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Theoretical Studies of Cycloaddition to Metal-Activated Substrates with Isocyanide Ligands

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Abstract—The results of theoretical studies of the reactions of cycloaddition to the metal-activated substrates with the isocyamide ligands performed by the author and coworkers within the recent five years are generalized and examined. The reaction mechanisms, main factors, and driving forces affecting the kinetic and thermodynamic parameters of the processes are considered.

Keywords: cycloaddition, isocyanides, reactivity, mechanisms of reactions, quantum-chemical calculations

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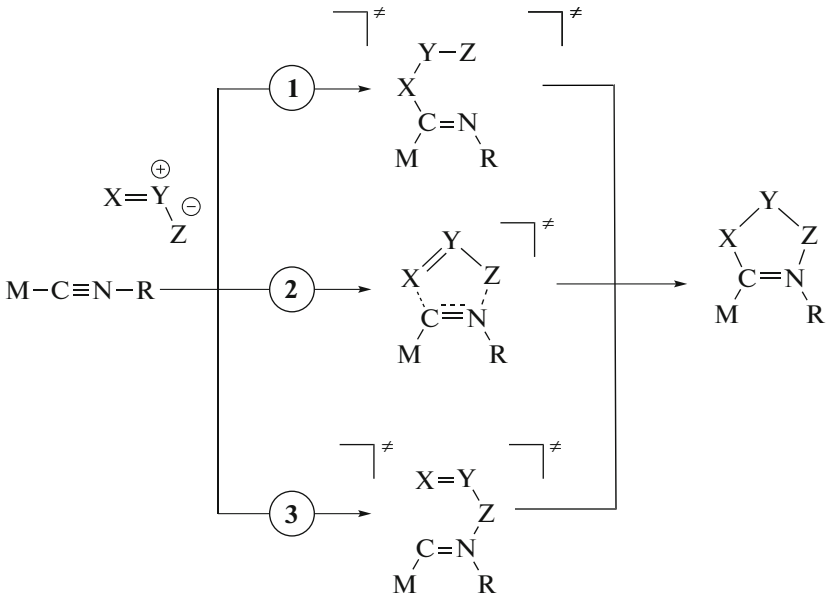
INTRODUCTION

Presently, compounds containing the C≡N bond (in particular, isocyanides C≡NR) are very promising as building blocks in cycloaddition reactions for the synthesis of diverse N-heterocyclic carbene ligands, which find wide use in industry and medicine [1]. Efficient catalysts based on these compounds can be developed for a series of important technological processes, such as Suzuki, Heck, and Sonogashira cross-coupling reactions and multicomponent reactions [2–5], as well as materials with valuable redox, magnetic, and optical properties promising for the production of light diodes and photocells for solar electric power stations [6, 7]. Substrates of this type form a basis for the synthesis of various heterocyclic derivatives (in particular, oxadiazolines and tetrazoles) exhibiting high physiological activity: antiviral, antimicrobial, anti-inflammatory, and anti-allergic [8–10]. Labels for neutron capture therapy for oncological diseases can also be synthesized on the basis of these substrates [11–14].

However, isocyanides in the free states are often inert in cycloaddition reactions. Therefore, an important task for their use in the synthetic practice is C≡N bond activation by this or another method. One of the methods for the activation of these substrates is the introduction of a strong electron-withdrawing substituent R' (CF_3, CCl_3, CH_2Cl) into the molecule. This method is traditionally used in organic chemistry but its application is restricted, because the method does not allow one to directly obtain products with alkyl substituents R. Another method (variation of the solvent) is also traditional for organic chemistry, but the acceleration of the reaction achieved in this case, as a rule, is low. The third method of activation is the coordination of the substrate bearing the C≡N bond by the Lewis acid (for example, metal ion). This type of activation substantially enhances the reactivity of isocyanides, finds wide and increasing use in the recent time, and can be considered as most promising [15].

Our research group uses the combined experimental and theoretical approaches to studying reactions of cycloaddition and nucleophilic addition to various metal-activated substrates containing the C≡N bond.[1] The results in the area of theoretical studies of cycloaddition processes involving the isocyanide complexes of transition metals performed by the author and coworkers within the recent five years are generalized and examined in the present brief review. Possible mechanisms of the 1,3-dipolar cycloaddition of various reagents to coordinated isocyanides (mechanisms **1** and **3** are stepwise and proceed via the formation of acyclic intermediates, and **2** is the concerted mechanism) are shown in the Scheme 1.

