Russian Chemical Reviews **75** (11) 935 – 960 (2006) © 2006 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2006v075n11ABEH001195

Theoretical studies on [3 + 2]-cycloaddition reactions

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Abstract. The results of theoretical studies on [3 + 2]-cycloaddition reactions carried out during the last decade are summarised. The reaction mechanisms are discussed. The catalyst, solvent, and substituent effects on the reactivities of compounds and on the mechanisms, regioselectivity and stereoselectivity of reactions are considered. The results of theoretical studies are compared with corresponding experimental data. The bibliography includes 328 references.

I. Introduction

Research on [3 + 2]-cycloaddition reactions began more than 100 years ago with a pioneering study by Buchner [1] who reported the reactions of ethyl diazoacetate with α,β-unsaturated esters. At present, the [3 + 2]-cycloaddition reactions are widely used in synthetic organic chemistry, in particular, for the synthesis of various five-membered heterocyclic systems that are used in industry and medicine and as synthons for fine organic synthesis.[2, 3]

In the 1950s – 1960s, the number of publications concerned with the [3 + 2]-cycloaddition reactions increased dramatically. This predetermined the need of summarising the results obtained and gave an impetus to studies, including theoretical ones, on the mechanisms of the processes in question. Systematic investigations of theoretical aspects of cycloaddition were initiated by Woodward and Hoffmann [4, 5] who developed a theory of pericyclic processes and by Huisgen [6 – 10] and Firestone [11 – 14] who reported a series of studies on the mechanisms of dipolar [3 + 2]-cycloaddition reactions.

However, wide use of theoretical methods became possible only in the 1980 – 1990s. This is due to progress in hardware and software (computational algorithms) development. Quantum-chemical methods are a powerful tool of studying chemical reactions including cycloaddition ones. Indeed, in addition to help in interpreting experimental data, which is of great value *per se*, theoretical calculations allow one to predict many properties of compounds and chemical reactions, sometimes providing a unique possibility of studying unstable compounds and intermediates. Additionally, they are successfully used for analysing the effects of various factors on the reactivities of compounds and on the rates, regioselectivity and stereoselectivity of reactions, *etc*. At present, cycloaddition processes are intensively studied by quantum-chemical methods.

In the last decade a number of monographs (*e.g.*, Refs 2 and 15 – 18) and reviews (*e.g.*, Refs 3, 19 – 22) summarising the results of experimental studies of cycloaddition reactions including [3 + 2]-cycloaddition were reported. However, most part of reviews of theoretical studies on the subject were published before 1995.[6, 23 – 26] Chronologically, the last available reviews of studies in this field were reported by Garcia *et al.*,[27] who analysed the effects of the secondary orbital interaction mainly in the Diels – Alder reactions and by Leach and Houk,[28] who considered theory of the Diels – Alder reactions involving oxygen molecules, nitroso compounds and hydrogenated triazolinediones.

The aim of this review was to summarise the results of theoretical studies on one of the most important types of cycloaddition reactions, namely, [3 + 2]-cycloaddition, carried out in the last decade (from 1994 up to 2005).

II. The cycloaddition reactions: a theoretical background

1. Classification of [3 + 2]-cycloaddition reactions with respect to the type of the interaction of frontier molecular orbitals

According to the frontier molecular orbital (FMO) theory [29] that underlies modern theory of chemical bonding, the course of chemical reactions is governed by the interaction between the highest occupied and lowest unoccupied MOs (HOMO and LUMO, respectively) of the reactant molecules. One of the first models that treated the cycloaddition reactions from the standpoint of the FMO theory was proposed by Woodward and Hoffmann (Woodward – Hoffmann rule).[5] This is the concept of the conservation of orbital symmetry, which became part of all textbooks of modern organic chemistry, being up to date a

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Received 19 January 2006
Uspekhi Khimii **75** (11) 1045 – 1073 (2006); translated by A M Raevskiy

powerful tool of qualitative description of cycloaddition processes.

Sustmann proposed a classification of dipolar [3 + 2]-cycloaddition reactions with respect to the character of the HOMO–LUMO interaction in the initial compounds.[30, 31] According to his classification, which is widely used at present, the [3 + 2]-cycloaddition reactions can be divided into three groups. Group I comprises the reactions controlled by the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction, or the so-called normal-electron-demand (NED) reactions. Processes governed by the $HOMO_{dipolarophile}$–$LUMO_{dipole}$ interaction, or the so-called inverse-electron-demand (IED) reactions, form Group III. If the energies of the valence MOs of two reactants are similar, the reaction is controlled by both types of the HOMO–LUMO interaction. These processes belong to group II (Fig. 1).

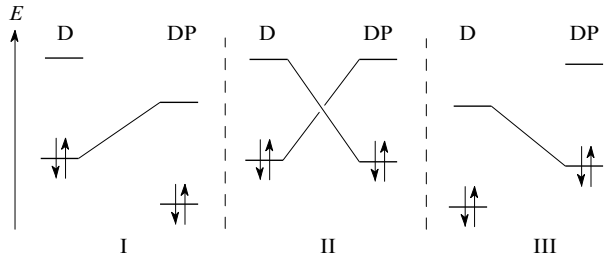


Figure 1. Classification of cycloaddition reactions according to Sustmann.
Hereinafter, 'D' stands for dipole and 'DP' stands for dipolarophile.

2. Main types of cycloaddition reaction mechanisms

There are two main mechanisms of cycloaddition reactions, namely, a concerted mechanism and a stepwise one. A concerted cycloaddition reaction occurs in a single step involving the formation of one transition state (TS) (Fig. 2 *a*).† The stepwise mechanism involves a number of stages. It begins with the formation of acyclic transition state and corresponding intermediate and completes with the ring closure and formation of final product (Fig. 2 *b*). The transition states and intermediates can be dipolar (zwitter-ionic), singlet or triplet biradical structures.

The concerted mechanism can be synchronous or asynchronous. In the former case the reactant molecules approach one another synchronously with the formation of new bonds in the transition state. In the latter case new bonds in the transition state are formed in turn. Different authors use different criteria for assessment of the synchronicity of processes. Often, the relative lengths of the contacts a···c and b···d in the transition state (see Fig. 2 *a*) are used as a measure of the synchronicity of the reaction mechanism. However, in practice this criterion can be applied only to the reactions with the same type of the interacting atoms. If new chemical bonds are formed between atoms of different elements, the lengths of these contacts can be appreciably different from each other even for the synchronous cycloaddition.

A more reliable criterion is provided by the bond populations (*e.g.*, the relative Wiberg indices[32]) for the contacts a···c and b···d, which depend on the nature of the interacting atoms. The smaller the difference between the Wiberg indices, the higher the synchronicity of the mechanism. However, in this case information on the synchronicity of the process is also incomplete because the analysis is restricted to only two bonds that are formed during the reaction. A more correct quantitative measure of the degree of synchronicity was introduced by Moyano *et al.*,[33] who proposed to allow for all bonds involved in the cycloaddition process. According to Moyano *et al.*,[33] the degree of synchronicity, S_y, of a reaction is given by

$$S_y = 1 - \frac{\sum_{i=1}^{n} |\delta B_i - \delta B_{av}| / \delta B_{av}}{2n - 2}. \qquad (1)$$

Here n is the number of bonds involved in the reaction (for the [3 + 2]-cycloaddition, $n = 5$) and δB_i is the relative variation of the Wiberg indices for the ith bond, which is calculated from the following relationship

$$\delta B_i = \frac{B_i^{ts} - B_i^{r}}{B_i^{p} - B_i^{r}},$$

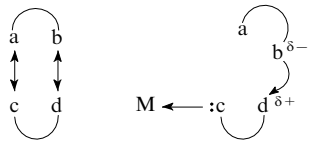
where the superscripts 'p', 'r' and 'ts' correspond to the product, reactants and transition state, respectively, and the average value of the δB_{av} is determined from

$$\delta B_{av} = n^{-1} \sum_{i=1}^{n} \delta B_i .$$

For true synchronous processes, $S_y = 1$, whereas for asynchronous ones $S_y = 0$.

Among various factors affecting the cycloaddition reaction mechanisms, the Lewis acid coordination to one of the reactants plays the key role. Usually, complexation is accompanied by an abrupt increase in the asynchronicity of the reaction or even by a change from concerted to stepwise reaction mechanism (see below). This change in the mechanism can be explained from the standpoint of charge control. The interaction of the Lewis acid with the reactant causes transfer of the electron density from the ligand to the catalyst (Scheme 1).

Scheme 1



As a result, the ligand becomes more electrophilic, which facilitates the attack of the second reactant by the negatively charged end.

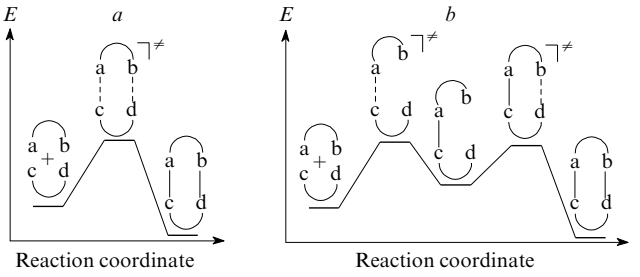


Figure 2. Energy profiles of concerted (*a*) and stepwise (*b*) cycloaddition reactions.

3. Substituent effects on the energy characteristics of cycloaddition reactions

Obviously, replacement of substituents in the reactant molecules should affect their reactivities in some way. This can be qualitatively interpreted in terms of the FMO theory. In particular, one can expect that introduction of electron-withdrawing substituents into the dipolarophile molecule and(or) electron-donating substituents into the dipole molecule will facilitate the NED reactions

† This mechanism is also called a 'one-step' and 'two-stage' mechanism. The latter term seems to be quite inappropriate; here the formation of transition state from reactants is treated as the first stage and the formation of reaction products from the TS is treated as the second stage.

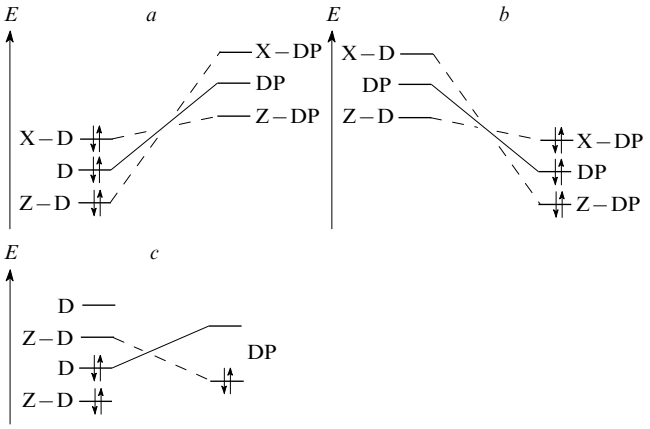


Figure 3. Substituent effects on the frontier MO energies.
Reaction type: a normal-electron-demand reaction (*a*), an inverse-electron-demand reaction (*b*), and a reaction accompanied by a change from 'weak' normal to 'weak' inverse electron demand interaction (*c*); X is the electron-donating substituent and Z is the electron-withdrawing substituent.

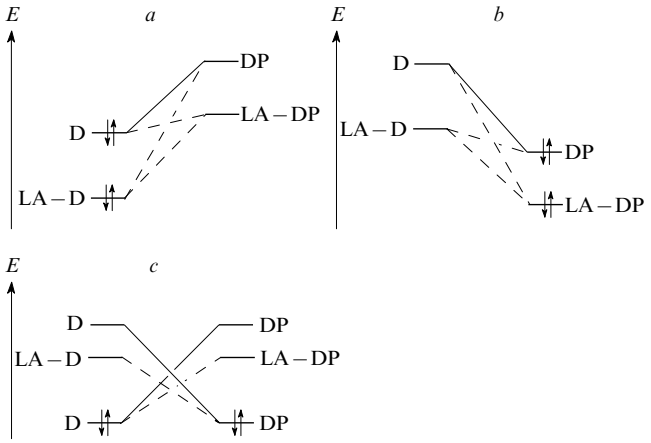


Figure 4. Lewis acid effect on the frontier MO energies.
Reaction type: a normal-electron-demand reaction (*a*), an inverse-electron-demand reaction (*b*) and an intermediate-type reaction (*c*); 'LA' stands for Lewis Acid.

due to a decrease in the energy difference between the dipole HOMO and dipolarophile LUMO (Fig. 3 *a*). On the contrary, the introduction of electron-donating substituents into the dipolarophile molecule and(or) electron-withdrawing groups into the dipole molecule should slow down the reactions due to an increase in the ΔE value for the FMOs. The reverse situation is characteristic of the IED reactions (Fig. 3 *b*). If the corresponding frontier MOs of the initial reactants have nearly equal energies, the introduction of the substituents that cause a significant redistribution of the electron density and act oppositely for different reactants should favour the occurrence of the reaction. Moreover, the type of the HOMO – LUMO interaction is often changed from, *e.g.*, 'weak' NED to IED or *vice versa* (Fig. 3 *c*). Examples are given in the text below.

It should be noted that this qualitative treatment of the substituent effects on the reactivities of reactants is simplified. In particular, the model ignores steric effects. Additionally, actual changes in the energies of the frontier orbitals are not always related to the type of the substituent introduced. Finally, the activation barrier is affected not only by the relative orbital energies of the reactants but also by other factors, *e.g.*, the nature of the transition state and the total energy effects of bond cleavage and formation in the formation of the transition state. Thus, investigations of the substituent effects on the course of a chemical reaction require detailed studies of its mechanism and estimation of the activation energy.

4. Effect of catalyst

Carrying out [3 + 2]-cycloaddition reactions often requires the presence of a catalyst, *e.g.*, a Lewis acid, which forms complexes with the reactant molecules. To a first approximation the effect of the Lewis acid on the course of cycloaddition processes can also be analysed from the standpoint of the FMO theory. The catalytic or promoting activity of the Lewis acid is first of all determined by the fashion of its coordination to the dipole, dipolarophile or to both reactants and by the type of the HOMO – LUMO interaction, the catalyst effect in most cases being similar to that of electron-withdrawing substituent. Selective coordination of the Lewis acid to dipolarophile accelerates the NED reactions due to a decrease in the energy difference ΔE between the dipole HOMO and dipolarophile LUMO. The Lewis acid coordination to the dipole leads to inhibition of the reaction, while coordination to both reactants has little effect on the reaction rate (Fig. 4 *a*). The reverse occurs in the case of the IED processes (Fig. 4 *b*). The use of Lewis acids in type II reactions favours the occurrence of the process if the catalyst is selectively coordinated to the dipole or to the dipolarophile; coordination to both reactants has no effect (Fig. 4 *c*).

The selectivity of the metal coordination to a reactant is often related to the hardness (softness) of the donor and acceptor centres. For instance, if the donor centre in the dipolarophile is a soft base and that in the dipole is a hard base, it is more appropriate to catalyse the NED reactions with soft Lewis acids that will selectively coordinate to the dipolarophile, thus causing the processes to accelerate. The hard donor centre in the dipolarophile requires the use of a hard Lewis acid. The reverse situation is valid for the IED reactions.

The aforesaid is valid if the process occurs under orbital control. However, in order to explain the catalyst effect, in some cases the charge control should also be taken into account in addition to the orbital control (especially for dipolar [3 + 2]-cycloaddition). Indeed, in the presence of a Lewis acid the process becomes more asynchronous (see above) and thus can to some extent be treated as a nucleophilic addition reaction. Such reactions are primarily driven by the effective charges of the interacting atoms. Consider a model NED reaction. The dipolarophile c – d is activated by the metal ion M. The dipole a – b asynchronously adds to dipolarophile M – c – d (see the right side of Scheme 1). For metals in high oxidation states (*i.e.*, harder metals) the electron density is more significantly shifted from the c – d fragment to the metal and the positive charge of the atom d increases, which facilitates the addition of the dipole a – b at the negatively charged end. Thus, the activation effect of the Lewis acid in intermolecular cycloaddition reactions is due to two factors, namely, the selectivity of coordination to one of the reactants and the extent of the electron density transfer. In our example, these factors act 'in parallel' if c is the hard centre and 'antiparallel' if c is the soft centre.

5. The solvent effect

Most often quantum-chemical calculations are carried out for the gas phase (more correctly, for isolated molecules); however, real processes usually proceed in solution. The solvation effects are included using a number of models that approximate the solvent effect. These are the Kirkwood – Onsager model and the polarised continuum model (PCM) and its modifications (CPCM, IEFPCM, IPCM, SCI-PCM). To a first approximation the solvent effect on the activation barrier is determined by the relative polarity of the reactant molecules and the transition state (if the solvent is not involved in the reaction, *i.e.*, is not a part of the transition state). The higher the polarity of the structure, the greater the decrease in its energy in polar media. If

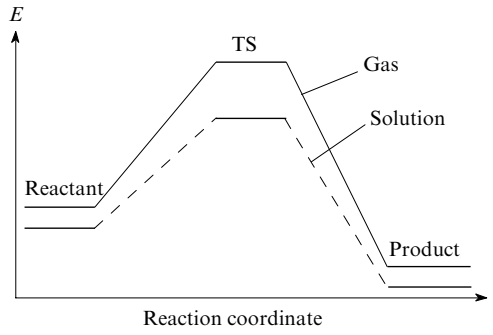
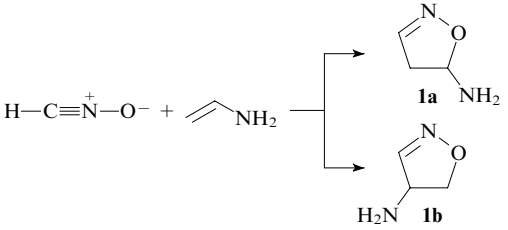


Figure 5. Influence of solvation effects on the activation energy: the case of high-polarity transition state.

the transition-state energy decreases to a greater extent compared to the reactant energies, the activation energy should decrease in a polar solvent (Fig. 5). *Vice versa*, if the overall polarity of the reactant molecules is higher than the polarity of the transition state, the reaction in high-polarity solvents will be inhibited.

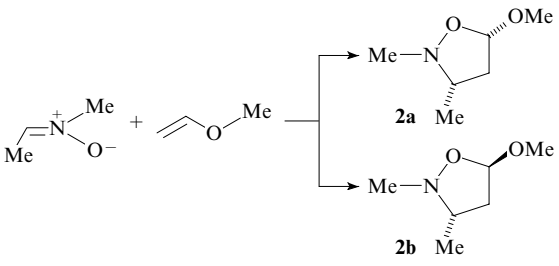
6. The chemoselectivity, the regioselectivity and the stereoselectivity

Many cycloaddition reactions are characterised by chemo-, regio- and stereoselectivity. The chemoselectivity of cycloaddition implies a selective addition of the reactant to one of several multiple bonds of the substrate. The regioselectivity of cycloaddition is associated with the addition of reactant to a given multiple bond of the substrate in a particular fashion. For instance, calculations predicted preferred formation of 5-amino-isoxazoline **1a** compared to 4-amino-substituted isomer **1b** in the reaction of formonitrile oxide $HC\equiv N^+-O^-$ (fulminic acid) with vinylamine.[34] In this review the 4- and 5-substituted isoxazolines will be called the *meta*- and *ortho*-isomers, respectively.



