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Theoretical Study of Chemo-, Regio-, and Stereoselectivity in 1,3-Dipolar Cycloadditions of Nitrones and Nitrile Oxides to Free and Pt-Bound Bifunctional Dipolarophiles†

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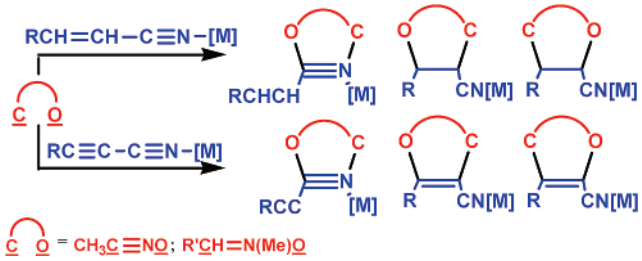

1,3-Dipolar cycloadditions of nitrones RCH=N(CH$_3$)O and the nitrile oxide CH$_3$C≡NO to the bifunctional cyanoalkynes N≡C−C≡CR′ and cyanoalkenes *E*-N≡CCH=CHR′ (R = H, Ph; R′ = H, Ph)—both free and ligated to Pt^{II} and Pt^{IV}—were investigated by theoretical methods at B3LYP and, for some reactions, CCSD(T) and CBS-Q levels of theory. Chemo-, regio-, and stereoselectivity of the processes and factors, which affect the reactivity and selectivity, were analyzed, and verified trends are discussed in details. Coordination of dipolarophiles to Pt^{II} and, particularly, to Pt^{IV} facilitates the CN relative to the CC additions of nitrones due to higher activation of the CN group in comparison to the CC group. The bonding of the ligands to platinum also favors the *meta* versus *ortho* pathways and *endo* versus *exo* pathways that sometimes lead to a switch of the reaction direction. Introduction of Ph groups into the reactant(s) molecules also leads to the promotion of the CN versus CC routes, and this effect is especially strong when both reactants are Ph-substituted. The substituent effect is accounted for by steric repulsions imposed by the Ph groups in transition states (TSs) and by the loss of a conjugation in phenylnitrone and phenylcyanoalkene molecules upon the TS formation. Solvation inhibits the CN and *meta*-CC additions and, hence, generally favors the CC versus CN pathway, the *ortho* versus *meta* pathway, and the *exo* versus *endo* pathway. All reactions except one proceed concertedly via a nearly synchronous mechanism for the CN and *meta*-CC additions to free ligands and asynchronous mechanism for the other processes. For the reaction CH$_2$=N(CH$_3$)O + **Pt^{IV}-1**, a stepwise route is realized.

Introduction

1,3-Dipolar cycloaddition (1,3-DCA) reactions are among the most important processes in organic chemistry allowing the synthesis of a great variety of five-membered heterocycles.[1] The 1,3-DCA of dipoles bearing the NO polar bond (e.g., of nitrones and nitrile oxides, typical representatives of dipoles of both allyl and propargyl/allenyl anion types, correspondingly) to a C=C

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double bond has been studied extensively by both experimental[1] and theoretical[2−14] methods. At the same time, their cycloadditions (CAs) to a C≡C triple bond[1,4,7a,15−22] and particularly to a heteroatomic C≡N triple bond[18,23−28] are much less explored because of the low reactivity of these dipolarophiles in CAs. The reactions with bifunctional dipolarophiles having both C≡C and C≡N triple bonds have been investigated only in a few works[29] despite the fact that these systems—being logical candidates to study various aspects of chemo-, regio-, and stereoselectivity in CAs—are of special interest, and one of the most intriguing problems related to such processes is the intentional switch of selectivity by modification of reactants and/or reaction conditions.