[1] See publications by N.A. Bokach and D.S. Bolotin (St. Petersburg State University) in the present issue.



Scheme 1.

RESULTS AND DISCUSSION

The results of detailed theoretical investigation of the properties, including the relative stability of various isomers, structural features, vibrational frequencies, the nature of coordination bonds, the atomic charge distribution, an analysis of the compositions and energies of the molecular orbitals, and the influence of the oxidation state of the complex-forming metal on the properties of coordinated isocyanides, of the $[RhCl(PH_3)(CNMe)_2]$ (**I**) and $[RhCl_3(PH_3)(CNMe)_2]$ (**II**) complexes with different oxidation states of the metal (Rh(I) and Rh(III), respectively) as promising reagents for the synthesis of N-heterocyclic carbenes are presented [16]. In the case of complex **I**, the *cis*-isomer is most stable, and the *cis-os*-isomer is most stable for complex **II**. A moderate effect of inverse π-donation is observed for complexes **I**. It was proved by the theoretical methods of quantum chemistry that the coordination of C≡NMe to the metal should result in the activation of this ligand in nucleophilic addition and cycloaddition reactions with the normal electron distribution and also should prevent the electrophilic attack to the N atom of isocyanide. The activation effect of the rhodium complexes can qualitatively be interpreted as a result of a decrease in the energy level of the lowest unoccupied molecular orbital centered at the CNMe ligand because of the coordination and charge factors (an increase in the positive charge on the carbon atom and a decrease in the negative charge on the nitrogen atom upon coordination).

The mechanism of the 1,3-dipolar cycloaddition of nitrone (CH_2=N(Me)O) to methyl isocyanide coordinated to Rh(I) and Rh(III) in complexes **I** and **II** was studied in detail by the theoretical quantum-chemical methods [17]. The molecular and electronic structures of the cycloaddition products, the nature of the transition states, the mechanism of the reactions, their kinetic and thermodynamic parameters, and the effect of the solvent were described. The reactions proceed via the concerted strongly asynchronous mechanism through the formation of the five-membered cyclic transition state. The use of the rhodium complexes as reactants noticeably decreases the activation barriers of the studied processes and increases the absolute values of the energy effects of the reactions. The Rh(III) complexes were proved to be the best activators of nitrone cycloaddition to Rh(I). It is assumed on the basis of the calculations performed that only one isocyanide ligand would participate in the cycloaddition of nitrone in the case of the Rh(I) complexes, whereas the participation of both CNMe ligands is quite probable for the Rh(III) complexes. It is theoretically substantiated that the solvation effects inhibit the reactions studied.

Various properties of the rhenium $[ReCl_4(CNMe)_2]$ and ruthenium $[RuCl_2(PH_3)_2(CNMe)_2]$ isocyanide complexes (relative stability of the isomers, structural features, vibrational frequencies, nature of coordination bonds, composition of molecular orbitals, and charge distribution) and their affinity to participation in the reactions of nitrone cycloaddtion were theoretically studied [18]. The reactivity of these compounds was interpreted from the viewpoint of the kinetic and thermodynamic factors. The coordination of CNMe to Re(IV) substantially activates this ligand toward cycloaddition (the efficiency is compa-