This phenomenon is often interpreted from the standpoint of the FMO theory following the rule that the reacting molecules interact through the atoms with similar (or largest) orbital coefficients.[35] At the same time the regioselectivity can also be governed by other factors, in particular, steric repulsion between substituents, secondary orbital interaction, formation of hydrogen bonds, *etc*.[36]

The stereoselectivity (diastereoselectivity and enantioselectivity) is due to preferred formation of the structures with a particular stereo configuration of the environment of the chiral atoms. For instance, in the reaction of *N*,*C*-dimethylnitrone MeCH=N(Me)O with methyl vinyl ether the addition resulting in diastereomer **2a** is more favourable than the process resulting in **2b**.[37]



7. The hard – soft acid – base principle

At present, one of the most widely used concepts in chemistry is the theory of hard and soft acids and bases,[38–40] which is successfully employed for describing the reactivity of compounds as an alternative to the FMO theory.[41–49] This concept is particularly widely used for interpreting the regioselectivity of various processes, *e.g*., cycloaddition of CH_2N_2, RN_3, N_2O, NCO, *etc*. to the molecules with multiple bonds.[50–54]

According to the theory of hard and soft acids and bases and the density functional theory (DFT), the total energy of intermolecular interaction can be represented by the sum

$$\Delta E_{int} = \Delta E_v + \Delta E_\mu , \qquad (2)$$

where ΔE_v and ΔE_μ are the energy changes at constant external and chemical potentials, respectively.[55–58] The first term corresponds to the processes of charge transfer between the reactant molecules. In the local–local approximation, it is expressed through the chemical potentials (μ) and 'softnesses' (S) of the reacting molecules A and B

$$(\Delta E_v)^{kl}_{AB} = -\frac{1}{2}\frac{(\mu_A - \mu_B)^2}{S_A f_{Ak} + S_B f_{Bl}} S_A S_B f_{Ak} f_{Bl} , \qquad (3)$$

where f_{Ak} and f_{Bl} are the Fukui functions which characterise the reactivities of the atoms k and l in the molecules A and B and depend on the type of the process under study, *i.e*., a nucleophilic (f^+), electrophilic (f^-) or radical (f^0) attack.[59] The μ and S can be calculated as follows

$$\mu \approx -\frac{I + A}{2} ,$$

$$S = \frac{1}{2\eta} \approx \frac{1}{I - A} ,$$

where I is the ionisation potential, A is the electron affinity and η is the molecular 'hardness'.[58]

The second term in Eqn (2) describes the charge reshuffling at constant chemical potential and is calculated using the expression

$$(\Delta E_\mu)^{kl}_{AB} = -\frac{1}{2}\frac{\lambda}{S_A f_{Ak} + S_B f_{Bl}} ,$$

where the parameter λ is proportional to the effective number of valence electrons involved in the reaction between A and B.[46, 56, 57]

A conventional analysis of the regioselectivity of cycloaddition involves calculations of the energies, ΔE_{int}, of possible regioisomers. Clearly, the higher the total interaction energy, the more preferred the formation of the corresponding isomer.

III. Computational methods used in studies of [3 + 2]-cycloaddition reactions

At present, semiempirical quantum-chemical methods (AM1, PM3, MNDO, INDO, ZINDO, *etc*.) belong to the simplest and cheapest (from the standpoint of computational cost) techniques employed for calculations of organic molecular systems. They differ from one another in parametrisation. Although in some cases the results obtained in these approximations agree well with experimental data,[60, 61] the properties predicted are more often significantly different from those observed experimentally.[62–64] Therefore, the results of semiempirical calculations should be interpreted with care. At the moment, semiempirical methods are inappropriate for studying low-molecular-mass organic systems. However, they can be useful for rapid assessment of general trends and correlations[65] rather than obtaining reliable quantitative energy characteristics and investigating the mechanism of the process under study as well as in studies of large molecules (*e.g*., macro- and biomolecules) where the use of more accurate approximations is difficult or impossible.

Until recently, the most widely used *ab initio* procedure was the Hartree – Fock (HF) method. Often, this approximation reproduces quite correctly the geometric parameters of molecules (first of all, the bonding distances between atoms of the first-to-third row elements).[66] However, the HF method ignores the electron correlation effects and therefore strongly overestimates the activation barriers and vibration frequencies. Indeed, the HF calculated activation energies for cycloaddition reactions are 1.5 – 2.5 times higher than experimental estimates or the activation barriers obtained from high-level approximations.[67 – 73] Thus, the HF method is inappropriate for studying cycloaddition reactions.

One of the 'simplest' *ab initio* methods with inclusion of electron correlation effects is the Møller – Plesset perturbative method (MP2 stands for the second-order Møller – Plesset level of theory). The results obtained in this approximation agree with experimental data better than the results of HF calculations; therefore, the MP2 technique is widely used, including studies of the cycloaddition reactions.[67, 70, 74 – 76] However, much higher computational cost of the MP2 calculations somewhat limits the field of application of the method (especially for the systems containing transition metal atoms). Additionally, in some cases the MP2 calculated geometric parameters are appreciably different from experimental data (the differences can be even larger than in the case of the HF method).[66] It is also known that the MP2 wave functions of high-spin systems are characterised by high degree of spin 'contamination', which can affect the results of calculations.[77 – 79] Nevertheless, this approximation remains one of the most popular methods for calculation of medium-size molecular systems.

There are also other high-level approximations, which often give the results that are in excellent agreement with experimental data. These are, *e.g.*, higher-order Møller – Plesset methods [MP3, MP4DQ, MP4SDQ, MP4SDTQ; the letters 'S', 'D', 'T' and 'Q' mean that the corresponding calculations allow for single, double, triple and(or) quadruple excitations], the coupled clusters method [CCD, CCSD, CCSD(T)], the quadratic configuration interaction [QCISD(T)] method, the multiconfiguration self-consistent field (MCSCF or CASSCF) method and the composite methods (G1, G2, CBS) that give the best approximation to the experimental energies (with an average deviation of 3 – 4 kJ mol^{-1}). It was also reported that the theoretical activation energies and energy effects of cycloaddition processes strongly depend on the level of theory at which electron correlation effects are included. For instance, the activation energies for [3 + 2]-cycloaddition reactions of (i) diazomethane, fulminic acid [35] and methyl azide [80] with C_2H_4 and (ii) ozone with isoprene [74] changed by 20 – 40 kJ mol^{-1} on going from the MP2 to the MP4, QCISD or CCSD(T) calculations. In contrast to this, the authors of other studies reported a weak dependence of the energy parameters on the computational method and basis set employed. For instance, the E_a value for the interaction of nitrone $CH_2{=}N(Me)O$ with acetonitrile varies from 48 to 59 kJ mol^{-1} when using the MP2/6-31G*, MP4SDTQ//B3LYP/6-31G*, MP4SDTQ//MP2/6-31G*, CCSD(T)//B3LYP/6-31G*, CCSD(T)//MP2/6-31G*, CBS-Q and B3LYP/6-31G* methods.[72]

Analysis of the published data on the effect of the approximation employed on the results of calculations of cycloaddition reactions revealed the following. The relative energies obtained from the MP4SDTQ, CCSD(T) and QCISD(T) calculations with the same basis set are often similar, being in good agreement with experimental data.[72, 81] The CASSCF method often overestimates the activation energies for the concerted cycloaddition mechanism. As a consequence, the stability of biradical structures and the possibility of stepwise mechanism are overestimated even when using a large active space.[82 – 84] However, the results of the CASSCF calculations with MP2 corrected energies (CASPT2//CASSCF) are similar to those of the CCSD(T), G2 and CBS calculations.[83, 85] Moreover, in some cases the open-shell systems (*e.g.*, biradical structures) and excited states can be correctly described only in the CASSCF and CASPT2 approximations. At the same time the MP4SDTQ, CCSD(T) and QCISD(T) methods can be recommended for theoretical studies of ground-state closed-shell structures. The G2 and CBS approximations belong to the most accurate ones and give the results that are in excellent agreement with experimental data. However, these techniques are of limited use because they are only applicable to small molecular systems.

Finally, there is yet another group of computational methods with inclusion of electron correlation effects. These are the DFT methods that combine a rather high accuracy of calculations and relatively low computational cost. This predetermines high popularity of DFT methods in studies of organic and organometallic molecular systems. Most DFT studies of cycloaddition reactions were carried out with the B3LYP functional. Often, the results obtained from B3LYP calculations are in good agreement with experimental data and this approximation can be considered optimum. Nevertheless it is clear that search for the most correct method of theoretical investigation of a new cycloaddition reaction requires evaluation of various approximations, as applied to the process under study, and comparison of the results obtained with experimental data. In the lack of experimental data (this is a quite typical situation) the applicability of a particular computational method can be indirectly assessed by comparing the results obtained with those found from the highest-level approximations [G2, CBS, CCSD(T), *etc.*].

In addition to the computational methods, the choice of the basis set can also affect the results of calculations. At present, most studies of the cycloaddition reactions of medium-size organic molecules are carried out with the 6-31G* split-valence basis set of Gauss functions. In most cases a correct description of the systems under study requires the use of polarisation functions. Additionally, investigations of anion structures require augmentation of the basis sets with diffuse functions (*e.g.*, the basis sets 6-31+G**, 6-31+G** and 6-31++G**). In studies of small molecules it is possible (and desired) to employ the extended basis sets (*e.g.*, 6-311G**, 6-311+G**, cc-pVDZ, cc-pVTZ, *etc.*). If the reacting molecules contain transition-element atoms, the core electrons in these atoms are usually approximated by pseudopotentials (LanL2DZ, LanL2MB, Stuttgart pseudopotentials, *etc.*), which can also allow for relativistic effects (this is of particular importance in the case of heavy fifth- and sixth-row elements).

The energy characteristics of cycloaddition reactions are often sensitive to the change in the computational method rather than the change in the basis set.[35, 72, 73, 80, 83] For instance, extension of the basis set from 6-31G* to 6-31+G**, 6-311+G*, 6-311++G** and 6-311++G(2df,2p) [methods MP2, CCSD(T) and MP4SDTQ, respectively] in studies of the reactions of CH_2N_2 and HCNO with C_2H_4 and C_2H_2 causes the activation energy to change only by 0.2 – 2.3 kJ mol^{-1} (see Refs 35 and 83). On the contrary, some authors reported strong differences between the activation barrier calculated with different basis sets.[71] Thus, studies of new cycloaddition reactions require evaluation of various basis sets in order to analyse the stability of the solution to the changes in the basis set.

IV. Reactions of allyl type dipoles

Most [3 + 2]-cycloaddition reactions represent a dipolar cycloaddition (one reactant molecule is a dipole while the other reactant molecule is a dipolarophile). The dipole molecules contain highly polar bonds and fragments the atoms of which bear integer positive and negative formal charges at least in one boundary structure. The dipoles are usually divided into two main classes, namely, the allyl and propargyl-allenyl type dipoles (Fig. 6). The first type of compounds has a bent geometry of the reactive fragment due to sp^2-hybridisation of the orbitals of the central atom; the second type of compounds is characterised by sp-hybridisation of AOs and linear geometry.

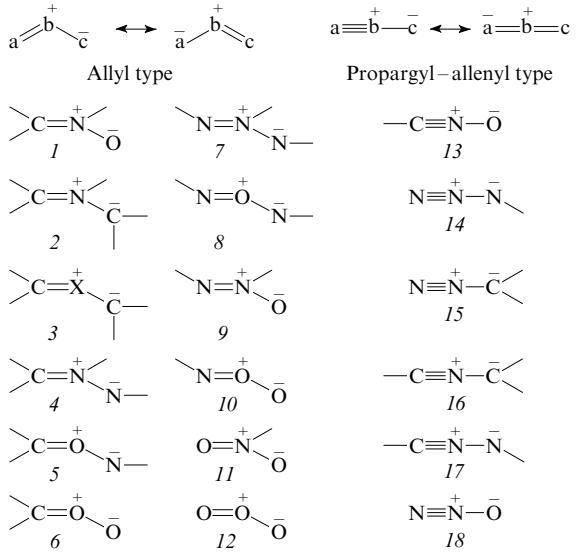


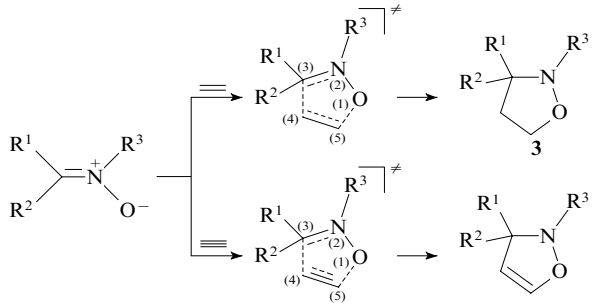
Figure 6. Main types of 1,3-dipoles.
Nitrones (*1*); ylides (*2*); carbonyl-, thio- and selenocarbonyl ylides (*3*); azomethine imines (*4*); carbonyl imines (*5*); carbonyl oxides (*6*); azoimines (*7*); nitrosimines (*8*); azoxy compounds (*9*); nitroso oxides (*10*); nitro compounds (*11*); ozone (*12*); nitrile oxides (*13*); azides (*14*); diazoalkanes (*15*); nitrile ylides (*16*); nitrile imines (*17*); and nitrous oxide (*18*).

The allyl-type dipoles comprise nitrones, ylides (including azomethine ylides, carbonyl ylides and thio- and selenocarbonyl ylides), azomethine imines, carbonyl imines, carbonyl oxides, azoimines, nitrosimines, azoxy compounds, nitroso oxides, nitro compounds and ozone. Additionally, the oxo ions and transition metal oxides can also formally be treated as dipoles.

1. Nitrones

The cycloaddition of nitrones to alkenes (Scheme 2) resulting in izoxazolidine **3** is one of the best studied dipolar [3 + 2]-cycloaddition processes.

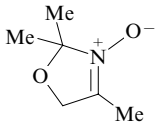
Scheme 2



The [3 + 2]-cycloaddition processes involving nitrones are often treated as Sustmann's type II processes.[86,87] By varying substituents in the nitrone or dipolarophile molecule one can readily change the type of the HOMO – LUMO interaction and therefore the type of the reaction, thus making it a NED or an IED process. Indeed, the cycloaddition of nitrones to such electron-deficient dipolarophiles, as acrylonitrile ($CH_2{=}CHCN$),[88] acrolein ($CH_2{=}CHCHO$),[89] methyl propiolate ($CH{\equiv}CCO_2Me$)[88,90] and methyl acrylate ($CH_2{=}CHCO_2Me$),[91] alkyne carbene chromium complex [$(CO)_5Cr{=}C(OH)C{\equiv}CH$],[90] fluorinated alkenes and alkynes,[92,93] nitroalkenes ($R^1CH{=}CR^2NO_2$)[94–97] and vinylsulfonyl chloride ($CH_2{=}CHSO_2Cl$)[98] are controlled by the $HOMO_{nitrone} - LUMO_{dipolarophile}$ interaction. On the other hand, the use of alkenes with electron-donating substituents, *e.g.*, methyl vinyl ether ($CH_2{=}CHOMe$)[37] causes the reaction type to be changed to the IED process.

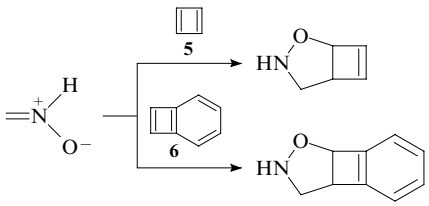
a. Reactions with alkenes and alkynes. The reaction mechanisms

Most authors have reported a concerted mechanism of thermally induced cycloaddition of nitrones.[37,82,88,93,98–103] For instance, studies of the reactions of (i) *N*,*C*-dimethylnitrone [$MeCH{=}N(Me)O$] with $CH_2{=}CHOMe$ (see Ref. 37) and (ii) cyclic nitrone **4** with methyl propiolate and acrylonitrile[88] showed that in the most stable transition states of these reactions the difference of the Wiberg bond indices for the C(3)···C(4) and O(1)···C(5) contacts (see Scheme 2) varies in the range from 0.13 to 0.27, thus indicating an asynchronous mechanism. Calculations of the S_y values for the cycloaddition of $CH_2{=}NHO$ to ethylene and acetylene showed that these processes are characterised by high synchronicity ($S_y = 0.92$).[99,100] Interestingly, a high synchronicity was also found for the reactions of $CH_2{=}NHO$ with such asymmetrical dipolarophiles, as $CH_2{=}CHCF_3$, $F_2C{=}CFCF_3$ and $CH{\equiv}CCF_3$.[93]



4

The mechanisms of nitrone ($CH_2{=}NHO$) cycloaddition to ethylene and cyclobutadienes **5** and **6** were studied.[82,104] The results of the B3LYP, CASSCF and QCISD calculations indicated a concerted mechanism of the nitrone interactions with $CH_2{=}CH_2$ and compound **6**; as to the addition to cyclobutadiene **5**, the concerted and stepwise mechanisms were found to be equiprobable due to clear antiaromatic character of compound **5**. In the case of nitrone reactions with allene ($CH_2{=}C{=}CH_2$) the stepwise cycloaddition involving the formation of biradical intermediate is energetically more favourable than concerted one.[105]



b. Effect of Lewis acid on the reaction mechanism

The introduction of a Lewis acid catalyst into the system leads to dramatic increase in the asynchronicity of the process[37,106,107] (for the reasons, see above). For instance, the reaction of $MeCH{=}N(Me)O{\cdots}BH_3$ complex with $CH_2{=}CHOMe$ is accompanied by an increase in the difference between the Wiberg indices for the contacts C(3)···C(4) and O(1)···C(5) in the transition state (see Scheme 2) from 0.13 (for non-catalytic process) to 0.27.[37] The effect of Lewis acid (BH_3 and BF_3) on the mechanism, energy characteristics, regio- and stereoselectivity of the reaction of $CH_2{=}NHO$ with acrolein was also studied.[106] If BH_3 is coordinated to acrolein, the activation energy decreases from 105 to 53 kJ mol^{-1} and the asynchronicity of the process increases. Coordination of this Lewis acid to nitrone causes inhibition of the reaction (E_a increases by 18 kJ mol^{-1}) and some increase in its synchronicity. The theoretical activation energies reported in this study should be treated with care, because they were obtained from HF calculations ignoring the electron correlation effects [*cf.* 65.7 kJ mol^{-1} for the experimentally determined enthalpy of activation of thermally induced reaction of $PhCH{=}N(Me)O$ with $CH_2{=}C(Me)CO_2Me$, see Refs 7 and 108]. Nevertheless, the character of the Lewis acid effect on the reactivity (*i.e.*, acceleration of the reaction upon selective coordination of BH_3 to dipolarophile) is in qualitative agreement with the FMO theory predictions for the NED processes to which the reaction in question belongs. Interestingly, the coordination of BF_3 used instead of BH_3 to nitrone causes the reaction mechanism

to change from concerted to stepwise. Corresponding calculations revealed a Michael-type intermediate for this reaction.