In general, chemo-, regio-, and stereoselectivity are determined by several factors, such as the electronic structure of reactants and transition states, steric factors, possible intra- or intermolecular interactions (which are able to stabilize a particular transition state), solvent effects, and the reaction mechanism.[2a] There are three main ways to control the selectivity of 1,3-DCA: (i) the alteration of substituents in the reactants' molecules, (ii) variation of the solvent nature, and (iii) coordination of the reactant(s) to a Lewis acid. While the first two routes of controlling CAs are commonly explored in organic chemistry, the third way is substantially less investigated despite the fact that the Lewis acid may exhibit the dual role in the CA reactions, that is, to serve as a possible switcher of the reaction selectivity and as an activator of the process.

Recently, using quantum chemical methods, we investigated the nature and driving forces of the activation, by coordination, of *monofunctional* nitriles N≡CR (R = CH_3, CF_3) in 1,3-DCAs with nitrones[30] and nitrile oxides.[31] The results demonstrate that the ligation of nitriles to Pt^{II} and, especially, to Pt^{IV} centers dramatically decreases activation barriers in 1,3-DCA, and hence, the application of platinum as a Lewis acid is a more promising and effective route for enhancement of reactivity of RCN species than the conventional activation of nitriles by very strong electron-withdrawing groups R such as, for instance, CF_3. Now we focused our attention on another important aspect of the 1,3-DCA processes, that is, reaction selectivity, and, therefore, extended our theoretical studies to the *bifunctional* dipolarophiles of C═C/C≡N and C≡C/C≡N types.

The main goal of this work is the complex study of factors determining the chemo-, regio-, and stereoselectivity of 1,3-DCAs to bifunctional dipolarophiles. Within this goal, the following questions were raised: (i) how the coordination of bifunctional alkenes and alkynes to Pt and the oxidation state of the metal center affect the chemo-, regio-, and stereoselectivity of the CAs; (ii) how the coordination of the ligands to Pt activates them toward CA to the C≡N bond, on one hand, and to the C≡C or C═C bond, on the other hand; (iii) how the nature of dipoles (those of allyl and propargyl/allenyl anion types) and dipolarophiles (unsubstituted and Ph-substituted cyanoalkenes and cyanoalkynes) affects the reaction selectivities; (iv) how the solvation and solvent nature influence the reactivity and selectivity. To answer these questions, the search for reaction mechanisms and the estimates of energetic characteristics have been performed for cycloadditions of the *Z*-nitrones *Z*-RCH═$N(CH_3)O$[32] (allyl anion type) and the nitrile oxide CH_3C≡NO (propargyl/allenyl anion type) to the bifunctional cyanoalkynes N≡C−C≡CR′ and cyanoalkenes *trans*-N≡CCH═CHR′ (R = H, Ph; R′ = H, Ph)—free and coordinated to Pt^{II}

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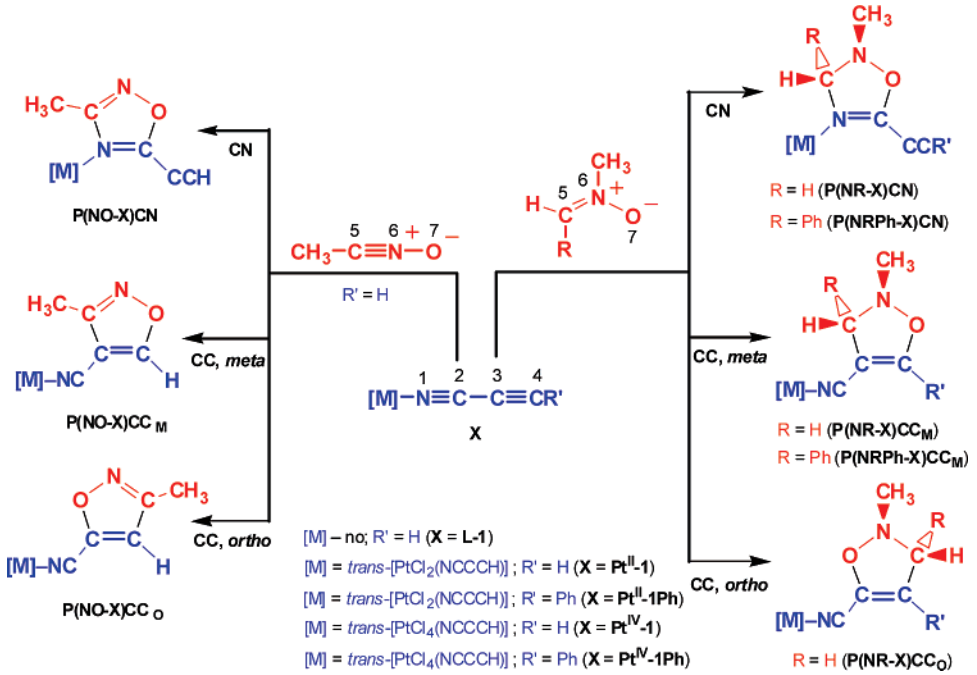
SCHEME 1. Cycloadditions of Nitrones and Nitrile Oxides to Cyanoalkynes