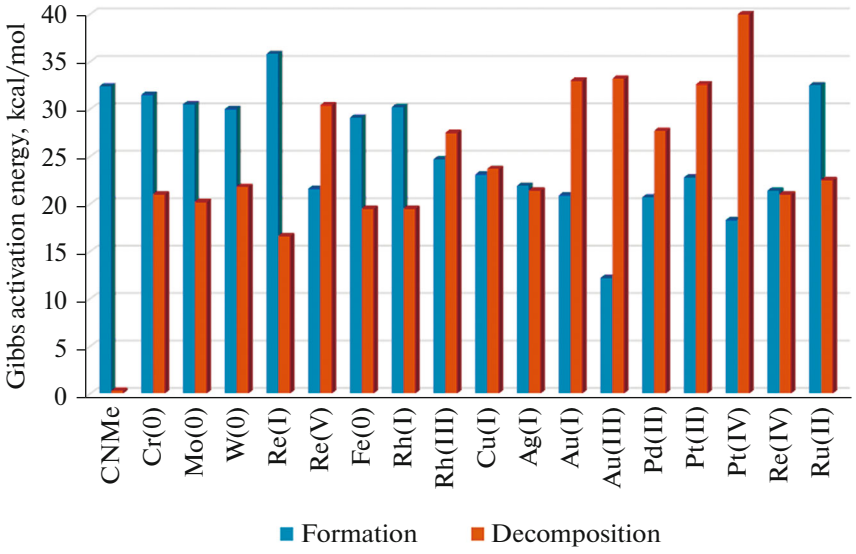


Fig. 1. Activation barriers for the formation of N-heterocyclic aminooxycarbenes by the [2+3] cycloaddition of nitrone CH_2=N(Me)O to the methyl isocyanide ligands of the complexes of various transition metals and by the side decomposition reactions of these heterocycles to imines and isocyanates.

rable with those of such metal centers as Pt(II) and Pd(II)), whereas the Ru(II) metal center exerts almost no effect on the reactivity of isocyanide in processes of this type. The mechanism of the studied cycloaddition reactions is concerted and substantially asynchronous and includes the formation of one five-membered transition state in which the C···O contact has a substantial fraction of covalence. It follows from the quantum-chemical calculations performed that the addition of the second nitrone molecule to these bis(isocyanide) complexes is unfavorable from both the kinetic and thermodynamic points of view. The nature of coordination bonds in the model systems was studied by the topological analysis of the electron density distribution in terms of Bader's formalism, an analysis of the natural bond orbitals, and the charge decomposition analysis according to Frenking. The coordination bonds were found to be polarized in the direction of the ligands.

A stronger activation of the isocyanide ligand in the gold(III) complexes toward nucleophiles compared to the gold(I) complexes was interpreted [19] from the orbital, charge, and "frequency" (vibrations of the C≡N bonds) points of view. In addition, the data obtained allow one to conclude that the isocyanide ligand in the gold(III) complexes is substantially activated toward the cycloaddition of various dipoles.

The comprehensive theoretical study of the formation of *N*-heterocyclic aminooxycarbenes by the [2+3] cycloaddition of nitrones to the isocyanide ligands of the complexes of various transition metals (Cr, Mo, W, Re, Ru, Fe, Rh, Cu, Ag, Au, Pt, Pd) and of the side decomposition of these heterocycles to imines and isocyanates (Fig. 1) was carried out [20].

Practically important predictions concerning the most efficient combination of the activator and substituents for the synthesis and stabilization of these compounds were made. The possibility of using nonplatinum metal centers for these purposes was proved. The possible mechanisms and the kinetics and thermodynamics of these processes were considered. In the absence of the metal center, oxadiazoline carbenes are inaccessble for two reasons. First, the activation barrier of the cross-coupling of nitrone with free isocyanide is too high. Second, uncoordinated *N*,*N*-substituted 1,2,4-oxadiazolines are unstable species and should immediately decompose to imine and isocyanate, which is confirmed by the very low activation barrier and strongly negative free Gibbs energy of this process. The metal centers Au(I, III), Pt(II, IV), and Re(V) are the most efficient promoters for the synthesis of the oxadiazoline carbene complexes by the [2 + 3] cycloaddition of nitrones to coordinated isocyanides. On the one hand, these metal centers should sharply activate the isocyanide ligands in these reactions (the rate of the process increases by 6.6×10^6–4.9×10^{14} times according to the Eyring equation). On the other hand, it is expected that these metals would efficiently stabilize the formed cyclic products and prevent their decomposition. It is shown that the activating and stabilizing effects of Au(I, III), Pt(II, IV), and Re(V) are higher than those of Pd(II), which is used as a reference with the known experimental data. The activation effect by the Cu(I), Ag(I), and Re(IV) complexes is comparable with that of the Pd(II) com-