Two possible mechanisms of the interaction of zinc-coordinated *N*-benzyl-*C*-(2-pyridyl)nitrone with allyl alcohol were studied.[62] However, the PM3 semiempirical method employed in that study precluded a correct description of the systems under study and the results obtained appeared to be in contradiction with experimental data.

c. Solvation effects

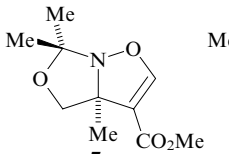
Usually, the dipolar [3 + 2]-cycloaddition reactions of nitrones occur *via* polar transition states, but the initial nitrone is also a dipole. If the second reactant has a sufficiently large dipole moment, the total polarity of the reactants becomes higher than the polarity of the transition state. Therefore, when using polar solvents, one can expect an increase in the activation energy for this type of reactions. This was confirmed experimentally [109–111] and theoretically.[37, 94, 100] In particular, Domingo [37] showed that the activation barrier to the reaction of $MeCH{=}N(Me)O\cdots BH_3$ with $CH_2{=}CHOMe$ increases by 7–8 kJ mol^{-1} on going from the gas phase to solution in CH_2Cl_2. A similar effect was also obtained for the reaction of $CH_2{=}NHO$ with non-polar ethylene; at the same time the interaction of this nitrone with acetylene is characterised by some decrease in E_a on going to solution in MeCN.[100] Additionally, solvation is accompanied by an increase in asynchronicity of formation of the corresponding transition state or even by a change from concerted to stepwise reaction mechanism due to, *e.g.*, stabilisation of polar acyclic intermediate in the polar solvent as in the reactions of $PhR^1C{=}N(Ph)O$ ($R^1 = H$, Ph) with nitroalkenes $R^2CH{=}CHNO_2$ ($R^2 = C_6H_4NO_2$-4, CN, CCl_3).[94, 101, 112]

d. Regioselectivity and stereoselectivity

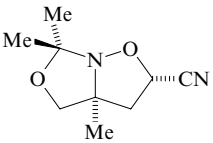
Elucidation of the nature of the regio- and stereoselectivity of the [3 + 2]-cycloaddition processes is one of the most interesting and important problems. The regioselectivity is often interpreted from the standpoint of the FMO theory as a result of preferred interaction of the dipole and dipolarophile atoms characterised by the largest orbital coefficients in the FMOs. At the same time in the case of nitrones both types of the interaction, $HOMO_{nitrone} - LUMO_{dipolarophile}$, and $HOMO_{dipolarophile} - LUMO_{nitrone}$, play a significant role and the orbital coefficients of all reacting atoms in the FMOs are similar. This is the reason for low regioselectivity of these reactions.[88, 113, 114]

As mentioned above, the introduction of electron-donating or electron-withdrawing substituents into the nitrone or dipolarophile molecule leads to predominance of a certain type of the HOMO – LUMO interaction and, hence, to an increase in the regioselectivity of the reaction. For instance, experimental [115–118] and theoretical [34, 37, 89, 93, 94, 98, 101, 118, 119] studies showed that reactions of nitrones with olefins usually result in preferred formation of *ortho*-isomers if the dipolarophile molecule contains an electron-donating substituent (*e.g.*, Alk, OAlk, NH_2) and *meta*-isomers if it contains an electron-withdrawing substituent (*e.g.*, CHO, CF_3, NO_2, SO_2Cl). By varying substituents in the nitrone molecule one can also change the regioselectivity. For instance, the use of nitrones $CH_2{=}N(R)O$ in the reaction with $CH_2{=}CHNO_2$ leads to exclusive formation of the *ortho*-isomer, whereas in the case of *C*-substituted nitrones the reaction results in the *meta*-isomer (*meta*-selectivity).[120, 121]

High *meta*-selectivity was predicted for the interaction of cyclic nitrone **4** with methyl propiolate.[88] According to calculations, isomer **7** should be the major product [the PCM-B3LYP/6-31G* calculated activation energy difference is 11 kJ mol^{-1}, which corresponds to an isomer ratio of 85 (*meta*) : 1 (*ortho*)], which agrees with experimental data on selective formation of the *meta*-isomer in the reaction of compound **4** with ethyl propiolate.[88]



7

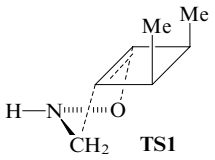


8

Even minor changes in the relative activation barriers to the formation of *meta*- and *ortho*-isomers lead to large variations of the relative yields of the regioisomers due to exponential dependence in the Boltzmann equation; therefore, the theoretical estimate of regioselectivity can strongly depend on the computational method and basis set employed. For the addition of nitrone **4** to acrylonitrile, B3LYP/6-31G* calculations [88] showed a low *meta*-selectivity, whereas B3LYP/6-31+G* computations using the basis set augmented with diffuse functions predicted a low *ortho*-selectivity (formation of product **8**). One can expect that further extension of the basis set and use of higher-level computational methods [*e.g.*, MP4 or CCSD(T)] will provide better agreement with conclusions about exclusive formation of the *ortho*-isomer in this reaction drawn from experiment.

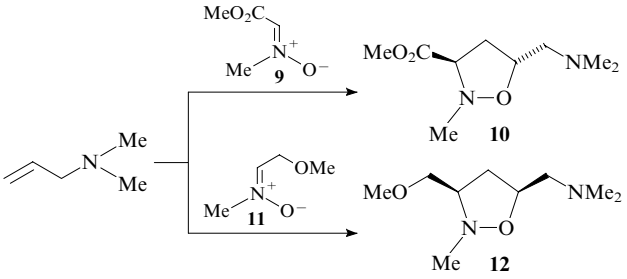
In some cases the regio- and stereoselectivity are governed by the nature of the solvent and the presence of the Lewis acid.[37, 100, 122, 123] In particular, the interaction of $CH_2{=}N(R)O$ with nitroethylene ($CH_2{=}CHNO_2$) shows no regioselectivity in the gas phase, but calculations with inclusion of solvent effect lead to preferred formation of the *ortho*-isomer *via* an *endo*-transition state in accordance with experimental data (see above).[100] Enhancement of the regio- and stereoselectivity upon the introduction of Lewis acid was observed [37] in calculations of the interaction of $MeCH{=}N(Me)O$ with $CH_2{=}CHOMe$. The *exo* : *endo* isomer ratio increases from 3.8 : 1 (obtained from B3LYP/6-31G* calculations of thermally induced reaction) to 29 : 1 for the BH_3-catalysed process. For comparison, the experimental *exo* : *endo* isomer ratio in the reaction of $\overline{CH_2OCMe_2OCH{=}N(O)CMe_2OCH_2}$ with $CH_2{=}CHOEt$ is 3 : 1.[88] The *exo*-stereoselectivity is due to the lack of steric hindrances to the formation of transition state in the case of *endo*-isomer.

Steric stabilisation is one of the main reasons for stereospecificity of the reactions of nitrones with *cis*-3,4-dimethylcyclobutene [124] and electron-deficient alkenes containing bulky substituents.[125] In the former case strong interaction between the nitrone atoms and the methyl groups of the dipolarophile leads to almost exclusive formation of the *anti*-isomer *via* an *exo*-transition state (**TS1**). The activation energy for the formation of the corresponding *syn*-product is 8.6 kJ mol^{-1} higher (theoretical and experimental *syn* : *anti* product ratios are 97 : 3 and $\geqslant$ 99 : 1, respectively), while the *endo*-addition is 33–39 kJ mol^{-1} less favourable than the *exo*-addition. The *anti*-addition is also preferable for the reactions of $CH_2{=}NHO$ with enol ethers, but here the stereoselectivity is mainly governed by electrostatic effects.[126]



TS1

The effect of the nature of the substituent in the dipole molecule on the stereoselectivity of cycloaddition was studied.[127] The reaction of the model compounds, namely, *E*-isomer of nitrone $MeO_2CCH{=}N(Me)O$ (**9**) and *N*,*N*-dimethylallylamine should result in preferred formation of *trans*-product **10** through *exo*-addition, whereas in the reaction of nitrone **11** should mainly afford the *cis*-isomer **12** (this process will occur under kinetic control).



The conclusions made [127] are in excellent agreement with experimental facts. Similarly, the *Si-exo*-facial stereoselectivity was calculated for the reactions of *C*-[(4,*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-*N*-methylnitrone with ethyl 2-acetoxyacrylate [128] (theoretical and experimental isomer ratios of the most stable *Si-exo*- and *Re-exo*-isomers are 7 : 1 and 2 : 1, respectively) and with vinyl acetate.[129] At the same time the cycloaddition of *C*-[(4,*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-*N*-methylnitrone to methyl acrylate,[130] *C*-(2-furyl)-*N*-methylnitrone to vinyl acetate,[131] and nitrones to unsaturated arylsulfones [132] and pyrazolon-*N*,*N*-dioxides to epoxynaphthalene [133] show *endo*-selectivity.

In some cases the stereoselectivity is governed by the effect of the secondary orbital interaction (orbital interaction between the atoms that are not involved in the cycloaddition reaction, *e.g.*, the atoms b and g or b and f, see Fig. 7). Obviously, a bonding secondary orbital interaction should stabilise a given stereoconfiguration and an antibonding interaction should destabilise it. Indeed, the *endo*-stereoselectivity theoretically predicted for the addition of nitrones to *s-cis*-acrolein ($CH_2{=}CH-CHO$) is governed by the bonding secondary orbital interaction between the nitrone nitrogen p-AOs and p-orbitals of the atoms in the carbonyl group of the dipolarophile.[34, 134] However, it should be noted that the authors of some studies (see, *e.g.*, a review by Garcia *et al.*[27]) cast some doubt on the role of the secondary orbital interaction in the stereospecific course of reactions.

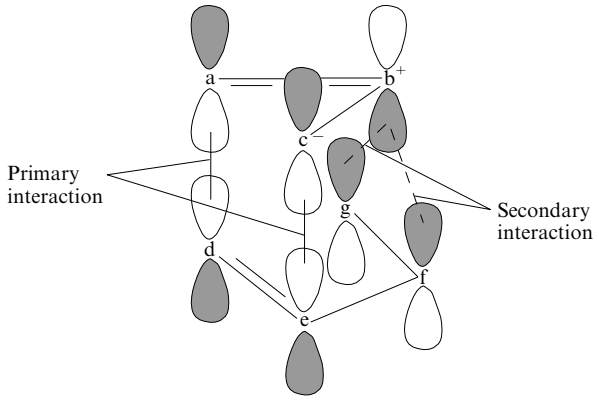
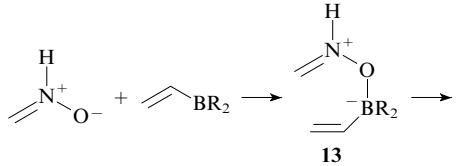
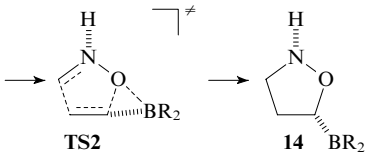


Figure 7. Primary and secondary orbital interactions.

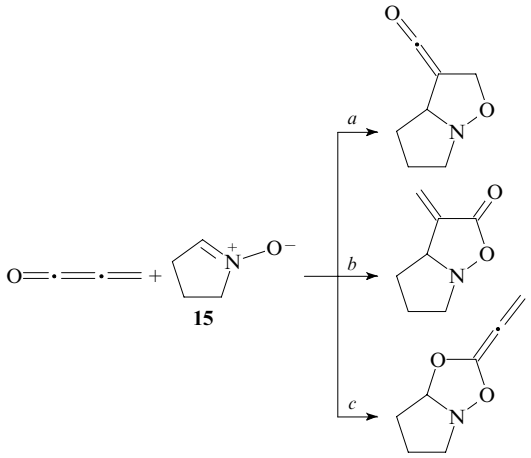
Model reactions of nitrone $CH_2{=}NHO$ with vinylboranes $CH_2{=}CHBR_2$ were studied.[135] The [3 + 2]-cycloaddition reaction should show regioselectivity and *endo*-stereoselectivity and proceed at high rate *via* acyclic complex **13** with the formation of *ortho*-isomer **14**.





The regioselectivity and low activation barriers are due to strong interaction between the boron and oxygen atoms in complex **13** and in the corresponding transition state **TS2**. Other possible mechanisms of this process, namely, cyclisation with the formation of six-membered boron-containing ring, *O*-boronation and oxidation are undoubtedly energetically less favourable compared to cycloaddition. The use of dimethyl-substituted vinylboranes $CH_2{=}CHBMe_2$ and $Me_2C{=}CHBH_2$ causes the activation energy to increase, whereas in the case of dichlorovinylborane $CH_2{=}CHBCl_2$ the activation barrier decreases consistently with the FMO theory predictions for the NED reactions. At present, these theoretical predictions cannot be substantiated or rejected due to the lack of corresponding experimental data.

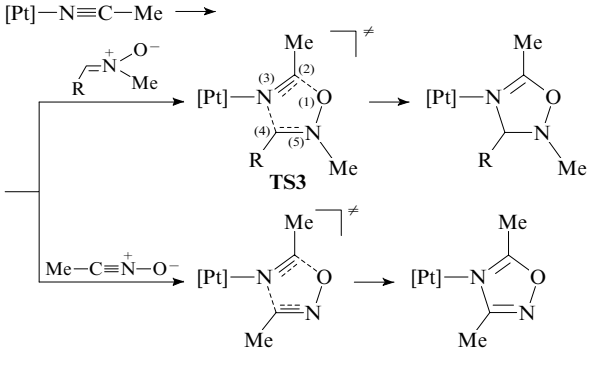
If the dipolarophile molecule has several multiple bonds, the dipole can selectively react at one of the bonds (this is called chemoselectivity). For instance, the chemoselectivity of the reaction of cyclic nitrone **15** with methyleneketene was studied.[136] The reaction can follow three pathways, among which the cycloaddition to the terminal C=C bond is the most kinetically favourable (B3LYP/6-31G* calculated activation energies for the pathways *a*, *b* and *c* are 16, 23 and 87 kJ mol^{-1}, respectively). This agrees with experimental data on the isolation of the corresponding regioisomer.



e. Other dipolarophiles

The results of studies on the reactions of cyclic and acyclic nitrones with free nitriles $RC{\equiv}N$ and platinum-coordinated nitrile constituents of the complexes *trans*-$[PtCl_2(NCMe)_2]$ (**16**) and *trans*-$[PtCl_4(NCMe)_2]$ (**17**) (Scheme 3) were summarised in two recent studies.[72, 137]

Scheme 3



[Pt] = *trans*-$[PtCl_n(NCMe)]$; n = 2, 4.

These studies were carried out to establish the reasons for the activation of nitriles in the complexes compared to free ligands and to thoroughly analyse the reaction mechanisms and the influence of various factors (solvent, nature of substituent, computational method) on the energy characteristics of the reactions. The experimentally observed [138, 139] enhancement of the reactivity in the series MeCN – **16** – **17** was interpreted as being due to a decrease in the nitrile LUMO energy in this series (orbital control) and an increase in the effective atomic charge of the nitrile β-carbon (charge control).[140] Analysis of the electron density distribution in the transition states **TS3** showed that the coordination of nitrile is accompanied by not only the change in the reaction type from the intermediate to the NED reaction but also a change in the reaction mechanism from synchronous for MeCN (S_y = 0.92) to intermediate between concerted cycloaddition and nucleophilic addition of the nitrone oxygen atom to the nitrile β-carbon (S_y = 0.69 and 0.53 for the reactions of compounds **16** and **17**, respectively). It is this change in the reaction mechanism that provides an explanation for dramatic enhancement of nitrile reactivity upon coordination. Nevertheless, ring critical points were located for all transition states (Fig. 8), which indicates the cyclic nature of the transition state even in the reaction of complex **17**.

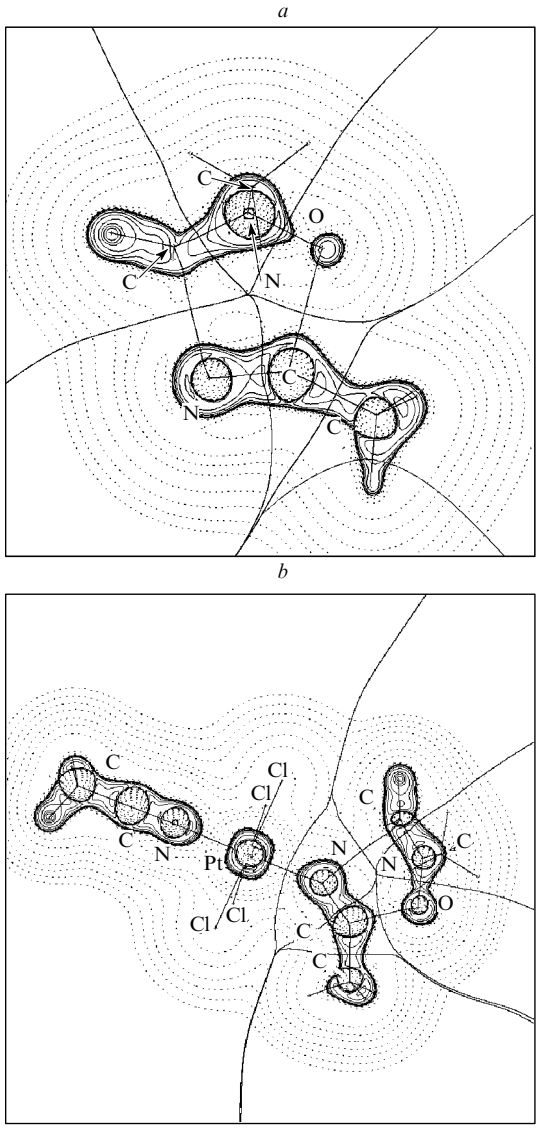


Figure 8. Contour map illustrating the distribution of the Laplacian of electron density $\nabla^2\rho(r)$, the bond pathway and the zero-flux surface for transition states of the reactions of nitrone $CH_2{=}N(Me)O$ with MeCN (*a*) and complex **17** (*b*).

