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General Introduction

Click chemistry, as introduced by Kolb and Sharpless in 2001¹, relates mainly to the Cu(I) catalyzed [3+2] cycloaddition reaction of azides with alkynes. This copper catalyzed cycloaddition reaction is highly useful for attaching fluorescent or other markers to a wide variety of biomolecules. Although azides are often unstable at elevated temperatures, they are stable at physiological conditions, have no intrinsic toxicity and have extraordinary chemical selectivity. Proteins and glycans have already been labeled with azides in laboratory mice using enzyme inhibitors and sugar azides.

Azides have cumulative double bonds and they are only a small section of the cumulenes encountered in organic chemistry. Cumulenes are often not stable at room temperature and they are isolated as their cyclic dimers, formed in a click reaction. In this case a [2+2] cycloaddition reaction occurs, and often no catalyst is required. Some of the more exotic cumulenes are matrix isolated at low temperatures. For example, alkyliminopropadienones, $\text{RN}=\text{C}=\text{C}=\text{C}=\text{O}$, the mono imides of carbon suboxide, are unstable. However, the neopentyl-, mesityl- and o-t-butylphenyl derivatives can be isolated at room temperature and their nucleophilic reactions provide a wide variety of heterocyclic compounds².

Several of the early Nobel prize winners were involved in the click reactions of cumulenes. For example, the [2+2] cycloaddition reaction of ketenes and imines to give β -lactams is often referred to as the Staudinger reaction. Another Nobel Laureate, Sheehan, has used this reaction to synthesize penicillin antibiotics. The reaction of iminophosphoranes with other cumulenes is called the aza-Wittig reaction. Also, Wittig received the Nobel Prize for his pioneering work in phosphorous chemistry. The [3+2] cycloaddition reactions, which include the cycloaddition of azides to alkynes named by Sharpless, also a Nobel Laureate, as a click reaction, are sometimes referred to as Huisgen reactions. Rolf Huisgen has extensively investigated the [3+2] dipolar cycloaddition reactions³. The [4+2] cycloaddition reactions are called Diels-Alder reactions, again named after two early Nobel Laureates.

The best example of a click polymerization reaction is the polyaddition reaction of diisocyanates with diols or polyols to produce polyurethanes. This reaction was discovered

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by Otto Bayer, at the IG Farben Laboratories (now Bayer AG) in 1937, and today the world wide consumption of polyurethanes exceeds 10 million tons per annum. In the formation of polyurethanes no solvents are required, the yields are quantitative and most reactions are conducted at room temperature. An exception is the RIM (reaction injection molding) of automotive bumpers which is conducted at elevated temperatures to increase the production rate. When this polymerization is conducted continuously in an extruder, the finished polymers are extruded, chopped and collected in drums. An example is the production of thermoplastic segmented polyurethane elastomers, appropriately sold by Dow under the tradename 'Pellethane'⁴. In the reaction of thermoset reaction polymers spray technology is also applied. For example, flexible polyurethane foams are continuously produced in buns and semirigid and rigid insulation foams are directly sprayed onto the substrate. Dendritic polymers are also constructed by reacting 1,3,5-benzene triisocyanate with amines⁵.

Copolymerization reactions of cumulenes are also of some significance. For example, copolymerization of carbon monoxide with alkenes affords polyketones, which are biodegradable and they also could undergo subsequent crosslinking reactions on the carbonyl group. When carbon dioxide is copolymerized with alkenes, polyesters are obtained. The polyaddition reactions of diketenes with diols to produce polyesters is not used, because of the tendency of ketenes to undergo dimerization reactions. Also, sulfur dioxide can be copolymerized with alkenes to produce polysulfones. Some of the cumulenes undergo homo-polymerization reactions. The homo-polymers derived from isocyanates and carbodiimides are of no commercial value because the homopolymers 'unzip' on heating. Intractable thermoset polymers are obtained from carbon suboxide or carbon disulfide.

More often the click reaction is used in the modification of biopolymers. An example is sugar-derived imaging in live animals. Glycans in live zebrafish embryos light up when the embryos are fed azide-derived sugars and are subsequently treated with difluorinated cyclooctyne derived probes⁶. Elastin-like hybrid polymers, based on the reaction of azide-terminated poly (ethylene oxide) (PEO) and alkyne functionalized peptides, are also developed. These polymers are intended to grow new vocal cords⁷.