and Pt^{IV} centers in the model complexes *trans*-[$PtCl_n$(N≡C−C≡CH)(N≡C−C≡CR′)] and *trans*-[$PtCl_n$(N≡C−CH=CH_2)-(N≡C−CH=CHR′)] (n = 2, 4) (Schemes 1 and 2). These platinum-mediated reactions are promoted rather than catalyzed by the metal, but in accord with experimental data,[33] the heterocycles could be liberated by ligand displacement reactions and the overall process (involving 1,3-DCA and the substitution) opens up the route to oxadiazoles and oxadiazolines, which cannot be obtained in the conventional metal-free organic synthesis. The choice of platinum as a Lewis acid was caused by the fact that Pt, being a soft acid, coordinates exclusively to the soft donor center of dipolarophiles but not to dipoles and, hence, provides the greatest activation effect in agreement with predictions of the FMO theory for the normal electron-demand process.[24a−c,30a] Although we found that the selectivities of these processes depend on a delicate balance of different factors (coordination of the dipolarophiles to Lewis acid, nature of dipoles and dipolarophiles, variation of substituents, steric repulsive interactions, intramolecular attractive interactions, and solvent effects), certain well-defined trends were verified and they are discussed in this article.

Computational Details

The full geometry optimization of all structures and transition states has been carried out in Cartesian coordinates with help of the Gaussian 98[34] and Gaussian 03[35] program packages at the DFT level of theory. The calculations have been performed using Becke's three-parameter hybrid exchange functional[36] in combination with the gradient-corrected correlation functional of Lee, Yang, and Parr[37] (B3LYP). A quasi-relativistic Stuttgart pseudopotential described 60 core electrons, and the appropriate contracted basis set (8s7p6d)/[6s5p3d][38] for the platinum atom and the 6-31G*[39] basis set for other atoms were used. Further, this level is denoted as B3LYP/6-31G* even for the Pt complexes despite the usage of the other basis set on the Pt atom. Some of the reactions have also been calculated at the B3LYP/6-311+G**//B3LYP/6-31G*, CCSD-