The results of calculations confirmed that coordination of nitrile in complexes **16** and **17** is followed by dramatic decrease in the Gibbs free activation energy and by an increase, in absolute value, in the energy change (ΔG) in the reaction (Table 1). This is in excellent agreement with the experimentally observed changes in the reactivity of nitriles. Interestingly, the 'electronic' activation energy calculated relative to the total energy of reactants for the interaction of $CH_2{=}N(Me)O$ with complex **17** is negative, being equal to −23 kJ mol^{-1} (obtained from B3LYP/6-31G* calculations). However, the E_a values calculated relative to the orientation complex that is formed in the early stages of the reaction and the Gibbs free activation energy calculated relative to the total energy of reactants become positive (20 and 34 kJ mol^{-1}, respectively). Thus, in the E_a scale (in essence, this parameter coincides with $\Delta H^{\neq}$ at 0 K) the energy of the orientation complex is lower than that of the reactants. Nevertheless, with allowance for the entropy factor one gets that the equilibrium is shifted towards formation of the initial compounds. This situation is typical of the cycloaddition reactions involving highly activated reactants (see, *e.g.*, Refs 141 – 143).

Table 1. Relative energy characteristics (in kJ mol^{-1}) of the cycloaddition of $CH_2N(Me)O$ to MeCN and to complexes **16** and **17** (obtained from B3LYP/6-31G* calculations; ECP on Pt atom).[a]

Reactant	E_a	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔE	ΔH	ΔG
MeCN	59 (66)	62	116	−100 (−83)	−88	−32
	67	[74][b]	[128][b]	*−91*	[−86][b]	[−30][b]
	[71][a]			[−97][a]		
	[71 (78)][b]			[−97 (−81)][b]		
16	13 (19)	14	82	−147 (−130)	−137	−64
	24			*−136*		
	[27][a]			[−129][a]		
17	−23 (−17)	−16	34	−170 (−152)	−155	−93
	−15			*−163*		
	[0][a]			[−151][a]		

Notes. 1. All values are given relative to the total energy of the reactants. 2. The values in parentheses and in square brackets denote the values corrected for zero-point vibrational energy and for solvation effect, respectively. The values corrected for the basis set superposition error are given in italic.

[a] Obtained from CPCM calculations using the gas-phase equilibrium geometry. [b] Full geometry optimisation was carried out in the CPCM-B3LYP/6-31G* approximation.

Studies of the effect of the substituent nature on the energy characteristics of reactions showed that the process proceeds more easily upon introduction of electron-withdrawing groups into the nitrile molecule. Indeed, the activation energies obtained for the reaction of $CH_2{=}N(Me)O$ with RCN are 59 and 54 kJ mol^{-1} at R = Me and Ph, respectively. *C*-Alkylnitrones are more reactive than *C*-arylnitrones ($\Delta G^{\neq}$ = 127 and 143 kJ mol^{-1} for the reactions of $MeCH{=}N(Me)O$ and *p*-$MeC_6H_4CH{=}N(Me)O$ with MeCN, respectively). The theoretical $\Delta H^{\neq}$ value for the reaction of *p*-$MeOC_6H_4CH{=}N(Me)O$ with PhCN is 83 kJ mol^{-1}, being very similar to the experimental value determined for the interaction of cyclic nitrone **18** with PhCN (84 kJ mol^{-1}).[144] Additionally, a linear correlation between the parameter $\Delta G^{\neq}$ and the synchronicity of cycloaddition was found (Fig. 9). Since both reactant molecules have high polarities, the use of a polar solvent should inhibit the reaction, namely, the activation energy increases by 12 – 23 kJ mol^{-1} on going from the gas phase to solution in CH_2Cl_2 and the ΔE value for this reaction decreases by 3 – 20 kJ mol^{-1} in absolute value.

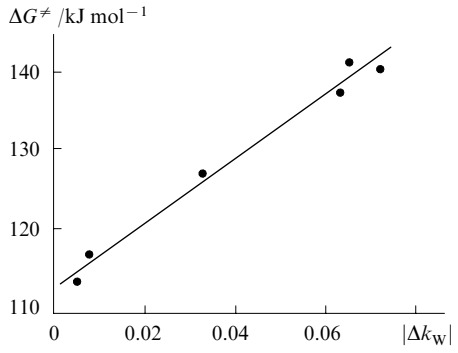
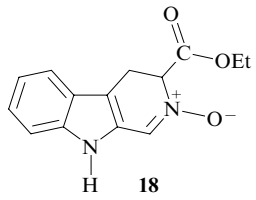


Figure 9. Parameter ΔG^{+} plotted *vs*. difference of the Wiberg indices (Δk_w) of the contacts O(1)N(5) and C(4)N(3) for the reactions of compounds R^1CN (R^1 = H, Ph) with $R^2CH{=}N(Me)O$ (R^2 = H, Me, *p*-MeC_6H_4, *p*-$MeOC_6H_4$); obtained from B3LYP/6-31G* calculations.



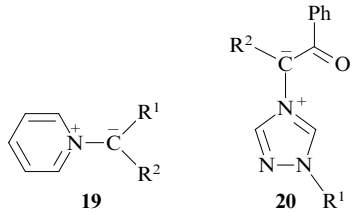
18

Salts with $[R^1C{\equiv}NR^2]^+$ cations, in which the nitrile is very electron-deficient, can be used to model the complexation of compounds RCN. The results of semiempirical AM1 calculations of the cycloaddition of pyridine *N*-oxide (C_5H_5NO) to $[MeC{\equiv}NMe]^+$ supported a stepwise reaction mechanism.[145]

Reactions of nitrones $R^1CH{=}N(R^2)O$ with singlet oxygen $^1O_2$ and molecular anion O_2^- were studied.[146] The intrinsic reaction coordinate was calculated and application of the virial theorem to the molecular system along the reaction pathway was considered. All processes, except for the interaction of $CH_2{=}NHO$ with O_2^-, occur with the formation of five-membered heterocyclic products. For the last-named reaction, attempts to locate such a product failed.

2. Ylides

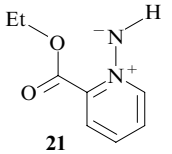
Ylides are a large class of 1,3-dipoles. Most of them belong to allyl-type dipoles (except nitrile ylides). Azomethine ylides $[R^1_2C{=}N(R^2)CR^3_2]$, carbonyl ylides and thiocarbonyl ylides ($R_2C{=}XCR_2$, X = O, S) have been best theoretically studied. Additionally, the behaviour of cyclic ylides **19** and **20** in the [3 + 2]-cycloaddition reactions was studied based on the results of the MO calculations of these dipoles.[147–149]



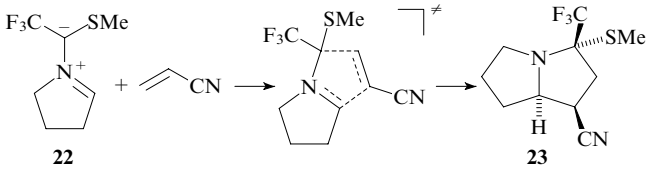
19 **20**

The reactions of ylides with dipolarophiles mainly belong to the NED processes.[86,87] Indeed, the cycloaddition of azomethine ylides to alkenes,[60,150,151] alkynes,[63,152] aldehydes,[153] imino alcohols,[154] as well as the cycloaddition of carbonyl ylides and thiocarbonyl ylides to alkenes,[155,156] aldehydes[157] and cyclopentenones[158] is governed by the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction. At the same time the reactions between *N*-arylazomethine ylides $R^1R^2C{=}N(Ar)CR^3R^4$ or carbonyl ylides $R^1R^2C{=}OCR^3R^4$ and dipolarophiles with electron-donating substituents represent IED processes.[86,87,159]

The mechanisms of ylide reactions are strongly dependent on the nature of the dipole and dipolarophile and on the character of substituents in the reactant molecules. For instance, the [3 + 2]-cycloaddition reactions of 2-ethoxycarbonylpyridinium *N*-aminide (**21**)[160] and cyclic azomethine ylide **22**[141] with acrylonitrile proceed by concerted asynchronous mechanism. The latter process shows regioselectivity and *endo*-stereoselectivity with preferred formation of isomer **23**, which agrees with experimental data, namely, the yield ratio of two *endo*-regioisomers is 24 : 1, whereas no *exo*-regioisomers were isolated.[161] The activation energy for this reaction pathway calculated relative to the total energy of reactants is negative (−9 kJ mol^{-1}, obtained from B3LYP/6-31G* calculations), being positive when calculated relative to the energy of the orientation complex (15 kJ mol^{-1}). Moreover, augmentation of the 6-31+G** basis set with diffuse functions leads to positive E_a values relative to the total energy of reactants (5 kJ mol^{-1}). Low activation barriers are confirmed by the fact that this reaction occurs at low temperature (−78 °C).[161] At the same time it was reported[162] that the addition of azomethine ylide ions $[CH_2{=}NCH_2]^-$ (and allyl and borallyl ions) to ethylene proceeds by stepwise mechanism, which is consistent with the results obtained by Sauers.[163]



21



22 **23**

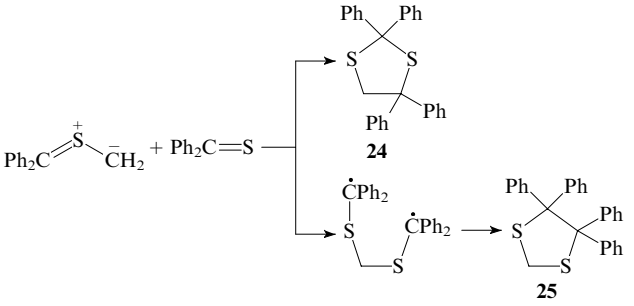
The substituent effects on the mechanisms of the reactions between ylides $R^1_2C{=}N(R^2)CHCHO$ and alkenes $CH_2{=}CHR^3$ were studied.[164] It was established that the reactions proceed by concerted mechanism at $R^1 = R^3 = H$ and R^2 = H, Li; by stepwise mechanism at R^1 = H, R^2 = Li, $R^3 = NO_2$ and R^1 = Ph, R^2 = H, $R^3 = NO_2$; and by an intermediate mechanism characterised by a synchronicity S_y of about 0.6 (for the reaction in acetonitrile) at $R^1 = R^2$ = H, $R^3 = NO_2$.

Butler *et al.*[165,166] analysed the effect of association of water clusters $(H_2O)_4$ and $(H_2O)_6$ with the dipolarophile molecule on the energy characteristics of the cycloaddition of azomethine ylides to alkenes. It was shown that taking into account the formation of such associates leads to considerable decrease in the Gibbs free activation energy (by 22–28 kJ mol^{-1}).

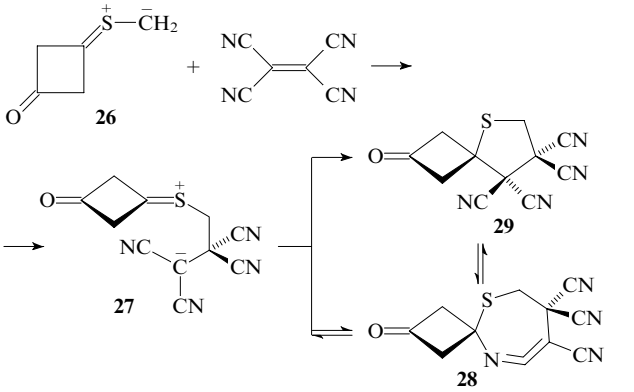
The mechanisms of the interaction of thiocarbonyl ylides $CR_2{=}SCH_2$ and thiocarbonyl imine $CH_2{=}SNH$ with symmetrical thioketones and ethylene were studied by the DFT, MCSCF, QCISD(T) and CBS methods.[85,167–169] Concerted cycloaddition was shown to be energetically more favourable than the stepwise mechanism. It is believed that the reaction of $CH_2{=}SCH_2$ with $CH_2{=}S$ proceeds barrierlessly, whereas the activation barriers to the other processes amount a few kcal mol^{-1}. At the same time the activation energies for concerted and stepwise mechanisms differ insignificantly; as a consequence, the possibility of the stepwise mechanism in the presence of substituents stabilising the biradical structure cannot be ruled out.

B3LYP/6-31G*//HF/3-21G* calculations[157] of the activation energy and energy change for the concerted mechanism of the [3 + 2]-cycloaddition of diphenylthiocarbonyl ylide $Ph_2C{=}SCH_2$ to thiobenzophenone $Ph_2C{=}S$ revealed kinetic and thermodynamic preference of the formation of regioisomer **24** (E_a = 27 and $\Delta E = -172$ kJ mol^{-1}). However, these results contradict experimental data, according to which product **25** is isolated in this reaction.[170] Further studies showed that the energetically most

favourable mechanism of this process is a stepwise mechanism with the formation of a *C*,*C*-biradical intermediate and regioisomer **25** as the end product. Thus, this reaction occurs under kinetic control.



A stepwise mechanism was also predicted for the reaction of thiocarbonyl ylide **26** with tetracyanoethylene.[171] The cycloaddition involves the formation of a zwitterionic intermediate **27**.



This species can undergo cyclisation to the seven-membered cyclic product **28** and to the thermodynamically most stable end product **29** (compounds **28** and **29** are in equilibrium). The energy profile of this reaction pathway is shown in Fig. 10. The activation energies for cyclisation of intermediate **27** to compounds **29** and **28** differ by 5 kJ mol^{-1}, which is in reasonable agreement with experimental data on the formation of compounds **28** (more correctly, corresponding *spiro*-lactim ether) and **29** in a 2 : 1 ratio;[172] hence, the process also occurs under kinetic control.

The regioselectivity of the reactions of azomethine ylides **30** with (*E*)-3-arylidene-4-chromanones **31** was studied[60] using the AM1 and PM3 semiempirical MO calculations. The results of calculations confirmed the experimental data on exclusive formation of product **32**. On the contrary, the FMO theory provides no explanation for the observed regioselectivity of dimerisation of thiocarbonyl ylide **33** ('head-to-head' addition pattern).[173]

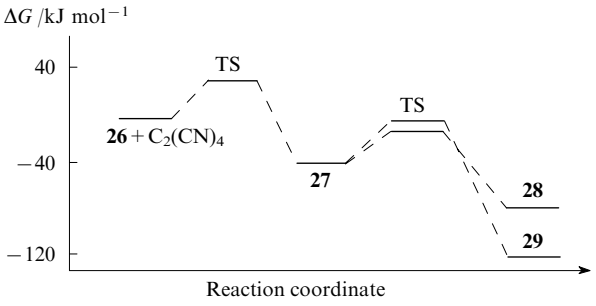
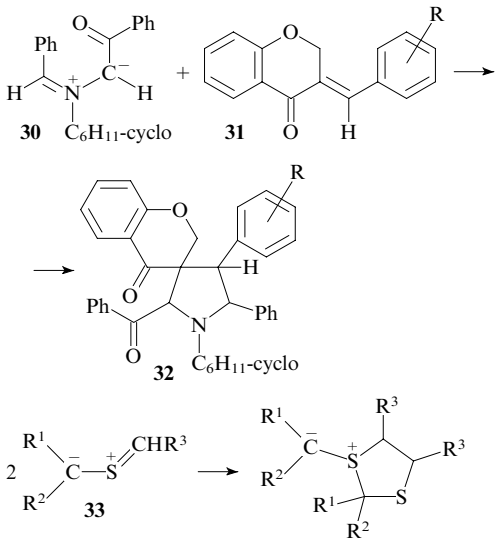


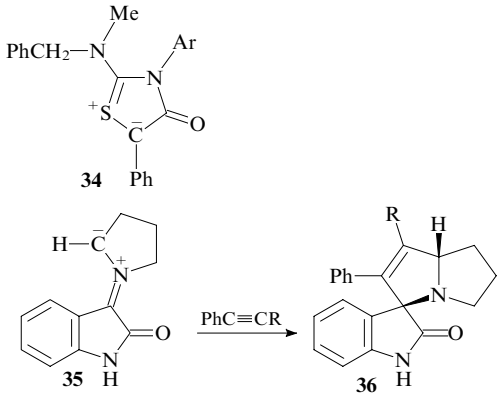
Figure 10. Energy profile of the reaction of thiocarbonyl ylide **26** with tetracyanoethylene.



R^1 = SMe, R^2 = SO_2Me, R^3 = $SiMe_3$.

It was concluded that in this case the regioselectivity is governed by charge control, *i.e.*, the carbon atom bearing the negative formal charge attacks the positively charged sulfur atom.

Theoretical studies of stereoselectivity were reported for the reactions of (i) isomunchnones and thioisomunchnones (*e.g.*, compound **34**) with alkenes[155, 174, 175] and alkynes,[176] (ii) azomethine ylides with olefins[177, 178] and maleimides[179, 180] and (iii) ylides **35** with phenylalkynes.[152] In the last-mentioned case the equilibrium transition-state geometry was only determined for one out of eight possible stereoisomers (compound **36**). This suggests a selective formation of this structure and was confirmed experimentally.

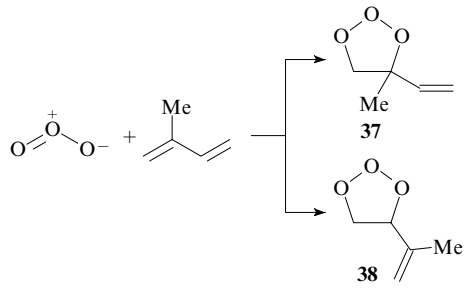


3. Ozone

The ozone molecule provides yet another example of allyl-type dipole, which can also undergo [3 + 2]-cycloaddition reactions. Analysis of the FMO energies showed that these reactions are governed by the $HOMO_{dipolarophile}$ – $LUMO_{ozone}$ interaction due to the low ozone LUMO and especially HOMO energies, thus being the IED processes. This reaction type remains unchanged even for the dipolarophiles containing electron-withdrawing substituents.[86, 87] Here, the reaction rate is appreciably lower than in the case of the cycloaddition to dipolarophiles with electron-donating groups due to larger energy difference between the corresponding MOs.

Ozonolysis of isoprene was studied theoretically.[74] It was shown that the process begins with dipolar [3 + 2]-cycloaddition. According to calculations, the reaction proceeds by concerted mechanism. The energy changes and activation energies for the reactions strongly depend on the approximation employed. For

instance, the DFT and MP2 methods give negative E_a values, thus suggesting a barrierless reaction; more accurate CCSD(T)/6-31G* calculations led to $E_a = 14$ kJ mol^{-1} for both reactions. This value is in agreement with experimental kinetic data for these processes (16–18 kJ mol^{-1}). Products **37** and **38** are similar in thermodynamic stability, the energy difference between them being 3 kJ mol^{-1}.

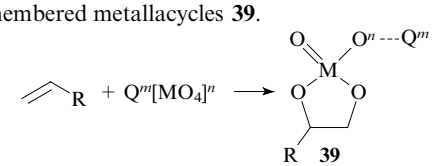


Similar results were also obtained for the ozone reactions with ethylene, benzene and phenol.[81] According to calculations, the reaction with ethylene proceeds most easily [$E_a = 14$, $\Delta E = -220$ kJ mol^{-1}, obtained from CCSD(T)/6-31G** computations], whereas the cycloaddition to benzene is characterised by much higher activation barrier and small energy change (66 and -79 kJ mol^{-1}, respectively). Ozonolysis of phenol occurs at positions 1 and 2 of the benzene ring with intermediate energies. The calculated energies are in reasonable agreement with experimental data. Namely, the E_a and ΔE values for the interaction $O_3 + CH_2{=}CH_2$ are respectively 21 and -188 ± 25 kJ mol^{-1} (Refs 181 and 182) and the activation energy E_a for the interaction $O_3 + C_6H_6$ is 61 kJ mol^{-1} (Ref. 183).