The cyclodimerization reaction of cumulenes is their most common click reaction, especially when the monomers are not stable at room temperature. Some of the cyclodimers serve as a ready source of the monomers, which are generated *in situ* and are trapped with suitable reagents. Sometimes, the retro reactions provide new cumulenes. In this book the latter reactions are referred to as 'exchange reactions'.

Cyclodimerization reactions can occur across either one of the cumulative double bonds giving rise to the formation of head-to-head or head-to-tail cyclodimers. The stable head-to-tail cyclodimers of ketenes and the head-to-head cyclodimers of isocyanates are good examples and only one type of cyclodimer is formed. In contrast, allenes often provide mixtures of cyclodimers. A 'super-click reaction' is observed in the cyclodimerization of bis-allenes, which occurs at room temperature in the solid state upon irradiation to give the cyclodimers in quantitative yields⁸.

The first example of a cumulene click reaction, the cyclodimerization of phenyl isocyanate, was reported by Hofmann in 1860⁹. In later years numerous cycloaddition reactions of cumulenes with a wide variety of double or triple bonded substrates were observed¹⁰.

In addition to the cycloaddition reactions of cumulenes their insertion reactions into numerous single bonds also often proceed at room temperature in high yields¹⁰. In fact,

even some nucleophilic reactions of cumulenes can be considered to involve click reactions, i.e. they occur at room temperature, sometimes without a solvent to produce linear reaction products in quantitative yields. Perhaps the most important click reaction in chemistry is the neutralization of an acid by a base which can be conducted at room temperature, often in water and the yields are always quantitative.

The most general definition of click chemistry is a reaction which proceeds at room temperature, often without a solvent or catalyst, to give the reaction product in close to quantitative yields. The yields in the reactions in this book are by no means optimized, but they often approach quantitative. As an industrial chemist I am well aware that yields can be dramatically increased with modest process development efforts. Sometimes, a change of reaction temperature can have a dramatic effect, as demonstrated by Wilson and Fu who obtained a < 2 % yield of β -lactones in their [2+2] cycloaddition reaction of ketenes with aldehydes at room temperature, while at $-78\text{ }^{\circ}\text{C}$ a 92 % yield of the cycloadduct is obtained¹¹.

The yields shown in the selected examples in this book are often the higher yields reported by the authors. More comprehensive lists can be found in my relatively recent books on isocyanates¹² and carbodiimides¹³. Of course, comprehensive lists of cycloadducts of heterocumulenes are also found in my 1967 book¹⁰.

Huisgen's introduction of the dipolar [3+2] cycloaddition reaction has provided an enormous variety of synthetically useful click reactions. The example quoted by Kolb and Sharpless¹ is 'only the tip of the iceberg'. Over 1000 literature references on this reaction were reported in recent years. I had summarized the cycloaddition reactions of heterocumulenes in 1967¹⁰, but in the meantime many new cumulenes have emerged and the cycloaddition reactions of carbon cumulenes, such as allenes, butatrienes and higher cumulenes, are also well investigated.

The cycloaddition reactions of cumulenes generally produce three- to six-membered ring compounds, which often cannot be obtained in a one-step reaction. When the cumulene or the substrate contain metal to carbon bonds, metallacycles are readily produced. Organometallic compounds are readily obtained in the insertion reactions of the cumulenes. In the latter reactions, linear compounds are obtained. Click chemistry therefore can provide not only a vast number of cyclic compounds but also numerous linear compounds and even linear and crosslinked polymers which have commercial significance.

Often the initially formed bonds at low temperature are not the ones that are isolated at room temperature. Also the electronic configurations play a part in product formation. For example, in the [2+2] cycloaddition reaction involving two carbodiimides the more nucleophilic carbodiimide attacks the more electrophilic carbodiimide giving rise to the formation of only one reaction product. The latter reactions proceed stepwise, while sometimes concerted reactions are observed. Sterical hindrance also plays an important role in product formation. We have utilized *N*-methyl-*N'*-*t*-butylcarbodiimide as a probe in determining the structure of the derived cycloadducts, because the reaction always proceeds via addition across the C=N bond with the methyl substituent. For example, in the [2+2] cycloaddition reaction with benzoyl isocyanate the reaction proceeds across the C=O bond of the isocyanate, because *t*-butyl isocyanate is the only product generated in the retro reaction¹⁴.