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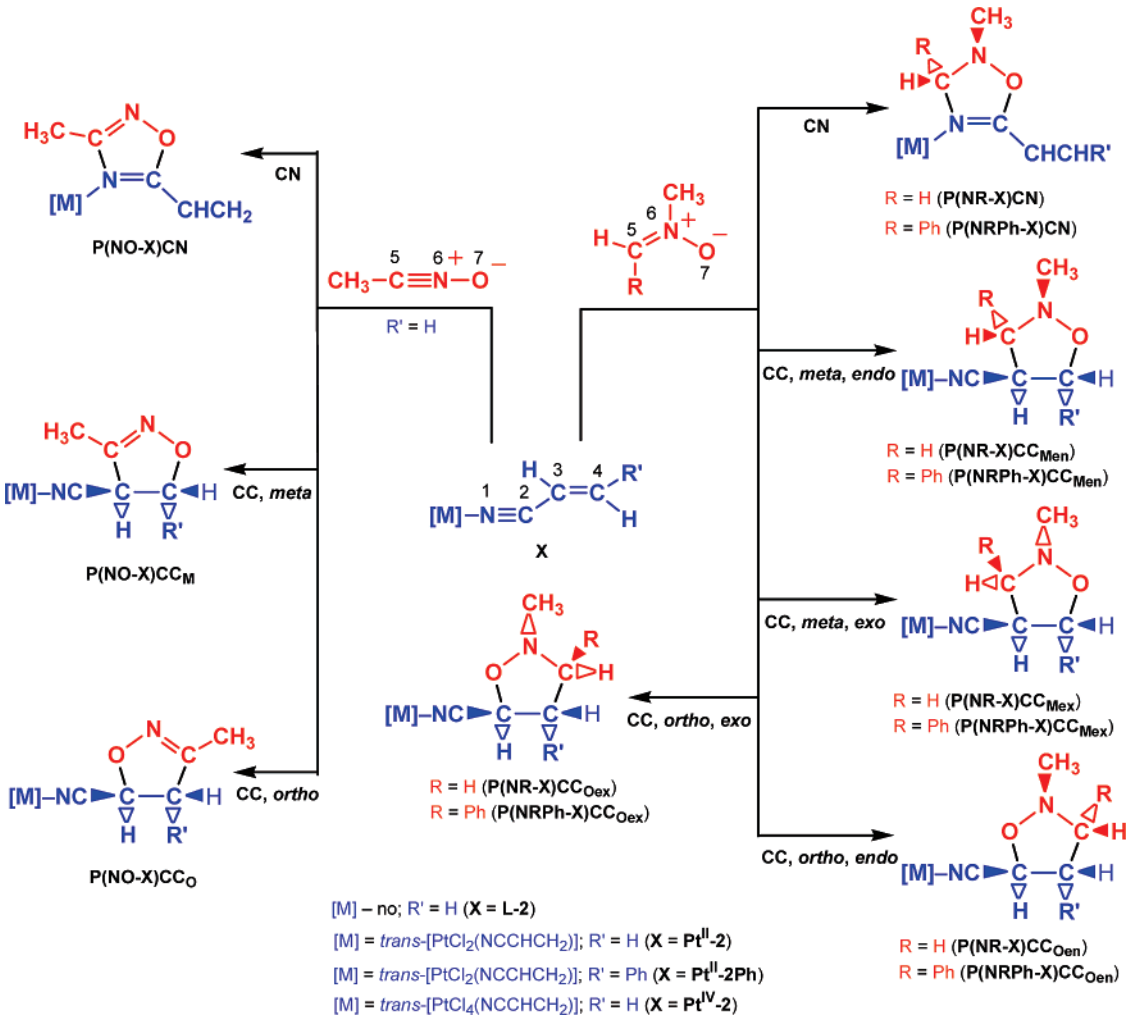
SCHEME 2. Cycloadditions of Nitrones and Nitrile Oxides to Cyanoalkenes



(T)/6-31G*//B3LYP/6-31G*,[40] and CBS-Q[41] levels, and a discussion of the influence of the computational method and basis set on the energetic characteristics is given in the Supporting Information. The basis set superposition error (BSSE) was not estimated because it affects weakly the activation and reaction energies, as it was shown previously.[30] Symmetry operations were not applied for all structures. For the stepwise mechanism, the calculations of possible biradical intermediate of the Michael-type have been performed at the unrestricted approximation. The stability test for equilibrium geometries of the intermediate and transition states of the stepwise mechanism was performed using the keyword STABLE in Gaussian 98.

The Hessian matrix was calculated analytically for all optimized structures in order to prove the location of correct minima (no imaginary frequencies) or saddle points (only one negative eigenvalue) and to estimate the zero-point energy correction and thermodynamic parameters; the latter were calculated at 25 °C. The nature of transition states was studied by analysis of vectors associated with "imaginary" frequency and by the calculations of the intrinsic reaction coordinates (IRC) using the Gonzalez–Schlegel method[42] for selected reactions.