The kinetics and mechanism were studied for the ozone reactions with ethylene, fluoroethylene and chloroethylene[184] and with acetylene.[185,186] The activation parameters and rate constants for these reactions were estimated. The cycloaddition to haloalkenes should proceed 20 to 25 times slower than the reaction with unsubstituted ethylene [$E_a = 20$ kJ mol^{-1}; obtained from CASPT2(10.9)/cc-pVTZ calculations], whereas the reactivities of chloroethylene and fluoroethylene are comparable ($E_a = 23$ and 24 kJ mol^{-1}, respectively). The results of calculations were also confirmed by experimental data [*e.g.*, the calculated and experimental rate constants for cycloaddition to ethylene are 1.02×10^{-18} and $(1.75 \pm 0.52) \times 10^{-18}$ cm^3 (molecule s)$^{-1}$, respectively]. It is believed that the reaction with acetylene proceeds by concerted mechanism because no biradical intermediates were located on the potential energy surface.[185] The theoretical rate constant for this process is 0.8 litre (mol s)$^{-1}$ and $\Delta H^{\neq} = 31$ kJ mol^{-1} [obtained from CCSD(T)/CBS calculations]; the latter value is consistent with the experimental values obtained earlier (29.7 ± 4.2 kJ mol^{-1}).[187]

4. Metal oxides

There is a number of theoretical studies on the reactions of cycloaddition of the permanganate ion MnO_4^- (Refs 188–191), associates $Et_4N^+\cdots MnO_4^-$ (see Ref. 188), ruthenium oxide RuO_4 (Refs 192 and 193) and associates $NH_3\cdots RuO_4$ (Ref. 192) to alkenes $XC_6H_4CH{=}CH_2$ and $CH_2{=}CH_2$, which result in five-membered metallacycles **39**.



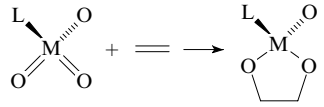
M = Mn: $n = 1-$, $m = 1$; Q = NEt_4; R = C_6H_4X (X = H, 4-Me, 4-Cl, 3-Cl, 3-Br, 3,4-Cl_2, 3-NO_2, 4-NO_2);
M = Ru: $n = m = 0$; Q = NH_3, R = H.

The effect of the substituent X on the energy characteristics of the reactions was studied and it was shown that the $\Delta G^{\neq}$ value decreases as follows for different X: 4-Me > H > 3-Br > 4-Cl > 3,4-Cl_2 > 3-Cl > 3-NO_2 > 4-NO_2. Good agreement between the theoretical and experimental activation parameters of the process was obtained (Table 2). For the reactions involving RuO_4 and MnO_4^- the [3 + 2]-cycloaddition processes were shown to be both thermodynamically and kinetically more favourable than [2 + 2]-cycloaddition.

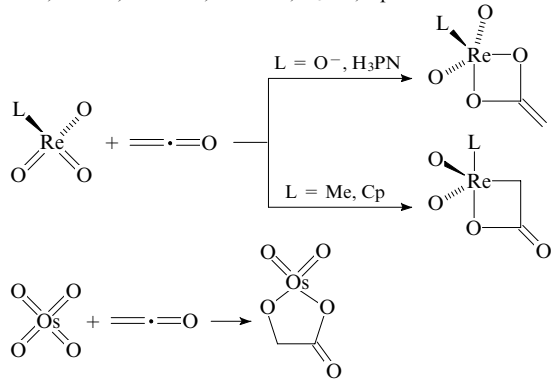
Table 2. Theoretical and experimental (in parentheses) activation parameters for the interaction of $Et_4N^+\cdots MnO_4^-$ with $XC_6H_4CH{=}CH_2$ (B3LYP/6-311 + G**//B3LYP/LanL2DZ calculations; geometry optimised with inclusion of Et_4N^+ counterion).[188]

X	$\Delta H^{\neq}$ /kJ mol^{-1}	$\Delta G^{\neq}$ /kJ mol^{-1}
4-Me	24 (20.3 ± 0.7)	79 (73.2)
H	21 (18.8 ± 1.5)	73 (72.7)
3-Br	18 (17.5 ± 1.1)	71 (70.7)
4-Cl	17 (15.9 ± 1.2)	69 (70.9)
3,4-Cl_2	14 (10.7 ± 0.7)	68 (69.9)
3-Cl	18 (18.0 ± 1.5)	67 (71.0)
3-NO_2	13 (11.4 ± 1.4)	61 (69.4)
4-NO_2	7 (15.6 ± 1.7)	58 (67.2)

The cycloaddition of OsO_4, MO_3^q and LMO_3^q [$q = 0$, 1−, 1; M = Mo, W, Mn, Tc, Re, Os; L = O, H_3PN, Cl, Me, η^5-C_5H_5 (Cp)] to olefins and ketene ($CH_2{=}C{=}O$) were studied.[193–200] The reactions of all compounds (except $MeReO_3$) with ethylene and the reaction of OsO_4 with ketene proceed by the [3 + 2]-cycloaddition mechanism, although the activation energies are high (59–197 kJ mol^{-1}). Other oxides react with ketene by the [2 + 2]-cycloaddition mechanism ($E_a = 46-92$ kJ mol^{-1}), ReO_4^- and $(H_3PN)ReO_3$ being added to the C=O bond and $MeReO_3$ and $CpReO_3$ being added to the C=C bond. The most recent data on the cycloaddition of metal oxides to the C=C double bond were summarised in a review by Deubel and Frenking.[201]



M = Os, L = O; M = Re, L = O^-, H_3PN, Cp.



V. Reactions of propargyl–allenyl type dipoles

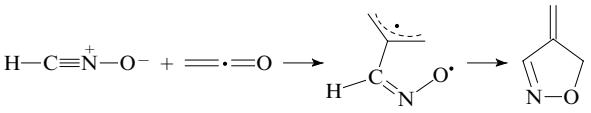
The propargyl–allenyl type dipoles include nitrile oxides, azides, diazoalkanes, nitrile ylides, nitrile imines and nitrous oxide (see Fig. 6).

1. Nitrile oxides

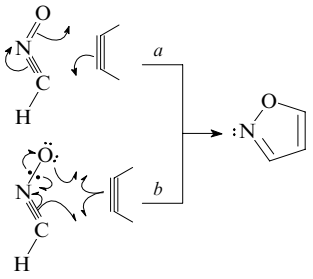
Following Sustmann's classification, reactions of cycloaddition of nitrile oxides $RC{\equiv}N^+{-}O^-$ are often treated as type III (IED) processes.[86,87] At the same time, carrying out reactions with electron-deficient dipolarophiles causes the reaction type to

change to the NED process due to a decrease in the dipolarophile LUMO energies.[92, 202, 203] For instance, the reactions of RCNO compounds with fluoroalkenes and fluoroalkynes [92] and halo- and cyano-substituted *p*-benzoquinones [202] are governed by the $HOMO_{dipole} - LUMO_{dipolarophile}$ interaction, their reactions with the methyl and methoxy derivatives of *p*-benzoquinone [202] and with 1,2,4-triazepine [204] are controlled by both types of the orbital interaction, while the addition of RCNO to dihydrofuranones belongs to the IED processes.[205]

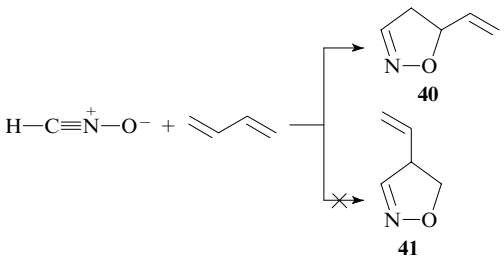
Most reactions involving nitrile oxides are assumed to proceed concertedly.[35, 99, 100, 104, 204, 206–211] Quantum-chemical calculations predicted a high synchronicity for, *e.g.*, the reactions of fulminic acid with ethylene and acetylene ($S_y = 0.79 - 0.81$ in the gas phase).[99, 100] The calculated activation barriers to the former process strongly depend on the approximation used. The results of MP4/6-31G*//HF/6-31G* calculations [35] ($E_a = 38$, $\Delta G^{+} = 74$ kJ mol^{-1}) are in good agreement with the experimentally determined ΔG^{+} value (84 kJ mol^{-1}) for the cycloaddition of PhCNO to $CH_2{=}CH_2$.[212] Various high-level calculations [B3LYP, MP2, CCSD(T), CASSCF, G2(CC)] of the interaction of HCNO with C_2H_2 give $E_a = 54 - 59$ kJ mol^{-1} (Ref. 213). This is consistent with the fact that alkynes are more inert than alkenes in the cycloaddition reactions with nitrile oxides.[214] These processes occur *via* planar aromatic transition states and the stabilising effect of π-aromaticity in them is insignificant. Similarly to nitrones, taking into account solvation effects causes an increase in the activation energy by 4–9 kJ mol^{-1} and a decrease in the synchronicity of the reaction. At the same time the energy of the transition state of the cycloaddition of fulminic acid to allene ($CH_2{=}C{=}CH_2$) following the biradical mechanism is 16 kJ mol^{-1} lower than the corresponding energy in the case of concerted mechanism.[105]



Some authors considered the reaction of fulminic acid with acetylene in terms of the valence bond approach.[215, 216] In particular, this reaction was treated [215] as proceeding by 'heterolytic' mechanism (*a*) *via* a non-aromatic transition state in contrast to the Diels–Alder reactions characterised by 'homolytic' mechanism and aromatic transition state.[217] Yet another version of the reaction mechanism, namely, pathway *b*, is also available.[216] Clearly, a correct determination of the mechanism of this reaction requires further investigations. This process was also studied using the catastrophe theory.[218]



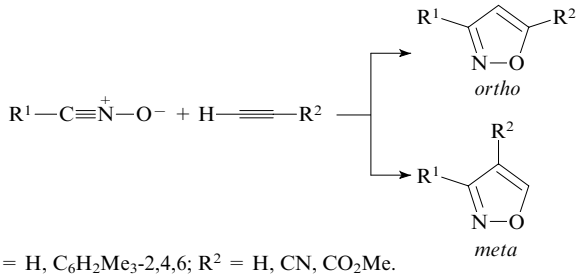
A number of studies are concerned with the regio- and stereoselectivity of the cycloaddition of nitrile oxides to buta-1,3-diene,[100] alkenes [35, 219–221] and fluoroalkenes,[222] acrylonitrile, methyl vinyl ether,[35, 223] cyclobutenes,[124, 224] dicyclopentadienes,[225] alkynes,[226–228] thionitroso compounds,[229] anthracene and acridine,[230] dihydrofuranones,[205] adamantane-2-thiones, 2-methyleneadamantanes,[231, 232] stilbenes [233] and 4-methylenetetrahydrothiopyran.[234] In the reaction with butadiene the activation energy for the formation of 5-vinylisoxazoline (**40**) is 14–15 kJ mol^{-1} lower than that needed for the formation of 4-vinyl-substituted product **41** both in the gas phase and in solution.[100] This agrees with experimental data on selective formation of compound **40** in the reaction of buta-1,3-diene with fulminic acid prepared *in situ*.[235] The aromaticity of the transition state does not determine the regioselectivity of the process. The cycloaddition to olefins, acrylonitrile and methyl vinyl ether shows regioselectivity with the formation of the *ortho*-isomers, which is also consistent with experimental facts.[236, 237] Enhancement of electron-donating ability of the substituent at the dipolarophile enhances the *ortho*-selectivity as in the reactions of nitrones.[34]



40

41

The regioselectivity of the cycloaddition of nitrile oxides to alkynes depends on both the nature of substituents in the dipole and dipolarophile molecules and on the solvent nature.[226, 228, 230] For instance, quantum-chemical computations of gas-phase interaction of fulminic acid with cyanoacetylene ($CH{\equiv}CCN$) predicted preferred formation of the *ortho*-isomer of isoxazole; on the contrary, the reaction of 2,4,6-trimethylbenzonitrile oxide (mesitonitrile oxide) with $CH{\equiv}CR$ (R = CN, CO_2Me) is expected to result in the *meta*-isomers (the activation energy difference, ΔE_a, between the *ortho*- and *meta*-pathways lies in the range 2–5 kJ mol^{-1}; obtained from B3LYP/6-31G* calculations).[226] A similar change in the regioselectivity depending on the substituent at the nitrile oxide was also experimentally observed for the reaction of RCNO with $CH{\equiv}CCO_2Me$ (ratio of *ortho*/*meta* isomers is 5.25 : 1 for R = H and 1 : 2.6 for R = 2,4,6-$Me_3C_6H_2$, see Refs 7, 10, 237). This can be interpreted as a result of enhancement of the nucleophilicity on going from HCNO to mesitonitrile oxide due to strong donor properties of the mesityl group. As a consequence the orbital coefficients on the oxygen atom increase and therefore the formation of the *meta*-isomer is facilitated (orbital coefficients at the unsubstituted carbon atom in the alkyne molecule are also larger than at the substituted carbon atom).



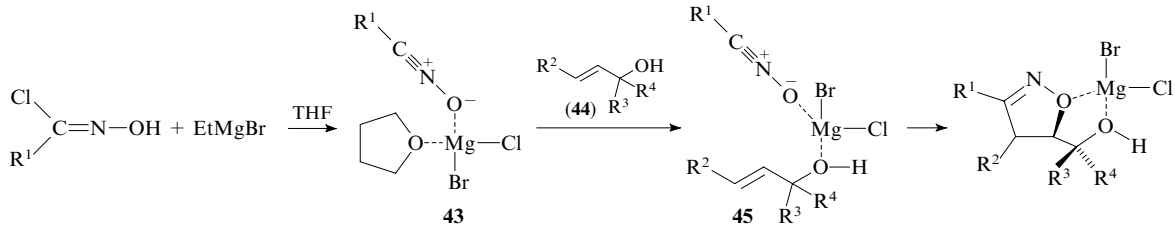
ortho

meta

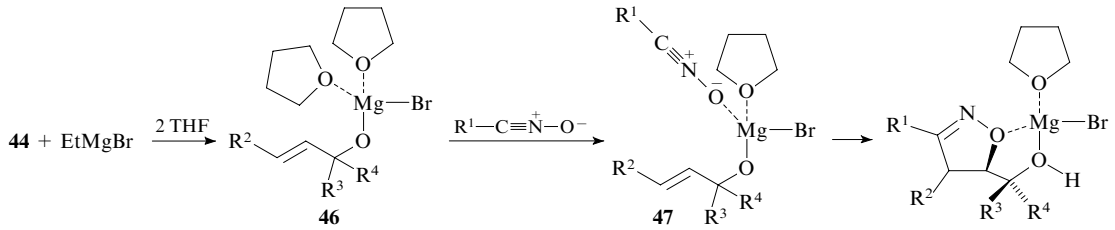
R^1 = H, $C_6H_2Me_3$-2,4,6; R^2 = H, CN, CO_2Me.

Solvation significantly facilitates the formation of the *ortho*-isomers (they should be the major products in high-polarity solvents, in particular, H_2O). This becomes understandable taking into account the fact that the TS of the reaction resulting in the *ortho*-isomer is characterised by a higher polarity than the TS on the pathway to the *meta*-isomer and therefore the former transition state is better stabilised in polar solvents. The theoretical ratio of the *ortho*- and *meta*-isomers in the reaction of mesitonitrile oxide with acrylonitrile in CCl_4 solution agrees with experimental data (2.3 : 1 and 1.3 : 1, respectively).[238] At the same time an increase in the solvent polarity causes an increase in the activation energies, which leads to inhibition of the process. DFT calculations of the reactions of benzonitrile oxide with ethynyl- and propynylboronates ($RC{\equiv}C\overline{B}OCH_2CH_2\overline{O}$) predict a change in the regioselectivity from the formation of the *ortho*-isomer

Scheme 4 *a*



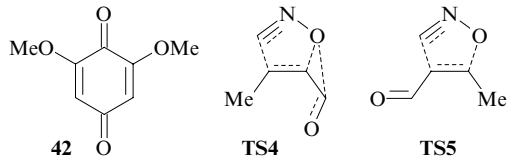
Scheme 4 *b*



R^1 = H, Ph; R^2 = R^3 = R^4 = H, Me.

(R = H) to *meta*-isomer (R = Me),[207] which is in agreement with experimental data.[239]

In some cases the chemo- and regioselectivity are influenced by the secondary orbital interaction. For instance, in the reaction of 2,4,6-trimethylbenzonitrile oxide with 2,6-dimethoxy-*p*-benzoquinone (**42**) the antibonding secondary orbital interaction between $HOMO_{quinone}$ and $LUMO_{dipole}$ is responsible for experimentally observed selective formation of the product of addition to the C=O rather than C=C bond.[240] The same effect governs a decrease in the regioselectivity of cycloaddition of fulminic acid to crotonaldehyde MeCH=CH−CHO.[241] Due to the secondary orbital interaction between the nitrile oxide oxygen AOs and the carbonyl carbon AOs in the transition state **TS4**, the energies of the structures **TS4** and **TS5** become similar (E_a = 57 and 55 kJ mol^{-1}, respectively; the calculated ratio of regioisomers is 2.2 : 1 and the experimentally determined ratio of the isomers for the reaction of PhCNO with MeCH=CH−CHO is 4.3 : 1).



The mechanisms and the regio- and stereoselectivity of the reactions of nitrile oxides with allyl alcohols controlled by magnesium ions were studied.[242,243] In particular, two reaction pathways were analysed. One of them (Scheme 4 *a*) leads to the formation of a magnesium complex with nitrile oxide and one THF molecule **43** due to the interaction of hydroxyiminoyl chloride R^1−C(Cl)=N−OH with EtMgBr in THF solution. Subsequent interaction between **43** and **44** yields complex **45** with both reactant molecules coordinated to magnesium. The second pathway (Scheme 4 *b*) begins with the formation of alkoxymagnesium complex **46** and then intermediate **47** containing coordinated nitrile oxide, alkoxide and THF molecules. Although the reaction between RCNO and compound **44** shows *ortho*-regioselectivity in the absence of Mg^{2+} (the activation energies for the formation of the *ortho*- and *meta*-isomers differ by 13 to 21 kJ mol^{-1}), the magnesium-controlled process (second pathway) results in exclusive formation of the *ortho*-isomer. This pathway is also kinetically more preferred. The coordination to magnesium also causes enhancement of the *syn*-stereoselectivity related to steric factors, but the activation energy changes insignificantly in this case.