By definition, cumulenes are compounds with double bonds adjacent to each other. The parent compound of carbon cumulenes is allene, $\text{CH}_2=\text{C}=\text{CH}_2$, in which the center as well

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as the terminal atoms are carbon. Extension of the double bonded system produces the higher cumulenes and often the number of double bonds are used to identify the higher cumulenes. When one or more of the atoms in the cumulative system are hetero atoms, such as oxygen, nitrogen, sulfur or selenium, they are known as heterocumulenes. The carbon containing heterocumulenes are sometimes referred to as heteroallenes.

I have organized the cumulenes according to the number of carbon atoms in the cumulative system. In Chapter 2 I have treated the cumulenes with one carbon atom in the beginning of the cumulative system. With the exception of the 1-aza-2-azoniaallene salts, the compounds are sulfur derivatives. The thiocarbonyl *S*-sulfides are excellent 1,3-dipoles, which participate in numerous [3+2] cycloaddition reactions. Huisgen has reviewed their chemistry in 1997¹⁵. In Chapter 3 the cumulenes with a center carbon atom are treated, which include the carbon oxides, carbon sulfides and carbon nitrides (isocyanates, isothiocyanates and carbodiimides). In this chapter the chemistry of carbon dioxide is of considerable interest, because the sequestering of carbon dioxide is a major problem in coping with global warming. The chemistry of isocyanates relates to polyurethanes, which are major industrial polymers, and carbodiimides play an important role in proteomics, the building blocks of life. Center carbon phosphoallenes and diarsaallenes are also treated in Chapter 3. The 1,2-dicarbon cumulenes are described in Chapter 4, which encompass the ketenes, thioketenes, ketenimines, 1-silaallenes, 1-phosphaallenes, as well as some metal allenes. In Chapter 5 the 1,3-dicarbon cumulenes, which are not too well known, are treated, and in Chapter 6 the 'all-carbon' cumulenes are summarized. This chapter encompasses the allenes and the higher carbon cumulenes. Higher carbon cumulenes have been detected in interstellar space by microwave spectroscopy, and in recent years many of the higher carbon monoxides, C₂O to C₆O and carbon dioxides, carbon monosulfides and carbon disulfides, have been matrix isolated at low temperatures. The carbon monoxides and carbon monosulfides have a linear carbene like structure. Finally in Chapter 7 the non-carbon cumulenes are described. This latter chapter includes the azides.

Cationic cumulenes are also known, and especially the azaallenium salts are known for their 1,3-dipolar character. These cationic cumulene salts undergo numerous [3+2] cycloaddition reactions with suitable dipolarophiles to give five-membered ring heterocycles, often in quantitative yields.

The cycloaddition reactions of all of the cumulenes under discussion are of considerable importance because in almost all cases only one compound is isolated in high yield. This renders these reactions as the most useful method to synthesize cyclic or heterocyclic compounds, which are often otherwise difficult to synthesize.

The first book on the reactions of carbon cumulenes, treating the cycloaddition reactions of ketenes in depth, was written by Staudinger in 1912¹⁶. Staudinger already realized that cycloaddition reactions of ketenes are common, and often ketenes were only isolated as cyclodimers. The cyclodimers of isocyanates became prominent in the development of polyurethanes in the IG Farben Laboratory in Leverkusen, Germany in the early 1930s¹⁷, and the cyclotrimerization of diisocyanates led to the development of polyisocyanurate foams, with thermal stability superior to rigid polyurethane foams in the 1960s. Today, polyisocyanurate foams are used in the insulation of the fuel tank of the space shuttle. Also, carbodiimide derived cellular plastics with improved thermal stability are of interest¹⁸. In recent years, cumulene derived polymers became of interest as one-dimensional molecular wires.

The chemical reactivity of the cumulenes under discussion ranges from highly reactive species to almost inert compounds. While some cumulenes can only be generated in a matrix at low temperatures, others are indefinitely stable at room temperature. For example, sulfines and sulfenes are only generated *in situ*, but some cumulenes with bulky substituents are sometimes isolated at room temperature: for example, :C=C=S was detected in interstellar space by microwave spectroscopy, and its spectrum was later verified by matrix isolation spectroscopy. In contrast, some cumulenes, such as carbon dioxide and carbon disulfide, are often used as solvents in organic reactions or in the extraction of natural products. The reactivity of some center carbon heterocumulenes in nucleophilic reactions is as follows: isocyanates > ketenes > carbodiimides > isothiocyanates. However these reactivities do not relate to the reactivities in cycloaddition reactions. Often reactive cumulenes are isolated as their cyclodimers. Aromatic diisocyanates are more reactive than aliphatic diisocyanates in nucleophilic as well as cycloaddition reactions.

