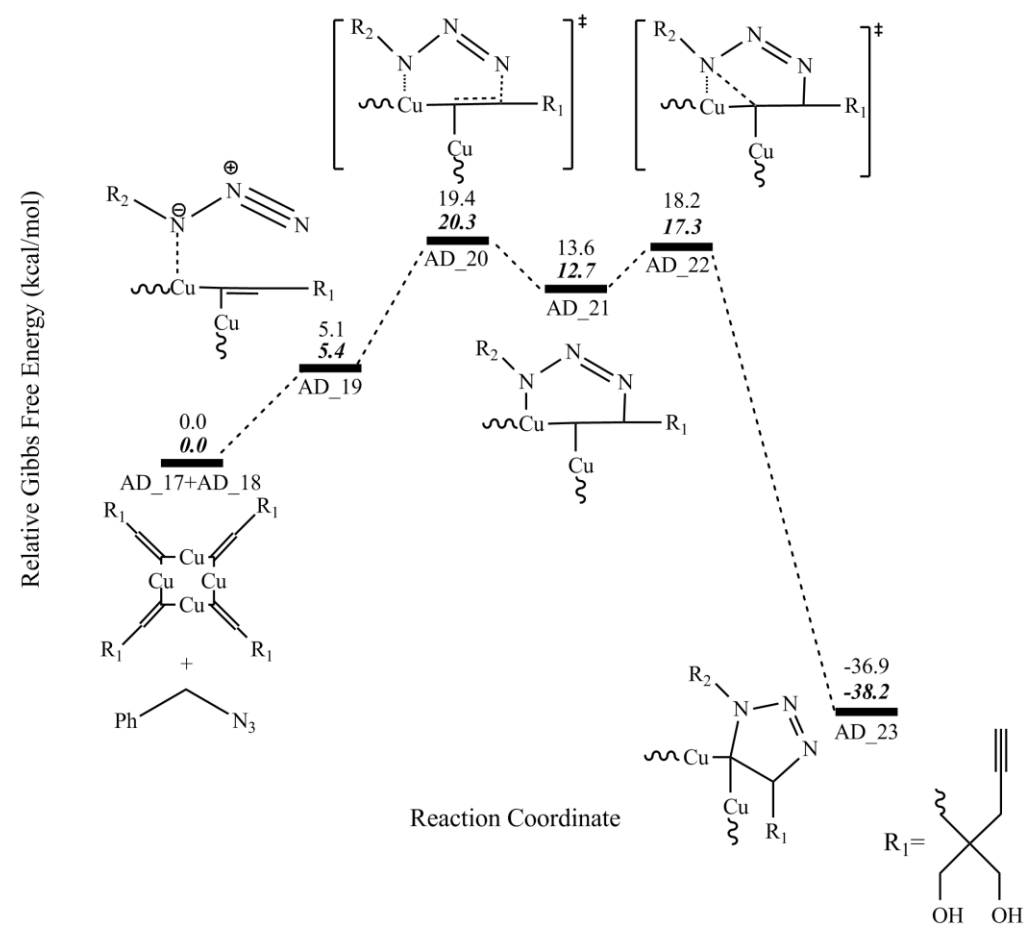


Figure 5.9 : The first stage of the reaction mechanism of copper-catalyzed azide-dialkyne cycloaddition reaction (R_2 =benzyl) (Bold and italic values refer to solvent with DMSO) (Energy values are not to scale).

The reaction can proceed via the attack of another azide molecule to one of the unreacted Cu-C≡C moieties in **AD_23**. However, modeling this possibility is excluded since it will resemble Figure 5.9 and this will lead to monotriazole.

After formation of **AD_23**, it may presumably undergo protonation to release the monotriazole structure (**AD_24**) and then the other alkyne moiety in **AD_24** (Figure 5.10) can attack empty copper site to form copper-acetylide **AD_25** (Figure 5.10). Once **AD_25** forms, there are four options depending on the attack site of azide, one of which leads to the bistriazole and the rest to monotriazole product. For the bistriazole formation, the reaction from **AD_25** follows the general azide-alkyne cycloaddition by the attack of azide to the triazole-substituted copper-acetylide. The highest point (**AD_26**) on the reaction coordinate is the cyclization step at 23.0 kcal/mol. From this path the bistriazole product can be obtained after further protonation.