pounds. However, it is expected for the latter that the corresponding cycloaddition products are less stable than the Pd-coordinated oxadiazolines. Therefore, the productivity of using these metals in real syntheses seems doubtful. The CNR ligand in the Cr(0), Mo(0), W(0), and Fe(0) carbonyl complexes and in the Rh(I) and Rh(III) bis(isocyanide) complexes is activated insignificantly compared to free isocyanide, whereas even the inhibition of nitrone cycloaddition is expected for the coordination of CNR to the Re(I) and Ru(II) compounds. In addition, the corresponding oxadiazoline complexes should be stable. It is unreasonable to use these metal centers for the synthesis of the oxadiazoline carbene complexes. The theoretical analysis of the effects of substituents showed that alkyl-substituted nitrones and isocyanides were more reactive in cycloaddition than the aryl-substituted species. The alkyloxadiazoline complexes were also found to be more stable to decomposition than the aryl derivatives. The reactivity of isocyanides toward nitrone cycloaddition can be interpreted on the basis of the orbital and electrostatic arguments. The critical factors controlling these reactions are the energy level of the free molecular orbital centered on the isocyanide ligand and the effective atomic charges on the nitrogen atoms of the C≡N group. The lower the energy of these free molecular orbitals and the lower the negative charge on the nitrogen atom, the more efficient the cycloaddition. The main factor causing the decomposition of oxadiazoline carbenes is the low stability of the N–O bond in the cycle, which is explained, in turn, by the electrostatic repulsion between two negatively charged atoms forming this bond. The results of the quantum-chemical calculations indicate that the mechanism of nitrone cycloaddition to the isocyanide complexes of transition metals is concerted and asynchronous in the most part of cases, except for the reactions CH_2=N(Me)O + [$Re^{I}Cl(PH_3)_4$(C≡NMe)], CH_2=N(Me)O + [$Au^{III}Br_3$-(C≡NMe)], and RCH=N(Me)O + [$Pd^{II}Cl_2$-$(C{\equiv}NMe)_2$] (R = Me, Ph), the mechanism of which is stepwise. The decomposition of the oxadiazoline carbene complexes includes the step of retrocycloaddition resulting in the formation of coordinated isocyanate MeNCO–[M] and imine CH_2=NMe followed by ligand substitution step, due to which the experimentally observed compounds are formed: coordinated imine [M]–N(Me)CH_2 and free isocyanate MeNCO. The retrocycloaddition mechanism is concerted. The mechanism of ligand substitution is dissociative, although the concerted route (type I_d according to the Langford–Gray classification) also has a fairly low activation barrier.

The possibility of applying the theoretical model of hard and soft acids and bases using quantum-chemical calculations in terms of the density functional theory to the investigation of the 1,3-dipolar cycloaddition of nitrones to the isocyanide ligands of the transition metal complexes was examined [21]. Investigations of this kind represent a fruitful addition to the approaches based on the application of the theory of frontier molecular orbitals, which are traditionally used for the study of cycloaddition reactions. The following descriptors of reactivity were calculated: chemical potential (μ), hardness (η), softness (S), global indices of electrophilicity and nucleophilicity (N), maximum amount of the electron charge that can be accepted by the electrophilic system (ΔN_{max}), and static charge transfer nucleophile → electrophile (Eqs. (1)–(7), energies of the highest occupied (E_{HOMO}) and lowest unoccupied (E_{LUMO}) molecular orbitals, respectively; nucleophile (Nu), electrophile (E), and tetracyanoethylene ($C_2(CN)_4$, TCNE) (reference in the Domingo nucleophilic scale [22–24])). Various isocyanide complexes of transition metals were classified by strength as electrophiles and nucleophiles. A fairly rigid linear correlation (R^2 = 0.94) between the difference in electrophilicity of the dipole–dipolarophile pair and the polarity of the cycloaddition was found. A linear dependence between the activation and reaction energies and the chemical potential of the dipolarophiles was observed. In addition, the relationships between the calculated unscaled vibrational frequencies ν(C≡N) in free isocyanide and in various isocyanide complexes and the kinetic and thermodynamic parameters of cycloaddition (R^2 = 0.89 and 0.91, respectively) were found when considering the 1,3-dipolar cycloaddition of nitrones to isocyanides as an attack of the dipole to the α-C and β-N atoms of the dipolarophile (Fig. 2).