The bonding nature in the TSs also was searched with the help of the AIM method of Bader.[43] For the calculations of the electron density distribution $\rho(\mathbf{r})$, the gradient vector field $\nabla\rho(\mathbf{r})$, and its associated Laplacian $\nabla^2\rho(\mathbf{r})$, the programs GRIDV, GRDVEC, CONTOR, and EXT94B were used.[44] The Wiberg bond indices[45] for the transition states have been computed by using the natural bond orbital (NBO) partitioning scheme.[46] The synchronicity of the reactions, Sy, has been calculated using the formula reported previously.[4,47]

Solvent effects were taken into account at the single-point calculations on the basis of the gas-phase geometries using the polarizable continuum model[48] in the CPCM version[49] with variety

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of solvents. The Gibbs free energies in solution (G_s) were estimated by addition of the ZPE, thermal, and entropic contributions taken from the gas-phase calculations (δG_g) to the single-point CPCM-SCF energy (E_s).

Results and Discussion

Previously, theoretical studies of the CC additions of nitrones $CH_2{=}N(H)O$,[10] $CH_3C(H){=}N(H)O$,[11] and $C(CH_3)_2OCH_2C(CH_3){=}NO$[7a] and fulminic acid $HC{\equiv}NO$[6c,10] to acrylonitrile $N{\equiv}CCH{=}CH_2$ and of $RC{\equiv}NO$ (R = H, 2,4,6-$(CH_3)_3C_6H_2$) to cyanoacetylene $N{\equiv}C{-}C{\equiv}CH$[29c] have been undertaken. However, theoretical analysis of the corresponding processes involving metal centers and the effect of a metal on the selectivity of reactions with these bifunctional dipolarophiles, to the best of our knowledge, has not been performed. Thus, results on the CAs to *free* cyanoalkenes and cyanoalkynes are given and discussed here mostly for comparison with metal-mediated reactions.

In the present article, the following naming scheme is used. Each reaction product or transition state is denoted by a name comprised of six or seven components: nature of the structure (P, reaction product; TS, transition state), dipole (NR, $CH_2{=}N(CH_3)O$, NRPh, $PhCH{=}N(CH_3)O$, NO, $CH_3C{\equiv}NO$), coordination type of dipolarophile (L, Pt^{II} and Pt^{IV}, free, coordinated to Pt^{II} and to Pt^{IV}), dipolarophile (1, $N{\equiv}CC{\equiv}CH$; 1Ph, $N{\equiv}CC{\equiv}CPh$; 2, $N{\equiv}CCH{=}CH_2$; 2Ph, $N{\equiv}CCH{=}CHPh$), chemoselectivity (CN, CC), regioselectivity (M, *meta*; O, *ortho*), and stereoselectivity (en, *endo*; ex, *exo*) (Schemes 1 and 2). For instance, the transition state for the *endo*-*meta*-CC addition of $CH_2{=}N(CH_3)O$ to **Pt^{II}-2** is marked as **TS(NR-Pt^{II}-2)CC_{Men}**.

All three types of the selectivity (chemo-, regio-, and stereoselectivity) may inhere in the reactions studied. The chemoselectivity is related to an addition either to the CN bond or to the CC bond (Schemes 1 and 2). The addition to the CC bonds may afford two regioisomers (i.e., *meta*- and *ortho*-isomers). The CAs to the CN bond also, in principle, may occur via two regioisomeric pathways, the first leading to the 1,2,4-oxadiazoles (**P(NO-X)CN**) and Δ^4-1,2,4-oxadiazolines (**P(NR-X)CN**) and the second resulting in the formation of the corresponding 1,2,5-isomers. However, only the 1,2,4-products were isolated experimentally, while the other regioisomers were never observed due to significantly higher activation barriers.[18] For this reason, in this article, we examine only the first regioisomeric pathway of the CN additions. Finally, the CA of *Z*-nitrones to the C=C bond may lead to formation of two stereoisomers along the *endo* or *exo* channels.