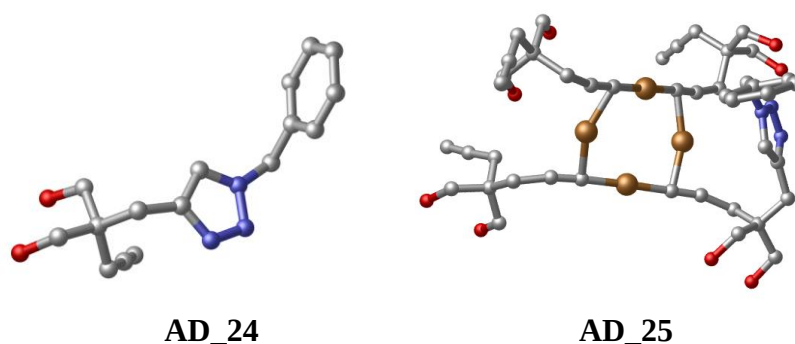


Figure 5.10 : 3D representation of structures **AD_24** and **AD_25**.

In the other three options, the azide bonds to the other copper sites of copper-acetylide (**AD_25**) which leads to transition states **AD_30**, **AD_31** and **AD_32** with relative energies of 21.5, 21.8 and 22.6 kcal/mol, respectively. Closeness of the energy barriers of monotriazole and bistriazole formations enables all four paths to be facile which can lead to both products. Additionally, after the formation of monotriazole-alkyne **AD_24**, the triazole ring can serve as a ligand for copper [58]. Hence, alkyne and triazole moieties in **AD_24** will compete for binding to copper atom.

Since the alkyne molecule contains hydroxyl groups, it has been observed that the interaction between lone pair electrons of the oxygen and the copper. In particular, in structure **AD_29** (Figure 5.11), according to NBO analysis, there is totally a 56.0

kcal/mol of stabilization interaction, this causes a distortion in copper-acetylide planarity. Recently, a tetranuclear copper triazole compound has been synthesized and spectroscopically observed as luminescent metal complex [129]

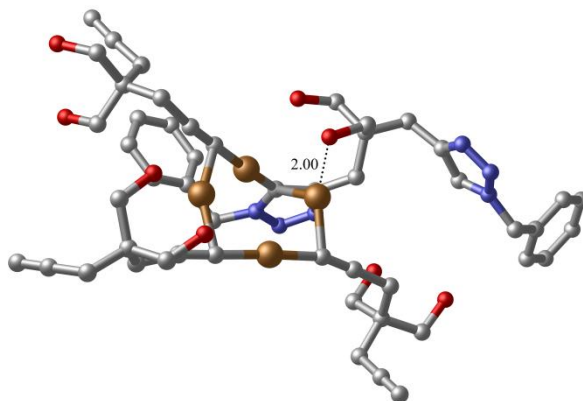


Figure 5.11 : 3D representation of structure **AD_29**.

Finally, the effect of the solvation has been taken into account using IEFPCM method with DMSO in accordance with experiments (Figure 5.12). There has been no significant change in energy values. Generally, there is a tendency to increase in energy values. Structure **DA_13** is the most increased one (4 kcal/mol) in DMSO.