Substituents attached to the cumulative system can influence their reactivity. The effect of the substituents can be both steric or electronic. For example, steric hindrance is often applied to stabilize a cumulene system, which normally cannot be isolated. For example, 2,4,6-trimethyl-phenyl groups are used in phosphorus cumulenes for this purpose, and 2,4,6-trichlorophenyl groups are used to stabilize 1,3-diaza-2-azaallenium cations. Also, ortho methyl groups in phenyl substituents are often sufficient to prevent cycloaddition reactions. An example is the selective dimerization of 2,4-tolylene diisocyanate involving the isocyanate group para to the methyl group. In methyl-*t*-butylcarbodiimide the [2+2] cycloaddition reactions proceed across the less hindered C=N bond.

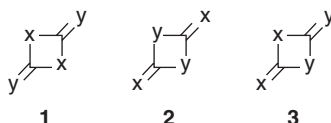
Also, substituents attached to phenyl groups in aromatic cumulenes influence their reactivity. For example in isocyanates electron withdrawing groups increase the electrophilicity of the center carbon atom, whereas electron donating groups reduce the electrophilicity. The reactivity of isocyanates in cycloaddition reactions is greatly enhanced in carbonyl-, thiocarbonyl-, imidoyl- and sulfonyl-isocyanates. While the sulfonyl isocyanates undergo [2+2] cycloaddition reactions readily, they do not undergo cyclodi- or trimerization reactions. The reactivity of ketenes in cycloaddition reactions is as follows: diphenylketene > dimethylketene > butylethylketene > ketene¹⁹.

The mechanism of the cycloaddition reactions of cumulenes involve concerted one-step processes as well as two-step processes, and both types of mechanisms are encountered. It seems that concerted processes are more the exception, and ionic linear 1:1 intermediates are sometimes trapped in cycloaddition reactions. The sometimes encountered [2+2+2] six-membered ring cycloadducts exemplify the stepwise reactions.

The cycloaddition reactions are subdivided into di-, tri- and oligomerization reactions, [2+1]-, [2+2]-, [3+2]- and [4+2] cycloaddition reactions and other cycloaddition reactions. The insertion reactions into single bonds are also discussed. The cyclodimerization or cyclotrimerization reactions are special examples of the [2+2] and the [2+2+2] cycloaddition reactions, respectively. The cumulenes vary in their tendency to undergo these reactions. The highly reactive species, such as sulfines, sulfenes, thioketenes, carbon suboxide and some ketenes, are not stable in their monomeric form. Other cumulenes have an intermediate reactivity, i.e. they can be obtained in the monomeric state at room temperature and only heat or added catalysts cause di- or trimerization reactions. In this group, with decreasing order of reactivity, are allenes, phosphorus cumulenes, isocyanates, carbodiimides and isothiocyanates.

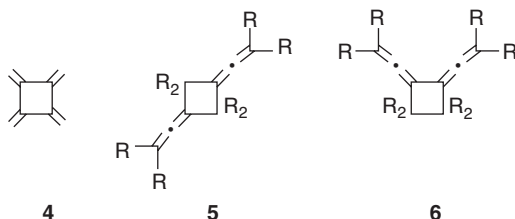
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In the cumulative systems, $X=C=Y$ ($X = CR_2, NR$; $Y = O, S, NR$), in $RP=C=X$ ($X = O, S, NR$) and in $R_3P=C=C=X$ ($X = O, NR$) three types of dimeric species are visualized. When the cycloaddition reaction proceeds across the $C=X$ double bond the cyclodimer **1** is formed. When the reaction proceeds across the $C=Y$ bonds the cyclodimer **2** is obtained and when the reaction proceeds across both bonds the asymmetric cyclodimer **3** is isolated.



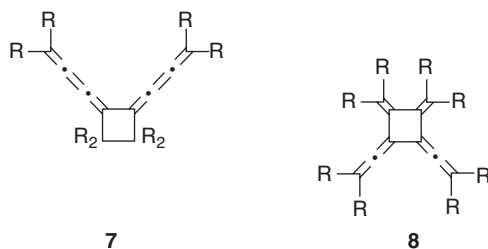
The cyclodimers **1** and **2** have an axis of symmetry, because dissociation in both directions affords the same products. Cyclodimer **3** has no axis of symmetry and cleavage in both possible directions affords different products. All three types of cyclodimers are encountered in the cumulenes $X=C=Y$ and the asymmetric dimers often undergo thermolysis contrary to their mode of formation. A typical example is cyclodimer **3** derived from dimethylketene, which affords tetramethylallene and carbon dioxide on thermolysis.