It was shown[2a] that the majority of 1,3-DCAs of nitrones and nitrile oxides with alkenes and alkynes occur via a concerted rather than stepwise mechanism. The same holds true also for the CAs to the C≡N bond where a switch of the mechanism to a stepwise one does not take place even upon coordination of the nitrile to Pt^{IV} despite the great decrease of the synchronicity.[30] Therefore, in the present work, we mainly focused on the concerted routes except the most asynchronous reaction of $CH_2{=}N(CH_3)O$ with **Pt^{IV}-1**.

Frontier Molecular Orbital Considerations. The qualitative analysis of the energies and composition of frontier molecular orbitals (FMO) of the reactants (Table 1S, Figure 1S, Supporting Information) leads to the following preliminary conclusions. First, all reactions (especially those with ligated species) belong to the normal electron-demand processes[50] with predominant $HOMO_{dipole}{-}LUMO_{dipolarophile}$ interaction. Second, coordination of the ligands to Pt^{II} and, particularly, to Pt^{IV} leads to a decrease of the LUMO energy (π^*_{CN} and π^*_{CC} orbitals) providing the activation of the ligands. Third, from FMO viewpoints, regioselectivity is determined "by the rule that the reacting centers choose the alternative of facing large−large and small−small" orbital coefficients.[6c] An inspection of the coefficients of reacting atoms indicates that the oxygen atom of dipoles and the terminal C(4) atom of dipolarophiles have the highest coefficients in the HOMO and π^*_{CC} LUMO, respectively. Hence, one can predict the preferred formation of *meta*-isomers upon the cycloadditions to CC bonds. Furthermore, the coordination of the ligands to platinum center(s) should increase the relative stability of the *meta*-isomer due to an enhancement of the difference in coefficients of the carbon atoms of the multiple CC bond. More detailed description of the FMO energy and composition is given in Supporting Information, while more accurate quantitative estimates of the energetic characteristics of the reactions are discussed below.

Equilibrium Structures of Reactants, Products, the Nature of Transition States and Reaction Mechanisms. In the initial step, the equilibrium structures of the reactants such as dipoles, free ligands $N{\equiv}CC{\equiv}CH$ and $N{\equiv}CCH{=}CH_2$, complexes **Pt^{II}-1**, **Pt^{IV}-1**, **Pt^{II}-2**, and **Pt^{IV}-2**, as well as of the reaction products (Schemes 1 and 2) have been calculated. The selected calculated bond lengths are given in Supporting Information (Table 2S). The computational results are in reasonable agreement with the experimental X-ray structural parameters for the ligands,[51] related cyanoalkenes,[52] cyanoalkynes,[53] 1,2,4-oxadiazole,[24c] and Δ^4-1,2,4-oxadiazoline[24a,b] complexes of the eight-group transition metals and for the cyanoisoxazolidines,[54] cyanoisoxazolines,[55,56] and cyanoisoxazoles.[56,57] The difference between the calculated and experimental bond lengths often falls within the 3σ interval of the X-ray data. Comparison of the structures **Pt^{II}-1**, **Pt^{IV}-1**, **Pt^{II}-2**, and **Pt^{IV}-2** with the acetonitrile complexes *trans*-$[PtCl_n(N{\equiv}CCH_3)_2]$ (n = 2, 4)[31] demonstrates that the conjugation results in some equalization of the CN and CC internuclear distances within the ligands.

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TABLE 1. Energetic Characteristics (in kcal/mol) of the Cycloadditions of CH_2=N(CH_3)O to Cyanoalkenes and Cyanoalkynes at the B3LYP/6-31G* Level[a]