The cycloaddition of benzonitrile oxides to alkenes CH_2=CHOC(O)R (**48**) and CH_2=C(Ac)OC(O)R (**49**) (R = 4-$NO_2C_6H_4$) was also described using the hard and soft acids and bases principle.[244,245] Consideration of the global–global interaction revealed that the term ΔE_v in Eqn (2) (see Section II) is much smaller than the term ΔE_μ at $\lambda = 1$ ($\Delta E_{int} = -4.83 - 209.75\lambda$ and $\Delta E_{int} = -6.37 - 217.30\lambda$ for the reactions with compounds **48** and **49**, respectively). Therefore, charge-transfer processes have little effect on the reactivities of compounds in the cycloaddition reactions of nitrile oxides.

The nucleophilic and electrophilic attack on the carbon and nitrogen atoms in the nitrile oxide molecule and on the double-bond carbon atoms in the alkene molecules were studied from the standpoint of local–global interactions. According to calculations, the energetically most favourable processes include the nucleophilic attack of alkene on the carbon atom in the dipole molecule and the electrophilic attack of the dipole on the terminal carbon atom in the alkene molecule. Thus, in accordance with experimental facts the hard and soft acids and bases principle correctly predicts the selective formation of the *ortho*-isomer.[246] The FMO theory gives incorrect results in this case.

The mechanism of reactions of acetonitrile oxide (MeCNO) with nitriles (see Scheme 3) and the reason for the activation of RCN in the platinum complexes **16** and **17** have been studied.[247] The activation of nitriles upon coordination was interpreted from the standpoint of orbital control as a result of a decrease in the nitrile LUMO energy. Indeed, if the reaction of free MeCN is described as an intermediate process [difference $\Delta\Delta E$ = $\Delta E(HOMO_{nitrile} - LUMO_{dipole}) - \Delta E(HOMO_{dipole} - LUMO_{nitrile})$ is 2.10 eV; obtained from B3LYP/6-31G* calculations], the cycloaddition to the nitrile complexes is more probably a NED process ($\Delta\Delta E$ = 3.70 and 5.06 eV for the reactions of complexes **16** and **17**, respectively).

The reactions proceed by concerted mechanism, but the asynchronicity appreciably increases on going from MeCN to complex **17**. The energies of the transition states and intermediates in the case of stepwise mechanism are 33–218 kJ mol^{-1} higher than the transition-state energies for the concerted mechanism. Calculations of the reactions of MeCNO with MeCN and complex **16** gave similar values of activation barriers (Table 3) in

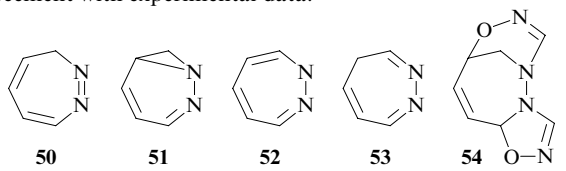
Table 3. Relative energy characteristics (in kJ mol^{-1}) of the cycloaddition of MeCNO to MeCN and to complexes **16** and **17** (obtained from B3LYP/6-31G* calculations; ECP on Pt atom).

Reactant	E_a	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔE	ΔH	ΔG
MeCN	59 (63)	60	109	−224 (−205)	−212	−154
16	51 (54)	51	108	−255 (−236)	−245	−169
17	24 (28)	22	94	−251 (−231)	−241	−157

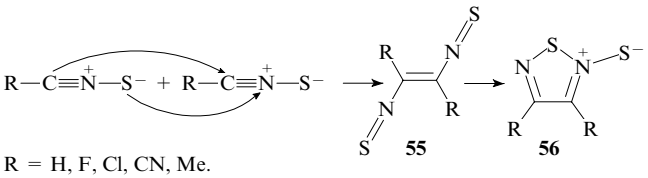
Note. All values are given relative to the total energy of the reactants. The values corrected for the zero-point vibrational energy are given in parentheses.

contrast to the results obtained for analogous reactions of nitrone $CH_2{=}N(Me)O$ characterised by considerable activation on going from MeCN to compound **16** (see Section IV.1.e).[72] The activation energy for the cycloaddition of nitrile oxides to complex **17** also decreases much smaller than in the case of cycloaddition of nitrones. Probably, this difference between the nitrone and nitrile oxide reaction kinetics is due to steric interaction of the methyl group in MeCNO with the platinum or chlorine atoms; this interaction is absent for $CH_2{=}N(Me)O$. Clearly, additional theoretical and experimental investigations are needed for solving this problem. The cycloaddition of MeCNO to compound **16** is characterised by large negative ΔG value. Thus, high reactivity of complex **17** is governed by kinetic factors, whereas the cycloaddition of nitrile oxides to compound **16** occurs under thermodynamic control. Interestingly, the reaction of radical cation $HCNO^{+\bullet}$ with HCN proceeds in a stepwise manner.[248]

Possible reactions of nitrile oxides with 1,2-diazepine were considered.[249] The dipolarophile can exist in two forms, **50** and **51**, whereas the formation of the other two forms (**52** and **53**) is kinetically unfavourable. Taking into account this fact, the thermodynamically most probable product of double cycloaddition of nitrile oxide to diazepine is compound **54**, which is in agreement with experimental data.[250]



Attempts to synthesise nitrile sulfides RCNS by thermolysis of 1,2,5-thiodiazoles were reported.[251] However, the reactions resulted in corresponding nitriles RCN and elemental sulfur instead of RCNS. To explain the experimental results, high-level quantum-chemical calculations [B3LYP, MPn, QCISD, QCISD(T), CCSD, CCSD(T)] of the decomposition mechanism of RCNS were carried out. It was shown that one of the key stages of the decomposition process is dimerisation of RCNS, which is in essence a reaction of dipolar [3 + 2]-cycloaddition in which one nitrile sulfide molecule acts as dipole and the other nitrile sulfide molecule plays the role of dipolarophile. The process proceeds by the stepwise mechanism and results in intermediate **55** (activation energy is 8 kJ mol^{-1}, obtained from B3LYP/6-31G** calculations). The low activation energy is due to low stability of RCNS in the condensed phase. With R = F or Cl, the activation barrier disappears, whereas for R = CN it increases to 53 kJ mol^{-1}. The reaction product, compound **56**, subsequently decomposes. Stepwise cycloaddition was also predicted for the dimerisation of nitrile oxides RCNO (R = Me, F).[252–255]



R = H, F, Cl, CN, Me.

2. Azides

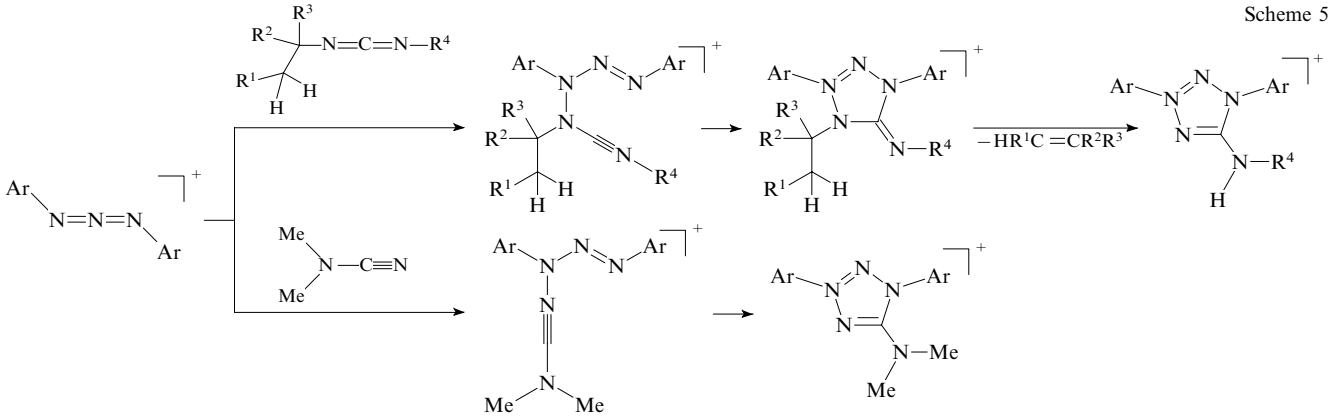
Another group of propargyl–allenyl type dipoles comprises hydrazoic acid derivatives RNN≡N. In the [3 + 2]-cycloaddition reactions involving these dipoles both types of orbital interaction, $HOMO_{dipole}-LUMO_{dipolarophile}$ and $HOMO_{dipolarophile}-LUMO_{dipole}$, often make similar contributions (type II processes according to Sustmann's classification).[86,87] Therefore, by varying substituents in the reactant molecules one can readily change the reaction type.[256,257] For instance, reactions of azides R^1N_3 (R^1 = H, Me) with alkenes $CH_2{=}CHR^2$ (R^2 = H, F, Cl, Me, OH) belong to the IED processes; however, if R^2 = CN (strong electron-withdrawing substituent), the reaction proceeds as the NED process. Reactions of azides with N_2, HCN, $CH_2{=}NH$, $NH{=}NH$, $CH_2{=}CH_2$, CH≡CH and vinylpyridine derivatives[258–260] also belong to the NED processes.

Calculations predicted a concerted mechanism for the [3 + 2]-cycloaddition of (i) methyl azide (MeN_3) to ethylene[261] and 1-nitropropene[262] and (ii) 1,3-diaza-2-azoniaallene cation $[ArN{=}N{=}NAr]^+$ to butyne.[263] Reactions of azide anion with some symmetrical molecules (N_2, *trans*-NH=NH, $CH_2{=}CH_2$, CH≡CH) are expected to proceed as synchronous processes; however, for *cis*-diazene (*cis*-NH=NH) high asynchronicity of the addition was predicted.[258] The calculated activation energy increases in the order: *trans*-NH=NH < HCN < CH≡CH < *cis*-NH=NH ≈ $CH_2{=}NH$ < $CH_2{=}CH_2$ ≪ N≡N, which is consistent with experimental data.[264] At the same time the interaction of $[ArN{=}N{=}NAr]^+$ with *N*,*N*-dimethylcyanamide ($Me_2N-C{\equiv}N$) and carbodiimides $R^1CH_2C(R^2R^3).N{=}C{=}NR^4$ is a stepwise process described by Scheme 5.[263]

As for other dipoles, the mechanism of cycloaddition of azides depends on the solvation effects and can be changed by varying the solvent. Baranski[265] showed that the interaction of MeN_3 with $MeCH{=}CHNO_2$ in the gas phase and in non-polar solvent (toluene) proceeds synchronously, whereas the reactions in polar solvents (acetonitrile, water) proceed by the stepwise mechanism because the polar acyclic intermediate is stabilised in solution. Noteworthy is that replacement of the solvent has no effect on the regioselectivity of the process.

The activation barrier to the reaction of methyl azide with ethylene decreases by 3 kJ mol^{-1} on going from non-polar (CCl_4) to dipolar aprotic solvent (dimethyl sulfoxide); this is accompa-

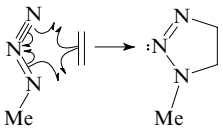
Scheme 5



R^1 = H, R^2 = Me; R^1-R^2 = $(CH_2)_4$; R^3 = H, Me; R^4 = Pr^i, Bu^t, cyclo-C_6H_{11}.

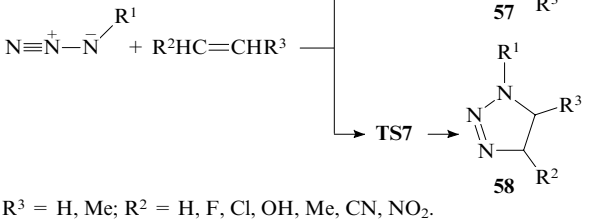
nied by a fourfold increase in the reaction rate.[261] Interestingly, the activation barriers calculated with inclusion of polar solvents (water and methanol) are higher than that obtained for CCl_4. Thus, the experimentally observed acceleration of the reaction of phenyl azide with norbornene in water can be explained by the hydrophobic effect rather than an incresase in the solvent polarity.

The mechanism of the reaction of methyl azide with ethylene was studied using the spin-coupled method of valence-bond theory.[80] The cycloaddition proceeds by the homolytic mechanism in contrast to the reactions of nitrile oxides and diazoalkanes that proceed by the heterolytic mechanism.[73, 215] The reaction is accompanied by synchronous cleavage of two π-bonds in the MeN_3 and C_2H_4 molecules, followed by formation of two new bonds. In the vicinity of the transition state the system behaves as a biradical structure.



The regioselectivity, mechanism and energy characteristics of the reactions of compounds R^1N_3 (R^1 = H, Me, NH_2) with alkenes $R^2CH{=}CHR^3$, thionitroso compounds (HN=S, $H_2NN{=}S$), nitriles and phosphaalkynes [RC≡N, RC≡P (R = H, Br, Cl, F, Me)] were studied using the DFT approach.[54, 229, 256, 262, 266] The calculated activation barriers to the reaction of hydrazoic acid with alkenes increase for different substituents R^2 as follows: CN < H < OH < F < Me < Cl; in the reaction of methyl azide the fluoroalkene becomes more reactive than vinyl alcohol. The reactions show regioselectivity and proceed with selective formation of isomer **57** (Scheme 6), except for the processes involving cyanoethylene and nitropropene that exhibit inverse regiospecificity, which leads to formation of compound **58**.

Scheme 6



R^1, R^3 = H, Me; R^2 = H, F, Cl, OH, Me, CN, NO_2.

The regioselectivity is related to the parameter

$$\Delta_{ij}^{kl} = \left(s_i^- - s_k^+\right)^2 + \left(s_j^- - s_l^+\right)^2,$$

where s are the local softnesses of the reacting atoms. This quantity is a criterion for validity of the hard and soft acids and bases principle. The Δ_{ij}^{kl} is smaller for *ortho*-cycloaddition at R^2 = H, F, Cl, Me, OH and for *meta*-cycloaddition at R^2 = CN.[256]

Molteni and Ponti [52] studied the dependences of regioselectivity of the process and the interaction energy at constant external potential ΔE_v [see Eqn (3)] taking the reaction of 4-$RC_6H_4N_3$ with HC≡CCO_2Me as an example. Based on a linear relationship between ΔE_a and

$$\Delta\Delta E_v = [\Delta E_v(i{-}k) + \Delta E_v(j{-}l)] - [\Delta E_v(i{-}l) + \Delta E_v(j{-}k)]$$

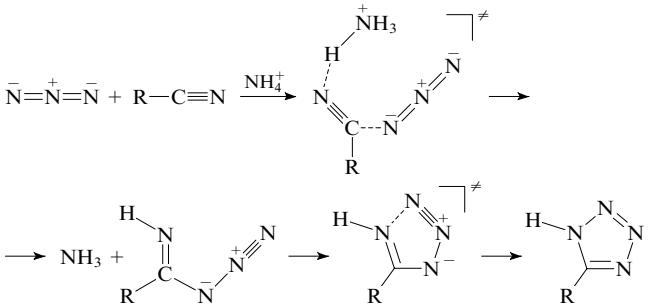
(ΔE_a is the difference between the activation energies for two regioisomeric reaction pathways, ΔE_v are the energies of the local–local interaction of the corresponding reaction centres i, j, k, l), one can assess the regioselectivity without locating transition states on the potential energy surface only using the global and local properties of the reactant molecules.

The energy (E_{int}) of the interaction between reactant molecules R^1N_3 and $CH_2{=}CHR^2$ in the transition states was calculated [266] as the sum

$$E_{int} = E_{def} + E_{es} + E_p + E_{ex} + E_{ct},$$

where the terms in the right side of the equation denote the deformation, electrostatic, polarisation, exchange and charge-transfer energy, respectively. The deformation energy makes the major contribution to E_{int}. The charge-transfer energy is sensitive to the nature of substituents R^1 and R^2, namely, it is maximum at R^2 = F, Me, OH, but is not responsible for regioselectivity. Inversion of the regioselectivity, which was found in the reaction of cyanoethylene (see above), can be explained by high polarisation energy for **TS7** and high deformation energy for **TS6** (see Scheme 6), whereas for other substituents the *ortho*-selectivity is controlled by the electrostatic component.

Reactions of azides with organonitriles (RCN) were studied more thoroughly than similar reactions of nitrones and nitrile oxides.[267–272] It was shown [267] that concerted mechanism is energetically most favourable for the cycloaddition of methyl azide and azide ion to non-activated nitriles. However, in the presence of acid catalyst (ammonium ion or some other proton donor) the reaction mechanism changes and the process proceeds in stepwise manner through transfer of a proton from NH_4^+ ion to the nitrogen atom of RCN with the formation of acyclic intermediate.



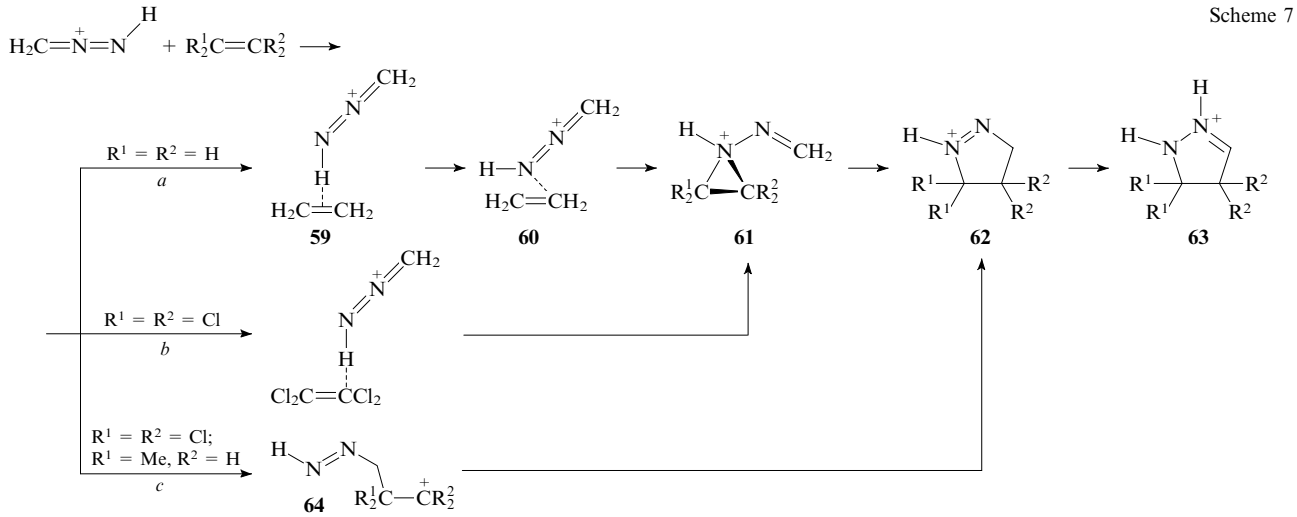
A similar change from concerted to stepwise mechanism and a considerable decrease in the activation barrier was also found for the BF_3- and BH_3-catalysed reactions of N_3^- with RCN.[268, 269] At the same time, B3LYP/6-31G** calculations gave a high activation barrier ($\Delta G^{\neq}$ = 275 kJ mol^{-1}) to the reaction of nickel azide complex $[Ni(\eta^1\text{-}N_3)]^+$ with nitrogen, which is not surprising with allowance for high inertness of N_2.[270]

It was shown that coordination of the azide ion to zinc in complex $[Zn(H_2O)_nN_3]^+$ (n = 3, 5) has little effect on the activation barrier of the reaction with acetonitrile compared to the thermally activated process [$\Delta H^{\neq}$ = 141 kJ mol^{-1} at n = 3 and 149 kJ mol^{-1} at n = 5; 132 kJ mol^{-1} for reaction MeN_3 + MeCN and 141 kJ mol^{-1} for reaction N_3^- + MeCN; obtained from B3LYP/6-311+G(2d,2p)//B3LYP/6-311G** calculations].[271] When nitrile or both reactants are coordinated to zinc, the enthalpy of activation decreases by 8–36 kJ mol^{-1}. Thus, the catalytic acceleration of the reaction is due to complexation of dipolarophile, which is consistent with the results of qualitative FMO analysis (see Section II) and makes it possible to treat this reaction as a NED process. The activation of nitriles upon coordination to the Lewis acid in the [3+2]-cycloaddition reactions with azides was confirmed experimentally. In particular, a decrease in $\Delta G^{\neq}$ on going from thermally induced to zinc-catalysed reaction of NaN_3 with 2-cyanopyrazine is 23.8 kJ mol^{-1} (Ref. 271).