In the cycloaddition reaction of higher cumulenes different types of cyclodimers are encountered. In [3] cumulenes the cycloaddition can occur across the center bonds to form [4] radialenes **4** or across their end groups to give cyclodimers **5** and **6**.



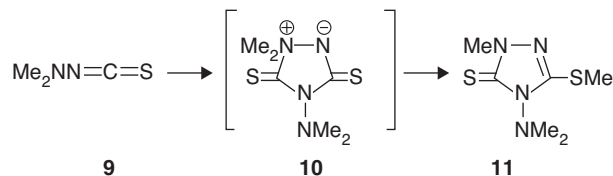
Radialenes are also obtained from [5] cumulenes.

Pentatetraenes dimerize across their end double bonds to form **7** or one of the center double bonds to give **8**.

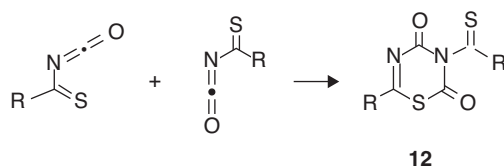


As a general rule ketenes undergo non-catalyzed [2+2] cycloaddition reactions across their $C=C$ bonds, with the exception of ketene itself. In contrast, disubstituted thioketenes undergo cyclodimerization across their $C=S$ bonds. Mono substituted thioketenes undergo dimerization via a [3+2] cycloaddition reaction, also involving the $C=S$ bonds.

N-Isothiocyanatodimethylamine **9** dimerizes at room temperature in less than one minute via a [3+2] cycloaddition to give **10**, which rearranges in solution to form **11**²⁰.

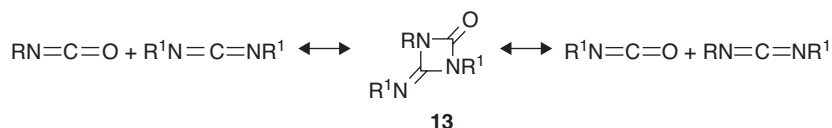


Another type of dimerization is observed in heterocumulenes, having the cumulative system attached to a carbonyl-, thiocarbonyl- or an imidoyl-group. Although these heterocumulenes can dimerize via a [2+2] cycloaddition sequence, more often a Diels–Alder-like [4+2] cycloaddition reaction occurs giving rise to the formation of six-membered ring heterocyclic dimers. Often these heterocumulenes are only generated *in situ* because they undergo rapid dimerization at room temperature. An example is the dimerization of thioacyl isocyanates in which the heterocumulene reacts as diene and dienophile to give the cyclodimer **12**²¹.



Thermal dissociation of the cyclodimers often generates the reactive monomers.

Dimeric intermediates are also postulated as intermediates in the exchange reaction of similar and different cumulenes. In these reactions thermal equilibria are established via [2+2] cycloaddition sequences. For example, in the heating of an isocyanate with a differently substituted carbodiimide a four-membered ring intermediate **13** is generated, which can either regenerate the starting materials or form a new set of heterocumulenes. When one of the new products is constantly removed from the reaction mixture (for example, the lowest boiling $\text{R}^1\text{N}=\text{C}=\text{O}$) the reaction produces the new set of heterocumulenes exclusively²².

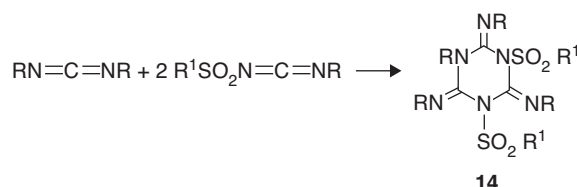


Upon addition of a second equivalent of $\text{RN}=\text{C}=\text{O}$ the sequence can be repeated, and the final product is $\text{RN}=\text{C}=\text{NR}$. The conversion of two equivalents of isocyanate into carbodiimide and carbon dioxide also involves an asymmetric isocyanate dimer as an intermediate.