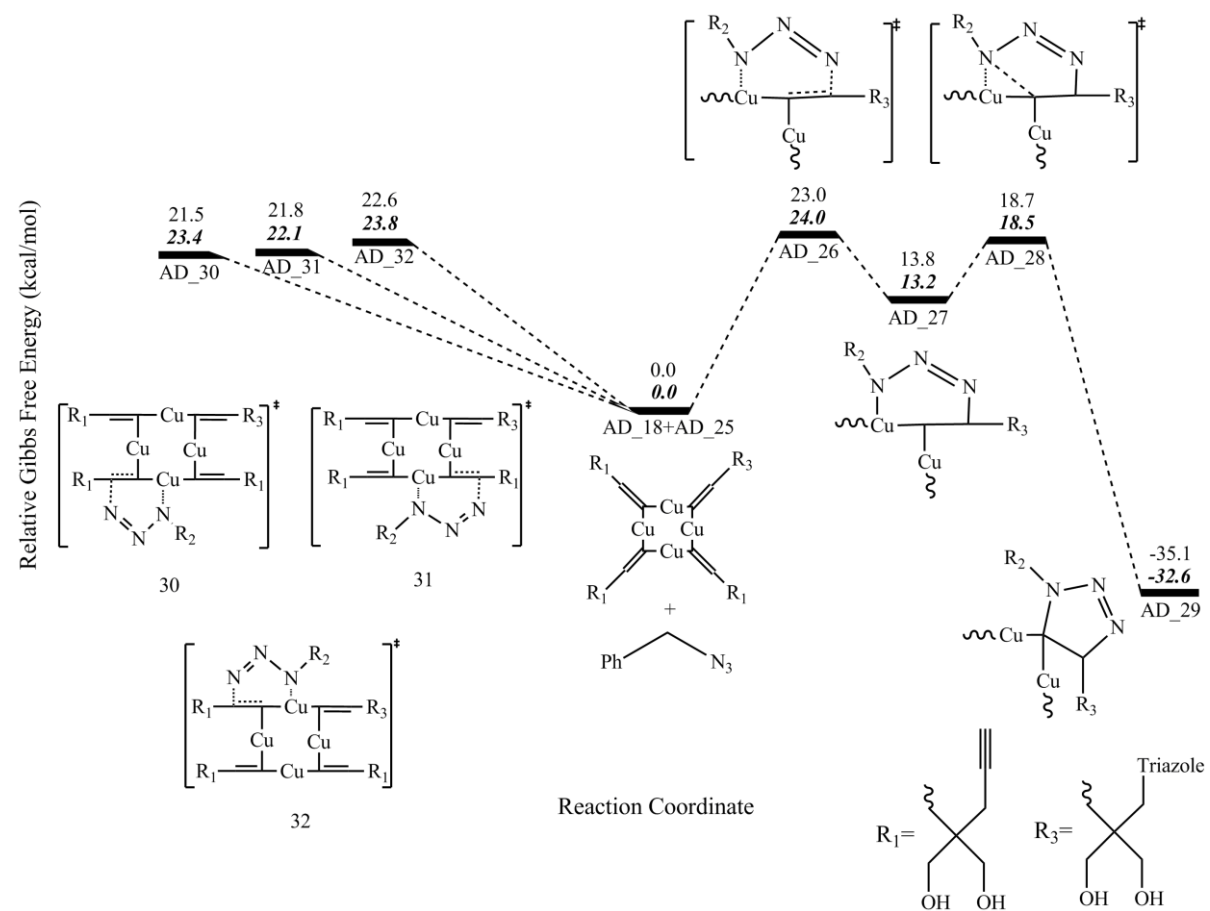


Figure 5.12 : The second stage of reaction mechanism of copper-catalyzed azide-dialkyne cycloaddition reaction (R_2 =benzyl) (Bold and italic values refer to solvent with DMSO) (Energy values are not scale).

6. CONCLUSION

In this thesis, two different copper catalyzed [3+2] cycloaddition reaction mechanisms have been investigated thoroughly with computational chemistry tools, by considering all experimental and hypothetical possibilities.

In the first part of the thesis, the reaction of two dioxepine molecules, namely 4,5-dihydro-2-methyl-1,3-dioxepine, with dimethyldiazomalonate (**DMDM**) in the presence of copper(II) acetylacetonate ($\text{Cu}(\text{acac})_2$) as catalyst, has been considered which yield mainly [3+2] cycloaddition and cyclopropane products. The reactions have been modeled with the DFT method at the B3LYP/6-31G* level of theory in order to elucidate the dynamics of catalytic [3+2] cycloaddition reaction mechanism and to explain the experimental product distribution by considering possible pathways and competing reactions.

Both cyclopropanation and [3+2] cycloaddition reactions start by the formation of copper-carbene, which involves the rate limiting N_2 extrusion step and the details of catalytic carbene generation have already been described in our earlier computational study. The interaction of the double bond in dioxepine molecules with copper-carbene at the onset of reaction is the main factor that affects product distribution.

The proposed mechanism for the [3+2] cycloaddition reaction accounts for the key experimental observations with 4,5-dihydro-2-methyl-1,3-dioxepine (**3a**) molecule. The formation of the experimental [3+2] cycloaddition product via stepwise path has shown to be more favorable relative to the concerted one for **3a**. The copper catalyst is responsible for the charge separation on the olefinic bond which enables the reaction mechanism to proceed via stepwise path rather than concerted one. The stepwise [3+2] cycloaddition reaction is more plausible relative to the cycloaddition via metallocyclobutane or cyclopropane intermediates in terms of free energy barriers. Thus, the formation of furan rather than the cyclopropane product, is supported both kinetically and thermodynamically for **3a**.