3. Diazoalkanes, nitrile imines and nitrile ylides

Diazoalkanes ($R_2C{-}N{\equiv}N$), nitrile imines (RC≡N–NR) and nitrile ylides (RC≡N–CR_2) also belong to propargyl–allenyl type dipoles. The [3+2]-cycloaddition reactions involving these

Scheme 7



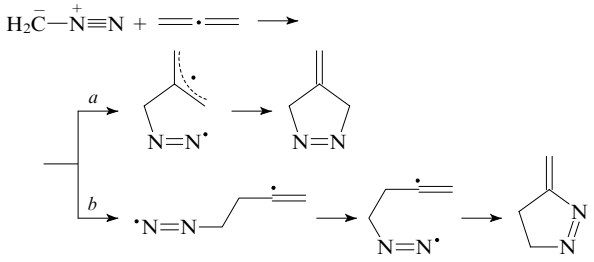
compounds result in such heterocyclic compounds, as pyrazolines and oxadiazolines. Since the LUMO energies in the diazoalkane and nitrile ylide molecules are high and, as a consequence, the $HOMO_{dipolarophile} - LUMO_{dipole}$ interaction becomes ineffective, these reactions should be treated as type I (NED) processes,[86, 87, 273–275] This particularly concerns the reactions with electron-deficient dipolarophiles (*e.g.*, acrylonitrile [35] or imidoyl chlorides [276]). The reactions of compounds R_2CN_2 with propylene and methyl vinyl ether and those of nitrile imines with unsubstituted alkenes are controlled by both types of the HOMO – LUMO interaction,[35, 86, 87] while the cycloaddition of nitrile imines to *N*-methylindole is an IED process.[277]

A number of studies on the mechanism of the [3 + 2]-cycloaddition reactions of these dipoles are available. An unexpected mechanism was calculated for the cycloaddition of 1-aza-2-azoniaallenyl ion ($CH_2{=}\overset{+}{N}{=}NH \leftrightarrow CH_2{-}\overset{+}{N}{\equiv}NH$), which can be treated as a diazomethane derivative, with alkenes [278] and carbodiimides $R^1N{=}C{=}NR^2$ (Ref. 279). The reaction with ethylene proceeds by the stepwise mechanism and begins with the formation of two orientation complexes **59** and **60** (pathway *a*, Scheme 7). This is followed by the formation of the three-membered intermediate **61**, which is transformed to pyrazolinium cation **62** and then to the end product **63**. The replacement of two hydrogen atoms in the ethylene molecule by methyl groups causes a change in the mechanism and now the reaction begins with the formation of acyclic intermediate **64** (pathway *c*). Finally, both pathways, *b* and *c*, are probable in the reaction with tetrachloroethylene. At the same time the addition of $R^1_2C{=}\overset{+}{N}{=}NR^2$ to ethynes $RC{\equiv}CR$ (Ref. 280) or to the CN bond of isocyanates RNCO (Ref. 281) proceeds concertedly, although being asynchronous.

Different regioisomeric pathways of the reactions of diazomethane with allenes [105] are characterised by different mechanisms. For instance, the energetically most favourable mechanism of the addition of the terminal nitrogen atom in CH_2N_2 molecule to a terminal atom of $CH_2{=}C{=}CH_2$ molecule involves the formation of one intermediate (pathway *a*, Scheme 8). The addition of the nitrogen atom of diazomethane to the central atom of allene molecule proceeds *via* two intermediates (pathway *b*). Comparison of the activation barriers to the two regioisomeric pathways, *a* and *b*, showed that the former is 13 kJ mol^{-1} energetically more favourable than the latter. This was confirmed by experimental data on selective formation of the corresponding regioisomer.[282] Interestingly, the activation barrier is much higher for the concerted rather than stepwise mechanism.

The effect of the nature of substituents in the dipolarophile molecules on the energy characteristics of the reactions of $HC{\equiv}NCH_2$ with compounds $CH_2{=}CR_2$ (R = NO, CN, Cl, OH, Me) was studied.[283] In accordance with predictions of the

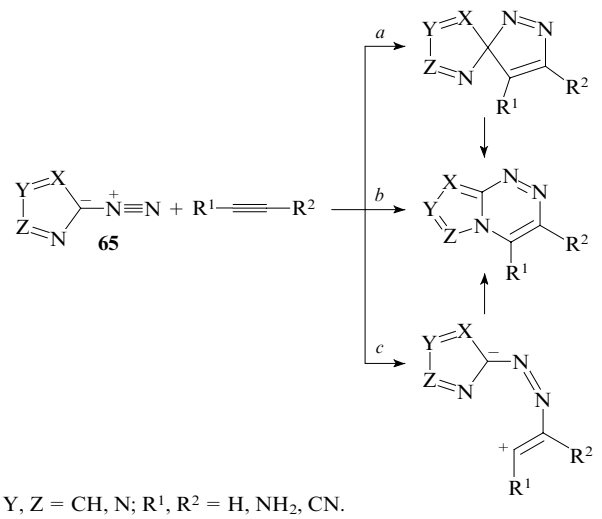
Scheme 8



FMO theory, the electron-withdrawing substituents (NO, CN) should accelerate the NED processes, which was confirmed by activation energy calculations. By and large the synchronicity of cycloaddition changes in parallel with the activation energy and antiparallel with the acceptor properties of substituents. The lower activation barriers to most asynchronous processes seem to be due to a strong effect of the charge factor.

By varying substituents in the reaction of cyclic diazoalkane **65** with ethynes one can change the mechanism of the process. In particular, the first stage of the reaction with acetylene proceeds as either a [3 + 2] or [7 + 2] concerted addition with similar activation barriers [284] (pathways *a* and *b* in Scheme 9). The reaction with ynamine $HC{\equiv}CNH_2$ most probably proceeds as a single-stage stepwise [7 + 2]-cycloaddition (pathway *c*). No transition states were located for the reaction with cyanoacetylene. Taking into

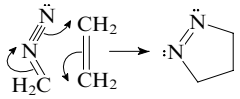
Scheme 9



X, Y, Z = CH, N; R^1, R^2 = H, NH_2, CN.

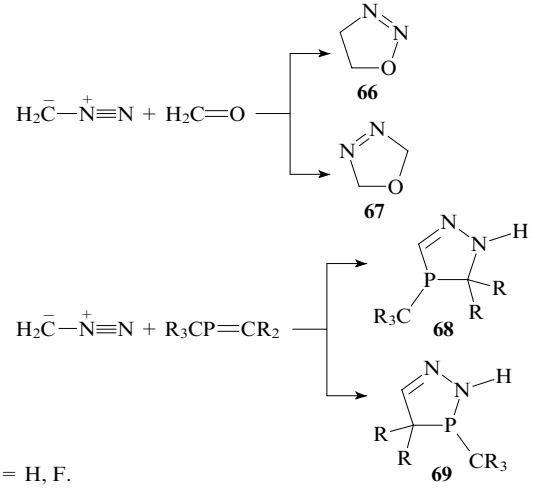
account this fact, it was concluded that no [3 + 2]-cycloaddition reactions of diazoazoles with cyanoacetylene should occur, which is indirectly confirmed by the lack of experimental data on these processes. However, unambiguous solution to this problem requires additional experimental and theoretical investigations of the cycloaddition to cyanoalkynes.

The interaction of diazomethane with ethylene was studied [73] using the spin-coupled method of valence-bond theory. It was shown that the reaction proceeds by the 'heterolytic' mechanism similar to that of the cycloaddition of fulminic acid to acetylene (see Section V.1).



A number of theoretical studies has been carried out on the regioselectivity of the reactions of (i) diazomethane with alkenes,[35] alkynes and phosphaalkynes,[54,285] formaldehyde,[286] phosphapropenes [287] and indenone,[274] (ii) nitrile imines with fluorinated alkenes and alkynes,[288] methyl propiolate,[289] (arylsulfonyl)allenes,[290] methylidene-butyrolactone derivatives [291] and pyridazinones [292] and (iii) nitrile ylides with benzaldehyde and imidoyl chloride.[276] For instance, calculations for the addition of CH_2N_2 to alkenes $CH_2{=}CHR$ (R = H, Me, CN, OMe) predicted preferred formation of 3-substituted pyrazolines (*ortho*-isomer) both in the gas phase and in solution (with allowance for solvation effects).[35] The relative yields of the *ortho*- and *meta*-isomers and the $\Delta G^{\neq}$ values for the *ortho*-pathway (7.5 : 1 and 96 kJ mol^{-1}, respectively, for the reaction of CH_2N_2 with $CH_2{=}CHMe$; obtained from MP4//HF/6-31G* calculations; solvation effects were included for solution in CCl_4) agree with the corresponding experimental data (7.3 : 1 for the reaction of CH_2N_2 with propene [293] and 103.3 kJ mol^{-1} for the reaction of CH_2N_2 with hex-1-ene [35]).

The reaction of diazomethane with formaldehyde results in oxirane as the end product. The reaction mechanism, which involves the formation of oxadiazoline as intermediate, was studied theoretically. The process occurs concertedly and yields 1,2,3-oxadiazoline (**66**) as kinetic product in the first stage; however, the other regioisomer, namely, 1,3,4-oxadiazoline (**67**) is thermodynamically more stable.[286] Nevertheless, no oxadiazoline intermediates of these reactions were isolated so far and therefore substantiation of theoretical conclusions requires additional experimental studies.



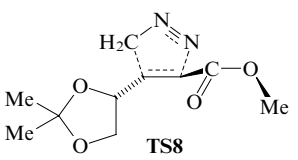
R = H, F.

Calculations for the interaction of CH_2N_2 with phosphapropene $MeP{=}CH_2$ showed that 1,2,4-diazaphosphole (**68**) is kinetically most favourable while 1,2,3-diazaphosphole (**69**) is thermodynamically most stable.[287] The reverse was found for the reaction with perfluorophosphapropene $F_3CP{=}CF_2$. Thus, experimental isolation of regioisomer **69** in the latter case indicates that the process proceeds under kinetic control.

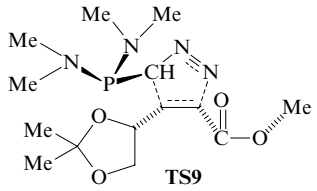
The stereoselectivity of the model reactions of diazomethane and bis(dimethylamino)phosphinodiazomethane [$(Me_2N)_2P.CHN_2$] with chiral alkenes was studied using the density functional theory (with BPW91 functional).[294] It was shown that stereoselectivity depends on the nature of the substituents both in the alkene and in the dipole molecules. For the reaction of diazomethane with dioxolanyl-substituted alkene, the *syn*-cycloaddition was the kinetically most preferable pathway (ratio of the *syn*- and *anti*-isomers is 96 : 1) and the *E*-isomer of the olefin was more reactive than its *Z*-isomer (**TS8** is the corresponding transition state). On the contary, the reaction of $(Me_2N)_2PCHN_2$ is characterised by the *Z-syn*-addition (**TS9**) (ratio of the *syn*- and *anti*-isomers is 518 : 1) and the reaction of CH_2N_2 with cyclobutyl-substituted alkene shows the *E-anti*-selectivity (**TS10**) (ratio of the *syn*- and *anti*-isomers is 1 : 8). The theoretical stereoselectivity qualitatively agrees with experimental data, namely, the ratios of the *syn*- and *anti*-isomers were 24 : 1, 16 : 1 and 1 : > 49 for the reactions of CH_2N_2 with (*E*)-$OCMe_2OCH_2CHCH{=}CHCO_2Me$, $(Pr^i_2N)_2PCHN_2$ with (*Z*)-$OCMe_2OCH_2CHCH{=}CHCO_2Me$ and CH_2N_2 with (*E*)-$OCH_2CH_2OC(Me)CHCH_2CH\{CH{=}CHCO_2Me\}CMe_2$.[294,295] respectively. In spite of some overestimation of the theoretical relative yields of the *syn*-isomers compared to the experimental data, the difference between the calculated and experimental (determined from the ratio of isomers) values

$$|\Delta\Delta G^{\neq}| = |\Delta G^{\neq}(syn) - \Delta G^{\neq}(anti)|$$

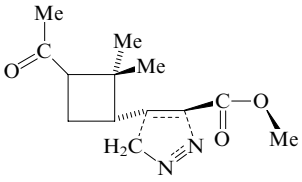
is only 3–9 kJ mol^{-1}, which is quite reasonable for the method employed.



TS8

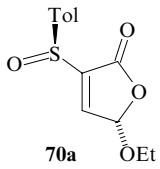


TS9

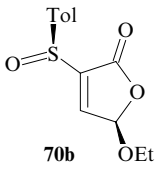


TS10

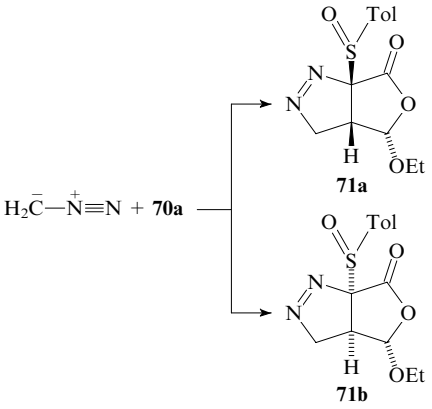
The stereoselectivity of the reactions of diazoalkanes with chiral furanones **70** depends on the stereoconfiguration of the dipolarophile.[296] Namely, in the case of the (5*S*,*SS*) configuration (compound **70a**) the activation barrier to formation of the *syn*-isomer **71a** is 14 kJ mol^{-1} lower than the barrier to formation of the corresponding *anti*-isomer **71b** (obtained from B3LYP/cc-pVTZ//B3LYP/6-31G* calculations). At the same time for the (5*R*,*SS*) configuration (compound **70b**) the stereoselectivity changes, which is consistent with experimental data. The stereoselectivity of the reaction of CH_2N_2 with oxazolone containing an acyclic double bond C=C was interpreted [297] based on the results of AM1 and HF calculations.



70a



70b



4. Nitrous oxide

The cycloaddition of N_2O to alkynes was studied.[298] The process is controlled by the $HOMO_{dipolarophile} - LUMO_{dipole}$ interaction, which is typical of this dipole.[86, 87] Investigation of the regioselectivity showed that in the reactions with mono-substituted alkynes HC≡CR (R = Me, Hal, OH, NH_2, PH_2, SH, SiH_3, CO_2H, CHO) the oxygen atom of the nitrous oxide molecule adds to the carbon atom bonded to the substituent R (the exception is $R = NO_2$; here the inverse regioselectivity was found). In the reacions with disubstituted alkynes MeC≡CR (R = CHO, NO_2) the oxygen atom adds to the carbon atom bonded to the methyl group.

VI. Reactions of heterocumulenes

Compounds that are usually not treated as dipolar structures can also be included in the [3 + 2]-cycloaddition reactions. These are, in particular, heterocumulenes, *i.e.*, compounds with triatomic reactive fragments in which the central atom (most often, a carbon atom) forms the double bonds with adjacent atoms and the contributions of other possible boundary structures are small.

Concerted cycloaddition of heterocumulenes CX_2, CSY, CY_2 (X = O, S, Se; Y = NH, PH) to acetylene is characterised by the following order of changes in the activation energies: O > S > Se (from 259 to 113 kJ mol^{-1} according to B3LYP/6-311+G** calculations) and NH > PH (from 152 to 107 kJ mol^{-1}) and the energy effects of the reactions change as follows: O > S ≈ Se (from 148 to −7 kJ mol^{-1}) and PH > NH (from −54 to −134 kJ mol^{-1}) (Table 4).[299] This is in qualitative agreement with the experimental data on higher reactivity of CSe_2 compared to that of CS_2 in the [3 + 2]-cycloaddition reactions. According to G3X(MP2) and B3LYP/6-311+G(3df) calculations, thermal decomposition of S_2O‡ begins with an exothermic or a weak endothermic (depending on the computational method employed) low-barrier [3 + 2]-cyclodimerisation [$\Delta H^{\neq}$ = 11 kJ mol^{-1}, obtained from G3X(MP2) calculations] with the formation of a five-membered product OSSSS=O, which then decomposes to S_3 and SO_2.[300, 301]

Mass spectrometric and theoretical studies[302, 303] concerned the mechanisms of the reactions of nitronium NO_2^+ and dithionitronium NS_2^+ ions with ethylene and acetylene, which result in O-nitrosated compounds $[CH_2{=}C{=}O\cdots NO]^+$, $[MeCHONO]^+$ and 1,4-dithia-7-azabicyclo[2.2.1]heptyl cations. Both reactions begin with concerted [3 + 2]-cycloaddition resulting in 1,3,2-dioxazol-2-yl-, 1,3,2-dioxazolidinyl- or 1,3,2-dithiazolidinyl cations as intermediate products. The cycloadduct of NO_2^+ with acetylene is aromatic in character, being therefore thermodynamically more stable that the product of addition to ethylene.

‡This compound is sometimes treated as a boundary structure S=S$^+$−O$^-$, *i.e.*, as an analogue of ozone. In this case the corresponding reactions can be considered as dipolar [3 + 2]-cycloadditions.