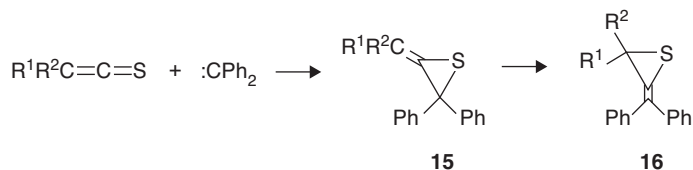
The cyclotrimerization of carbon cumulenes is usually initiated by heat or catalysis. Especially, the use of a catalyst assures that trimerization can be accomplished in quantitative yields. The base catalyzed cyclotrimerization reaction seems to be limited to ketenes, isocyanates, isothiocyanates and carbodiimides. In the trialkylphosphine catalyzed trimerization of methyl isocyanate an asymmetric trimer is obtained.

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Interesting is the participation of sulfonyl isocyanates and sulfonyl carbodiimides in mixed trimerization reactions although these monomers do not undergo cyclotrimerization reactions themselves. For example, dicyclohexylcarbodiimide reacts with two equivalents of *N*-*p*-toluenesulfonyl-*N'*-cyclohexylcarbodiimide to give the six membered ring [2+2+2] cycloadduct **14** in 93 % yield²³.

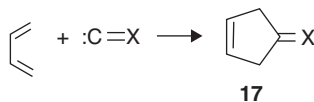


In cycloaddition reactions of carbon cumulenes with suitable substrates, [2+1], [2+2], [3+2] and [4+2] cycloaddition reactions giving rise to the formation of cyclic compounds are observed. In general, [2+1] cycloaddition reactions afford three-membered ring compounds with an attached double bond, and sometimes the initially formed cycloadducts rearrange to form an isomeric three-membered ring cycloadduct. An example is the addition of diphenylcarbene to dialkylthioketenes where the initially formed cycloadduct **15** on photolysis produces the isomer **16**, with bulky substituents on the three-membered ring²⁴.

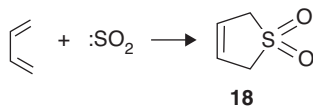


The carbenes, including carbon monoxide and isocyanides, readily participate in these cycloaddition reactions and because of their lone pair of electrons they can be considered to be pseudocumulenes.

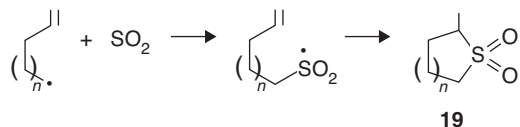
Also, [4+1] cycloadditions of carbon monoxide or isocyanides to 1,3-dienes are observed to afford five-membered ring cycloadducts **17**, often in high yields.



A similar reaction, resulting in the formation of five-membered ring sulfur heterocycles **18**, is the chelotropic addition of sulfur dioxide to 1,3-dienes.



The lone pair of electrons on sulfur dioxide can also participate in free radical annulation reactions with formation of sulfolanes **19**.



Carbon cumulenes undergo [2+2] cycloaddition reaction with numerous double or triple bonded substrates to give four-membered ring cycloadducts. Examples of cycloaddition to $\text{C}\equiv\text{C}$, $\text{C}=\text{C}$, $\text{C}=\text{O}$, $\text{C}=\text{N}$, $\text{C}=\text{S}$, $\text{N}=\text{O}$, $\text{N}=\text{N}$, $\text{N}=\text{S}$, $\text{S}=\text{O}$, $\text{P}=\text{C}$, $\text{P}=\text{O}$, $\text{P}=\text{N}$ and $\text{P}=\text{S}$ bonds are known. When the two adjacent double bonds in the cumulenes are different, cycloaddition across either one of the double bonds occurs, and sometimes addition across both bonds is observed. However, more often the cycloaddition reactions follow only one pathway. As a general rule, in ketenes the non-catalyzed cycloaddition occurs preferentially across the $\text{C}=\text{C}$ bond, whereas catalyzed cycloaddition reactions proceed across the $\text{C}=\text{O}$ bond. In thioketenes, isothiocyanates and sulfenes addition mainly occurs across the $\text{C}=\text{S}$ bond. In isocyanates addition across the $\text{C}=\text{N}$ bond is preferred.