It is reported that under the same experimental conditions, (Z)-2-methyl-4,7-dihydro-1,3-dioxepine (**4a**) gave mainly cyclopropane product. Our calculations based on the

hypothetical [3+2] cycloaddition and cyclopropanation of **4a** have shown that formation of cyclopropane product is favored over furan derivative. Possible cyclopropanation mechanisms of **4a** have been modeled by considering both the chair and the twist-boat conformers of the dioxepine ring due to their comparable energies. Although the twist-boat conformer could not distinguish between the 3 and 4-centered pathways, the barriers for the two paths have differed significantly from each other on behalf of 4-centered pathway with chair conformation of **4a**.

In the second part, the mechanism of CuAAC reaction and the copper acetylides has been investigated with quantum mechanical methods, namely B3LYP/6-311+G(d,p). The structure of copper-acetylides is the most ambiguous point in CuAAC reactions since they cannot be isolated. Therefore, initially, a detailed examination has carried out to unveil the structure with the lowest energy. All calculations and literature findings indicate four-copper-membered structures, namely **M4A** and **M4B**. Applying the earlier proposed mechanism to a model then to an experimentally worked system with tetracopper acetylide have mechanistically revealed similar results. The copper catalyst transforms a concerted uncatalyzed reaction to a stepwise process, thereby lowers the activation barrier. The negatively charged site of the azide and the positively charged site of the copper enable a favorable complexation and bring the azide and the alkyne to a suitable geometry for the attack to take place. In a recent study, the activation energy for the uncatalyzed dipolar cycloaddition has been found to be correlated with the energy to distort the reactants into transition geometry [59]. Hence, the copper catalyst is helping the substrates to overcome this difficulty by bringing them closer with the help of electronic effects. The devised mechanism is generally consistent with mechanisms in the literature.

For 1,5-triazole to form, the terminal nitrogen should be complexed with the copper of the acetylides. However, this is electronically not preferred and the concerted reaction requires higher activation barrier than 1,4-triazole formation, thus, leads to a regioselective synthesis, as shown by the calculations.

Additionally, protonation and removal of triazole ring from copper-triazolide have also been modeled at B3LYP/6-31+g(d) for Cu and N and B3LYP/6-31g(d) for the rest of atoms. A higher barrier than the general CuAAC was found for protonation. Protonation is one of the most decisive points in the CuAAC reactions, particularly in the diazide-dialkyne reactions part. If the protonation is difficult to occur in a

system, copper-triazolide species is not reluctant to separate as triazole product and it may become rate-limiting step depending on the conditions. In some cases, the reaction times can be reduced substantially, by facilitating protonation step which depends on the solvent, substituents on azide and alkyne, and some auxiliary additives such as carboxylic acid.

Solvents calculations in acetonitrile and water have shown slightly higher barriers for both the catalyzed and the uncatalyzed reactions, however, the acceleration of reaction as compared to that of uncatalyzed is almost the same in both solvents, consistent with the reaction taking place in a variety of solvents.

The kinetic studies being secondary with respect to copper indicates the presence of multinuclear species and the dynamic nature of the reaction rather than the strict nature of acetylide species containing two coppers. The barriers being facile with both tetra and dicopper acetylide species may enable the reaction to start with 4-centered acetylide species and proceed with two-centered species when the alkyne concentration decreases.

Subsequently, in the final step, the mechanisms of diazide-dialkyne CuAAC reactions have been studied. While diazide-alkyne reaction gives a ditriazole as a major product, azide-dialkyne reaction gives a monotriazole-ditriazole mixture. In the reaction of diazide-alkyne, the easeness of second triazole formation before protonation, as compared to that of monotriazole steps is the main driving force for ditriazole formation. In the dialkyne-azide case, both monotriazole and ditriazole formations have almost similar barriers. Protonation of the copper-triazolide ring in azide-dialkyne reaction is necessary to ensure deprotonation of the other alkyne moiety. The ligand functionality of monotriazole species for copper atom hinders partially the attachment of alkyne moiety to copper atom to produce copper-acetylide formation.

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