$$\mu \approx \frac{E_{HOMO} + E_{LUMO}}{2}, \quad (1)$$

$$\eta \approx E_{LUMO} - E_{HOMO}, \quad (2)$$

$$S = \frac{1}{\eta}, \quad (3)$$

$$\omega = \frac{\mu^2}{2\eta}, \quad (4)$$

$$N = E_{HOMO,\,Nu} - E_{HOMO,\,TCNE}, \quad (5)$$

$$\Delta N_{max} = -\frac{\mu}{\eta}, \quad (6)$$

$$\Delta N^0 = \frac{\mu_{Nu} - \mu_E}{\eta_{Nu} + \eta_E}, \quad (7)$$

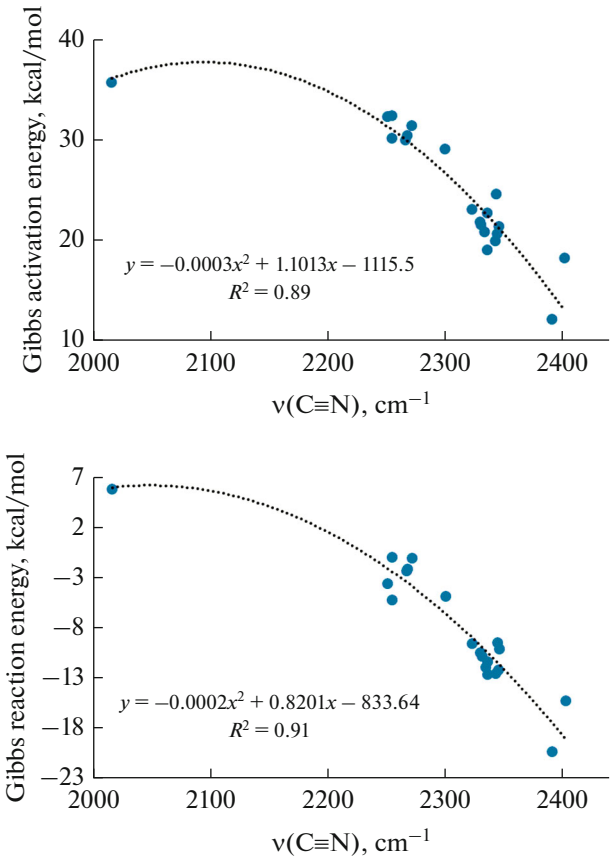


Fig. 2. Relationships between the calculated unscaled vibrational frequencies ν(C≡N) in free isocyanide and in various isocyanide complexes and the kinetic/thermodynamic parameters of the cycloaddition process.

The mechanisms of the Pd-promoted cross-coupling of azides and isocyanides leading to the synthesis of the tetrazolate structures were studied [25]. It is proved that the reaction involves free azides and isocyanides coordinated to the metal center and the formal cycloaddition is the stepwise process proceeding via the formation of acyclic intermediates followed by the rate-determining cyclization step. It is shown on the basis of the quantum-chemical calculations that the Pd-promoted cross-couplings of azides and isocyanides are kinetically and thermodynamically favorable. In addition, the thermodynamic stability of the model *trans*-[$PdCl(PH_3)_2(CN_4Me)$] tetrazolate complexes in which the heterocyclic monodentate anionic CN_4Me^- ligand is coordinated to the metallocenter via all known modes was studied in terms of this work. The coordination of this ligand by the carbon atom was shown to be energetically most favorable.

To conclude, the promotion of syntheses of diverse *N*-heterocyclic carbene ligands and their stabilization are important problems of the modern organometallic and coordination chemistry. The cycloaddition of various dipoles (in particular, nitrones and azides) to the isocyanide complexes of transition metals can successfully be used for these purposes. We performed the series of theoretical invesigations aimed at studying the mechanisms of this type of reactions as well as the main factors and driving forces affecting their kinetic and thermodynamic parameters. Practically important predictions were made about the relatively more efficient combination of the activator and substituents for the synthesis and stabilization of oxadiazolines and tetrazoles (metal centers in high oxidation states and aliphatic substituents are promising in this context). In the majority of cases, the cycloaddition of various nitrones to the isocyanide ligands of the transition metal complexes proceeds via the concerted mechanism through the formation of the cyclic transition state, whereas the heterocyclization proceeds stepwise via the formation of acyclic intermediates when azides are used as dipolarophiles. The key factors controlling these reactions are the energy level of the unoccupied molecular orbitals centered on the isocyanide ligands and the effective aromic charges on the nitrogen atoms of the C≡N group. The lower the energy of these unoccupied molecular orbitals and the lower the negative charge on the nitrogen atom, the more efficient the cycloaddition.

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