The cycloaddition to isolated $\text{C}=\text{C}$ bonds is generally slow, and only highly reactive species, such as sulfonyl isocyanates, react well. The cycloaddition to activated olefins, such as allenes, cyclopentadiene, styrene etc., occurs more readily and many sulfonyl isocyanates and ketenes react at room temperature. The less reactive olefins, such as ethylene, react in the presence of nickel (0) compounds to give five-membered ring metallacycles. Substitution of the olefins by amino or alkoxy groups increases their reactivity in cycloaddition reactions. The approximate order of reactivity is: vinyl ethers < enamines < ketene O,O-acetals < ketene *N,N*-acetals < tetraalkoxyethylene or tetraaminoethylene.

In [2+2] cycloaddition reactions of carbon cumulenes, often only one four-membered ring compound is obtained. This reaction is of considerable importance in the synthesis of β -lactams from ketenes and $\text{C}=\text{N}$ double bond containing substrates. The β -lactam structure is present in a variety of antibiotics. Also, β -thiolactams are obtained from thioketenes and imines.

The obtained four-membered ring cycloadducts sometimes rearrange to more stable linear products. When the substrate has β -hydrogen atoms attached to the cumulative system, rearrangement to the linear product is the preferred mode of reaction. Also, fragmentation of the initially formed cycloadduct is sometimes observed.

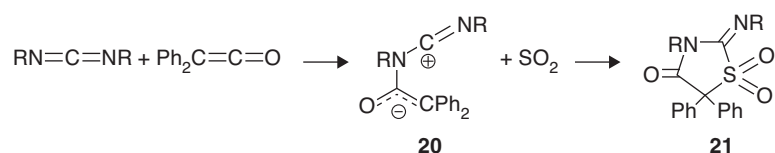
Compounds containing phosphorous double bonds are special cases, because the reaction with heterocumulenes across $\text{C}=\text{O}$ or $\text{C}=\text{S}$ bonds affords phosphorous oxides or sulfides with generation of a new double bond. These reactions are generally referred to as Staudinger or Wittig reactions. A well known example is the aza-Wittig reaction involving iminophosphoranes and isocyanates. A concerted four-centered transition state is postulated in order to explain the retention of configuration observed in these reactions. The $\text{P}=\text{N}$ bonds in heterocyclic compounds often undergo [2+2] cycloaddition reactions with heterocumulenes.

The cumulative double bonds in cumulenes can also participate in [2+2] cycloaddition reactions with the same or another cumulene to give rise to the formation of four-membered ring cycloadducts.

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The general nature of these reactions was first recognized by Staudinger and his coworkers in the reaction of ketenes with olefins. Huisgen and his coworkers²⁵ demonstrated that the cycloaddition reaction of diphenylketene with vinyl ethers is stereospecific, indicating a concerted one-step mechanism. However, more often the [2+2] cycloaddition reactions proceed in a stepwise fashion. In recent examples it was demonstrated that the initial reaction of ketenes with several substrates produces adducts which are different from the isolated ones (see Chapter 4, Section 4.1.4.2)²⁶. Also switter ionic intermediates are detected by low temperature spectroscopy. For example, Machiguchi and coworkers²⁷ have detected the formation of 1,4-switter ionic species as intermediates in the reaction of bis(trifluoromethyl)ketene with ethyl vinyl ether.

Also in the reaction of a carbodiimide with diphenylketene in liquid sulfur dioxide the [2+2+1] cycloadduct **21** is obtained by trapping the linear adduct **20**²⁸.



The linear ionic intermediate can also be intercepted with either one of the reagents, for example, in the cycloaddition reaction of ketenes with aliphatic imines (Chapter 4, Section 4.1.4.2). Sometimes [2+2+2] cycloadducts resulting from the reaction of the initially formed linear adduct with either one of the reagents are observed. The basicity of the imine plays a role because aliphatic imines react in this manner, while aromatic imines produce the four-membered ring [2+2] cycloadducts²⁹.

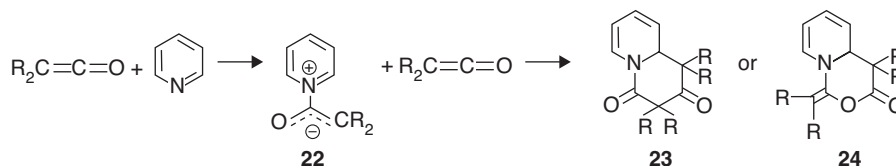
Substituents attached to the cumulenes can influence the mechanism of the cycloaddition reactions by rendering one molecule more nucleophilic and thereby deciding the course of the addition, i.e. determine which molecule is the electron donor to attack the electrophilic center of the other molecule³⁰.