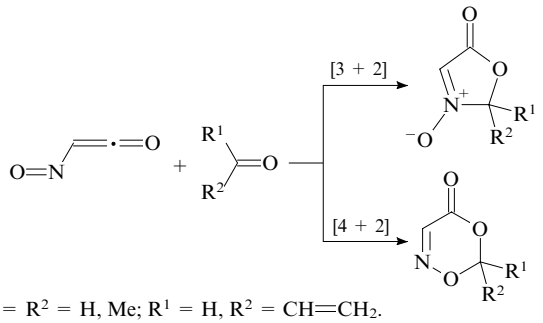
Table 4. Activation and reaction energies (kJ mol^{-1}) for heterocumulene reactions with C_2H_2 (obtained from B3LYP/6-311 + G** calculations).[299]

Reactant	E_a	ΔE
CO_2	259	148
CS_2	134	8
CSe_2	113	−7
S=C=NH	140	−68
S=C=NMe	142	−63
S=C=NPh	149	−44
$C(NH)_2$	152	−134
$C(NMe)_2$	140	−154
$C(NF_3)_2$	140	−118
$C(PH)_2$	107	−54

The mechanism of radical [3 + 2]-cycloaddition of NCO to acetylene derivatives HC≡CR (R = H, F, Cl, CN, Me) was studied.[53] All reactions, except that with R = CN, are controlled by the $HOMO_{alkyne} - LUMO_{NCO}$ interaction, show regioselectivity and proceed by the stepwise mechanism with the formation of acyclic intermediates OCNCH=CR (R = Cl, CN, Me) or OCNC(R)=CH (R = F). The activation barrier increases in the following order of substituents: F < Cl < CN < Me < H. The regioselectivity was interpreted from the standpoint of the hard and soft acids and bases principle by comparing the Fukui radical functions on the reactive atoms (maximum f^0 and, hence, s^0 values were obtained for the unsubstituted carbon atom in the alkyne molecule).

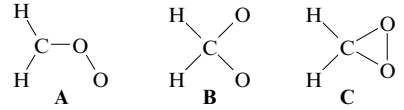
VII. Other reactions

The cycloaddition of nitrosoketene O=N−CH=C=O to formaldehyde, acetone and acrolein was described by the *ab initio* methods HF/6-31G* (Ref. 304), MP2/6-31G* and MP4(SDQ)/6-31G*//MP2/6-31G* (Ref. 75). The [3 + 2]-cycloaddition is kinetically more favourable than its alternative, [4 + 2]-cycloaddition; however, the six-membered reaction product is thermodynamically more stable than the five-membered product. Thus, experimental isolation of the five-membered cyclic product of this reaction[305, 306] indicates that the process occurs under kinetic control. The reaction proceeds concertedly and involves the formation of a planar pseudopericyclic transition state.



$R^1 = R^2 = H$, Me; $R^1 = H$, $R^2 = CH{=}CH_2$.

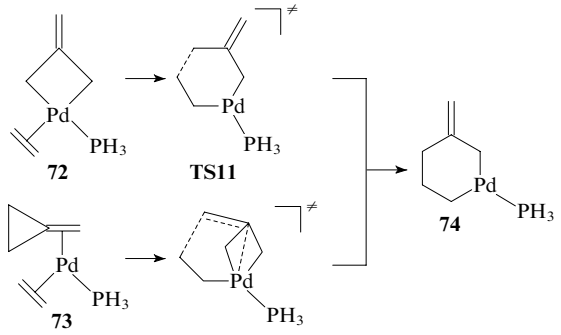
According to the results of high-level *ab initio* calculations, carbonyl oxide (**A**) and methylenebis(oxy) (**B**) react with ethylene to give 1,2-dioxolane and 1,3-dioxolane, respectively, and dioxirane (**C**) enters into the reaction of ethylene epoxidation.[307]



Some of these results were experimentally confirmed by Reiser *et al.*[308] and Graziano *et al.*[309] who observed the formation of 1,2-dioxolanes in the reactions of carbonyl oxides with alkenes.

Studies [310, 311] of the [3 + 2]-cycloaddition of NO_3 radical to alkenes showed that in the first stage the concerted cycloaddition resulting in the five-membered intermediate is energetically more preferable than the addition of alkene to one oxygen atom of NO_3 reported earlier.

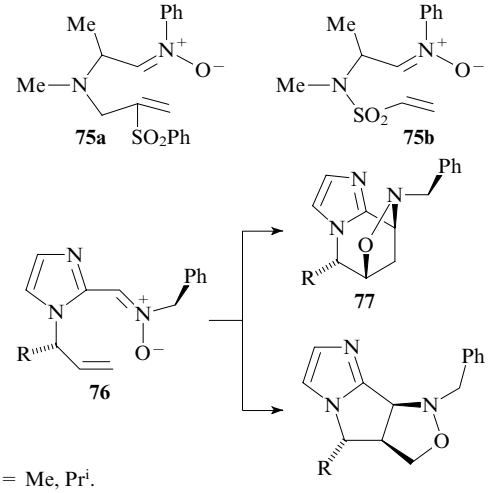
The mechanism of a palladium-catalysed reaction of methylenecyclopropane with ethylene was studied by high-level MP4(SDQ)/BS2//MP2/BS1 and B3LYP/BS2//B3LYP/BS1 calculations.[312, 313] The concerted mechanism is kinetically unfavourable (E_a = 186 kJ mol^{-1}) and the interaction between the palladium-coordinated reactants proceeds in a stepwise manner. Two mechanisms were considered, one involving an intermediate palladacyclobutane structure **72** and the other passing *via* η^2-methylenecyclopropane complex **73**. Intermediate **73** is thermodynamically more stable than compound **72**. However, the addition of coordinated ethylene molecule to the palladacyclobutane fragment in compound **72** with the formation of methylenepalladacyclohexane **74** *via* transition state **TS11** followed by reductive elimination of methylenecyclopentane in the last stage is kinetically more preferable.[313] Interestingly, similar reactions of oxo- or azatrimethylenemethane with ethylene proceed by the [2 + 1] mechanism. This change in the cycloaddition mechanism depending on the nature of the reactants is consistent with experimental data.[314–317]



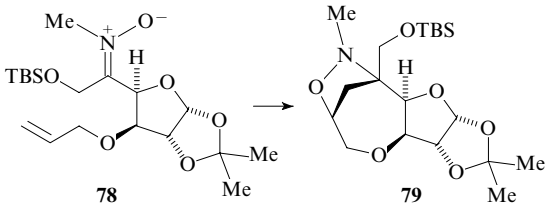
VIII. Intramolecular cycloaddition reactions

In addition to intermolecular cycloaddition, intramolecular cycloaddition reactions may also occur. Here, the reacting molecules or fragments are not isolated, being constituents of the entire molecular system that affects (sometimes, strongly affects) the course of these reactions. In this review, the cyclisation reactions with the formation of only one new bond upon ring closure are left out of consideration, because these processes do not belong to the cycloaddition reactions.

The regioselectivity [318] and stereoselectivity [319] of intramolecular cycloaddition reactions of nitrones **75a**,**b** and **76** were considered based on the results of semiempirical and *ab initio* calculations. The reaction of methyl derivative **76** results in isomer **77** as the kinetically and thermodynamically favourable product. Calculations [318] predicted a lower regioselectivity of the reaction with R = Pr^i, which is consistent with experimental data. Calculations using the ONIOM(B3LYP/6-31(d) : AM1) hybrid method followed by single-point B3LYP/6-31* energy calculations for the reaction of ketofuranonitrone **78** made it possible to interpret the experimentally observed selective formation of isomer **79**.[320]

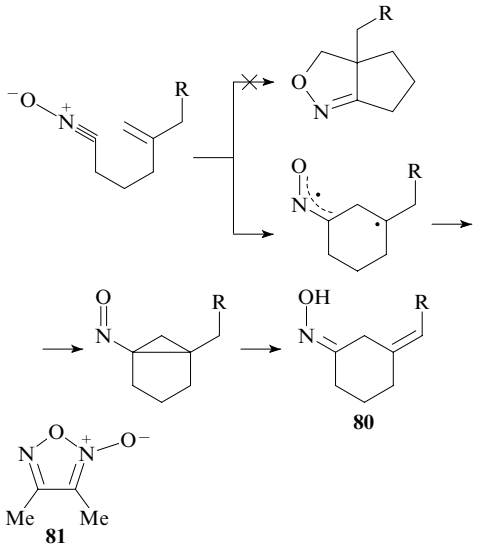


R = Me, Pr^i.



TBS is *tert*-butyldimethylsilyl.

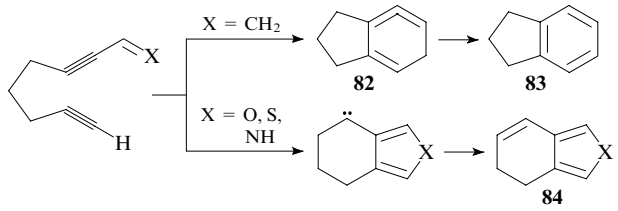
Intramolecular interactions between nitrile oxide and alkene fragments (including intramolecular cycloaddition) have been studied in detail.[321] If the initial molecule contains R = $SiMe_3$, the reaction proceeds by the mechanism leading to compound **80** as the end product instead of intramolecular [3 + 2]-cycloaddition. Replacement of trimethylsilyl group by hydrogen atom makes the [3 + 2]-dimerisation of the nitrile oxide fragments resulting in furoxan structure **81** the most favourable.



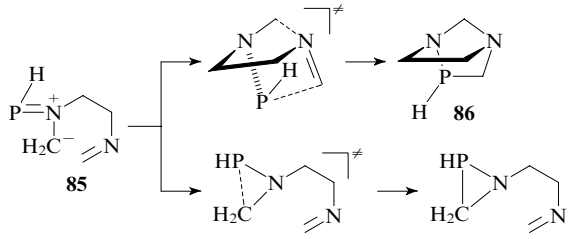
Azido-nitrile systems can enter into intramolecular cycloaddition reactions with the formation of condensed tetrazoles. However, unlike intermolecular processes, the electron-withdrawing character of substituents has little effect on the course of intramolecular reactions.[322] On the contrary, the length of the bridge connecting the azide and nitrile fragments is an important factor affecting the reactivity. For instance, the $\Delta G^{\neq}$ value for the cyclisation of $N{\equiv}CS(CH_2)_nN_3$ increases with n = 2, 3, 4 (142, 143, 157 kJ mol^{-1} respectively; obtained from B3LYP/6-311G** calculations) and the higher activation barrier obtained for n = 4 seems to be due to the formation of the seven-membered ring. This agrees with experimental data on isolation of the [5,5]- and [6,5]-type bicyclic adducts in the reactions of intramolecular cycloaddition of thiocyanates, whereas no [7,5]-type bicyclic products are formed under the same conditions.[323]

A comparative B3LYP, MP2 and MP4(SDTQ) study on the mechanisms of intramolecular cycloaddition of compounds containing conjugated enyne fragments C≡C—CH=X (X = CH_2, O, S, NH) was reported.[76] According to calculations, the [4 + 2]-cycloaddition resulting in fused allene-type structure **82** is expected for X = CH_2. Structure **82** is stabilised by a double

1,2-proton shift and then transformed to a benzene-type system **83**. The heteroatomic fragments are involved in the [3 + 2]-cycloaddition reactions and eventually form condensed five-membered aromatic heterocycles **84**. The results of calculations agree with experimental data,[324–327] namely, with the fact that the reactions of carboenynes proceed *via* a cyclic allene-type intermediate and that the intramolecular cycloaddition of heteroenines involves formation of heterocyclic carbenes.



A study of the mechanisms of two possible reactions of intramolecular cycloaddition of ylides **85** was reported.[328] The [3 + 2]-cycloaddition resulting in diazaphospholane **86** (its analogue was isolated experimentally) was shown to be kinetically and thermodynamically most favourable (E_a = 45 kJ mol^{-1}; obtained from B3LYP/6-31G* calculations).



IX. Conclusion

Computational quantum-chemical methods provide a powerful tool for studying versatile chemical processes including the [3 + 2]-cycloaddition reactions. In some cases experimental studies of the reactivity of compounds and especially the reaction mechanisms are difficult or impossible at all (if, *e.g.*, the initial compounds are poorly soluble, the reaction rate becomes too high or, on the contrary, too low to carry out kinetic studies or if the process involves the formation of short-lived intermediates that cannot be characterised experimentally). In these situations theoretical calculations are put in the forefront, because they present the one and only alternative to experimental methods.

In this review we analysed the literature on the [3 + 2]-cycloaddition reactions and showed that the simplest qualitative models traditionally used in organic chemistry (first of all, the FMO theory) are still useful in interpreting experimental data. Moreover, in some cases they help to choose the reaction conditions. The overall reactivities of compounds depend on a bunch of factors, namely, the nature of substituents and solvent, the presence or the absence of catalyst, *etc*. Knowing the composition and the relative energies of the frontier MOs of the reactants, one can draw particular conclusions about the effects of these factors on the reactivity. In particular, the NED processes require the introduction of electron-donating substituents into the dipole molecule and electron-withdrawing groups into the dipolarophile molecule. The acceleration of such intermolecular reactions is achieved by selective coordination of catalyst to the dipolarophile. The reverse holds for the IED reactions.

However, this qualitative approach to the description of the reactivity is essentially simplified because it ignores, *e.g.*, steric effects. Additionally, changes in the FMO energies are not always related to the type of the substituent introduced. Finally, the activation barrier is affected by not only the relative orbital energies of reactants but also other factors, in particular, the nature of the transition state and the energy balance between cleavage and formation of chemical bonds in the formation of transition states. Clearly, the cases where the FMO theory is inapplicable require detailed studies of the mechanisms of the processes and estimation of the activation energy. Thus, investigations on the reactivity of chemical compounds are often closely related to the reaction mechanisms, which play a key role for some reasons.

First, theoretical calculations of the activation barriers and reaction rates (this is of greatest value when experimental kinetic studies are impossible) have some sense only if the mechanism of the process is known, *i.e.*, the possible reaction pathways are elucidated and the energetically most favourable mechanism is available.

Second, the FMO theory predictions are usually applicable to the 'classical' synchronous processes that occur under orbital control. However, a [3 + 2]-cycloaddition reaction proceeding by the highly asynchronous mechanism behaves to some extent similarly to nucleophilic addition. Here, the role of the charge factors becomes significant. The need of taking into account the charge control complicates the choice of appropriate catalyst. On the one hand, the catalyst should provide selective coordination of the Lewis acid to the reactant (for intermolecular processes). On the other hand, it should provide a maximum possible degree of transfer of the electron density to the Lewis acid in order to attain the largest charge difference between the atoms in the reactant molecules. Therefore, experimental design in the field of catalytic syntheses requires knowledge of the reaction mechanisms.

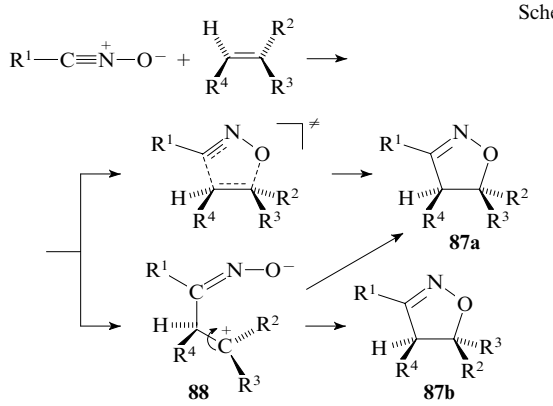
Third, the nature of the solvent belongs to the factors responsible for the reactivity. By varying the solvent nature the reaction can be appreciably accelerated. Location of transition states in the minimum energy path and the inclusion of solvation effects in the course of quantum-chemical calculations make it possible to predict how the change in, *e.g.*, the solvent polarity will affect the rate of the process under study. It should also be noted that the type of the mechanism is related to the solvation effects, namely, in some cases a stepwise cycloaddition is accompanied by the formation of high-polarity intermediates and transition states, which favours acceleration of the reactions in polar media. Finally, in some cases the solvent forms strong complexes with reactants and thus becomes a constituent of the transition state, being involved in the reaction. Here, comprehensive theoretical studies of the mechanism with inclusion of coordinated solvent become even more important.

Fourth, the mechanism of the process governs the regio- and stereoselectivity of the reaction. Analysis of the available literature on the subject showed that these phenomena are controlled by a group of factors that can often be interpreted only using theoretical methods. First of all these are the electronic effects of substituents where the introduction of an electron-donating group into the dipolarophile molecule leads to preferred formation of the *ortho*-isomer, whereas the electron-withdrawing substituents are responsible for the *meta*-selectivity. Important factors also include the nature of the solvent, selective coordination of the Lewis acid to the reactant molecule, steric effects and the secondary orbital interaction. All of them act on the transition-state level.

Sometimes, the general type of the reaction mechanism (concerted or stepwise) is responsible for the stereoselectivity. The example presented in Scheme 10 shows that in the case of concerted cycloaddition only one stereoisomer **87a** can be formed, whereas the stepwise mechanism makes it possible to obtain two isomers (**87a** and **87b**) due to free rotation about the C–C bond in intermediate **88**.

The mechanisms of some [3 + 2]-cycloaddition reactions can be changed with ease. For instance, the inclusion of solvation effects or the use of high-polarity solvents, catalysts, or (in some cases) a simple repacement of substituents favour the change from concerted to stepwise reaction mechanism.

Scheme 10



Therefore, if there is a need of carrying out stereoselective synthesis, it is possible to use the results of theoretical calculations of the reaction mechanisms for choosing the reaction conditions (catalyst, solvent, substituents) in such a way that they will provide a sufficiently high reaction rate on the one hand and will not change the reaction mechanism on the other hand. In this connection it should be noted that progress in computer science (computational methods) and hardware allows corresponding theoretical estimates to be obtained in a rather short time, *i.e.*, quantum-chemical methods become fast methods that help in experimental design.

Considering prospects for theoretical studies of [3 + 2]-cycloaddition, yet another two points should be noted. First, most publications are concerned with the reactions with alkenes and more rarely alkynes as dipolarophiles and nitrones, nitrile oxides, azides and diazoalkanes as dipoles. At the same time the number of theoretical studies devoted to the analysis of the reactivity of compounds with other multiple bonds (C═N, C═O, C═S, C═P, C═Si, N═N, C ≡ N, C ≡ P) or such dipoles as azimines, nitrile imines, azoxy compounds, carbonyl imines, carbonyl oxides, nitrosimines and nitroso oxides is relatively low and corresponding processes undoubtedly require more thorough investigations.

Second, theoretical studies aimed at analysing the role of catalysts and the mechanism of their action on the [3 + 2]-cycloaddition processes are also scarce compared to the literature on non-catalytic processes. Additionally, the importance of research into correlations between the nature of the catalyst, solvent and substituents, on the one hand, and the rate, regio- and stereoselectivity of the reaction, on the other hand, becomes obvious.

Thus, knowledge of the mechanism and the driving forces of chemical reactions is very useful in the design of chemical experiments, attainment of optimum reaction conditions and in performing targeted synthesis. Modern computers and theoretical methods allow the [3 + 2]-cycloaddition reactions to be studied using high-level approximations, as indicated by dramatic increase in the number of publications on the title subject reported in the last five to seven years.

This work has been written with the financial support from the Russian Foundation for Basic Research (Project No. 05-03-32 504).

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[a] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*
[b] — *Chem. Heterocycl. Compd. (Engl. Transl.)*