The [3+2] cycloaddition reactions of cumulenes as 1,3-dipolarophiles are also well known. Huisgen in 1963³ demonstrated the wide scope of the dipolar [3+2] cycloaddition reactions, which often proceed in high yields, and consequently these reactions rival the Diels–Alder reactions as valuable synthetic tools. The oldest example of a [3+2] cycloaddition reaction is the reaction of isocyanates with nitrones, discovered by Beckmann in 1890³¹, but the general character of this reaction was discovered much later. Because of the dual character of heterocumulenes, such as isocyanates, the reaction can occur across either one of the double bonds and sometimes both reaction products are isolated. In general, the [3+2] cycloaddition reaction proceeds across the same double bonds, which also participate in the [2+2] cycloaddition reactions. Ketenes react predominantly across their C=C bonds, isocyanates across their C=N bonds and sulfenes across their C=S bonds.

The 1,3-dipolar systems involved in the cycloaddition reaction with cumulenes include azides, nitrile oxides, nitrile imines, nitrones, azomethine imines and diazo compounds. However, some 1,3-dipolar systems are also generated in the reaction of precursors with catalysts. Examples include the reaction of alkylene oxides, alkylene sulfides and alkylene carbonates with heterocumulenes. Carbon cumulenes also participate as 1,3-dipols in [3+2] cycloaddition reactions. Examples include thiocarbonyl sulfides, R₂C=S=S, and 1-aza-2-azoniaallenes.

The [4+2] cycloaddition reaction of dienes with dienophiles, which is generally known as the Diels–Alder reaction, is one of the most useful reactions in synthetic organic chemistry. Many examples of carbon cumulenes participating as dienes, dienophiles, or both, are known. Even aryl substituted cumulenes sometimes react as dienes in [4+2] cycloaddition reactions.

A 1,4-dipolar cycloaddition reaction also affords six-membered ring cycloadducts. For example, a 1,4-dipole can be generated in the reaction of ketenes with *N*-heterocycles, such as pyridine. The generated dipole **22** undergoes cycloaddition reaction with a second molecule of the ketene to give the cycloadduct **23**. Staudinger had assigned structure **23** to the cycloadducts but later work demonstrated that part of the cycloadducts had the isomeric structure **24**.



I have also included in this book the insertion reactions of carbon cumulenes into polarized metal single bonds, which can be perceived as an initial [2+2] cycloaddition, which subsequently rearranges to give a linear adduct. The reactivity of the metal substituent appears to be $NR_2 > OR > SR$. When the metal compound contains several reactive groups, stepwise insertion occurs. For example, $Sn(OR)_4$ reacts with phenyl isocyanate to give the tetracarbamate $Sn[N(Ph)COOR]_4$. Mixed insertion products are obtained using different isocyanates. In the insertion reactions of carbodiimides sometimes ionic cyclic amidinate complexes are formed.

A variety of other cyclization reactions are also observed with many of the carbon cumulenes. Especially, allenes and ketenes undergo many of these reactions and gold catalysis has achieved a new dimension in selectivity. From bis-allenes, complex natural products, such as 18,19 norsteroids, are generated in one step.

In order to monitor the cycloaddition reactions of carbon cumulenes infrared spectroscopy is most useful, because their asymmetric stretching absorption at approximately $2300\text{--}1900\text{ cm}^{-1}$ occurs in a region which is relatively undisturbed. Although fundamentally four vibrations can be visualized in the linear cumulene system (two stretching and two bending vibrations) only the stretching vibrations are of significance, and often the symmetric stretching absorptions of cumulenes at approximately $1400\text{--}1100\text{ cm}^{-1}$ are too weak to be recognized because of the proximity of methyl and methylene absorptions in this region.

Proton magnetic resonance spectroscopy can also be used to identify carbon cumulenes. The protons attached to the same carbon atom to which the cumulene group is attached are deshielded by the cumulene group and the chemical shifts of these protons are sufficiently separated from that of ordinary alkyl protons to allow characterization and also quantization. Of course, this method is only of value in the aliphatic series because in aryl substituted cumulenes only β protons are present and the deshielding effect is minimized.

The reactions shown in this book, up to 2008, are only examples to demonstrate the general scope of cumulene click reactions. New reactions are being reported constantly and many new reactions are expected to be discovered at an ever increasing rate.

12 Cumulenes in Click Reactions

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