dipolarophile	type of addition	E_{ag} (E_{as})	$\Delta G_g^{\ddagger}$ ($\Delta G_s^{\ddagger}$)	ΔE_g (ΔE_s)	ΔG_g (ΔG_s)
N≡CC≡CH	to CN	13.50 (15.17)	25.72 (27.39)	−21.26 (−21.63)	−6.20 (−6.57)
	to CC, *meta*	6.81 (7.34)	18.68 (19.21)	−51.75 (−53.07)	−36.13 (−37.45)
	to CC, *ortho*	8.23 (7.61)	19.77 (19.15)	−45.85 (−46.68)	−30.58 (−31.41)
Pt^{II}-1	to CN	3.33 (5.93)	16.49 (19.09)	−32.28 (−28.88)	−15.54 (−12.14)
	to CC, *meta*	−1.50 (0.04)	10.76 (12.30)	−56.10 (−56.99)	−40.12 (−41.01)
	to CC, *ortho*	3.57 (2.68)	15.78 (14.89)	−46.71 (−47.13)	−29.41 (−29.83)
Pt^{IV}-1	to CN	−5.44 (−1.31)	7.79 (11.92)	−38.06 (−33.89)	−20.24 (−16.07)
	to CC, *meta*	−7.74 (−2.78)[b]	5.60 (10.56)[b]	−11.40 (−13.17)[b]	+3.15 (+1.38)[b]
		−10.86 (−11.68)[c]	4.28 (3.46)[c]	−58.30 (−58.83)[c]	−42.06 (−42.59)[c]
	to CC, *ortho*	2.02 (1.39)	15.79 (15.16)	−47.83 (−47.64)	−31.91 (−31.72)
N≡CCH=CH_2	to CN	13.33 (16.27)	26.83 (29.77)	−25.47 (−24.40)	−8.81 (−7.74)
	to CC, *meta*, *endo*	8.31 (9.18)	22.47 (23.34)	−25.75 (−26.76)	−8.54 (−9.55)
	to CC, *meta*, *exo*	9.27 (9.20)	23.28 (23.21)	−25.39 (−26.93)	−8.28 (−9.82)
	to CC, *ortho*, *endo*	8.30 (7.69)	22.22 (21.61)	−25.45 (−26.60)	−8.37 (−9.52)
	to CC, *ortho*, *exo*	8.90 (7.98)	22.55 (21.63)	−24.32 (−25.89)	−7.74 (−9.31)
Pt^{II}-2	to CN	2.11 (6.63)	17.14 (21.66)	−36.16 (−31.62)	−17.67 (−13.13)
	to CC, *meta*, *endo*	2.31 (5.13)	17.24 (20.06)	−26.03 (−25.94)	−8.86 (−8.77)
	to CC, *meta*, *exo*	5.27 (4.70)	21.09 (20.52)	−25.25 (−26.61)	−8.51 (−9.87)
	to CC, *ortho*, *endo*	2.42 (3.57)	17.35 (18.50)	−25.90 (−25.79)	−8.30 (−8.19)
	to CC, *ortho*, *exo*	5.11 (4.06)	18.71 (17.66)	−24.01 (−25.05)	−7.51 (−8.55)
Pt^{IV}-2	to CN	−5.83 (−0.50)	5.82 (11.15)	−42.06 (−36.68)	−25.24 (−19.86)
	to CC, *meta*, *endo*	−2.98 (−0.07)	9.23 (12.14)	−27.25 (−26.30)	−10.80 (−9.85)
	to CC, *meta*, *exo*	0.37 (−4.16)	12.99 (8.46)	−26.11 (−26.97)	−10.19 (−11.05)
	to CC, *ortho*, *endo*	0.90 (3.33)	12.33 (14.76)	−26.42 (−25.58)	−10.02 (−9.18)
	to CC, *ortho*, *exo*	3.85 (3.17)	16.19 (15.51)	−24.34 (−24.94)	−11.19 (−11.79)

[a] Energies corrected on the solvent effects in parentheses (CH_2Cl_2 as a solvent). [b] Energies of **TS(NR-Pt^{IV}-1)CC_{M1}** and **I(NR-Pt^{IV}-1)CC_M** relative to reactants. [c] Energies of **TS(NR-Pt^{IV}-1)CC_{M2}** and **P(NR-Pt^{IV}-1)CC_M** relative to **I(NR-Pt^{IV}-1)CC_M**.

For the concerted mechanism, one transition state was found for each of the reactions studied (Schemes 1 and 2) except the *meta*-CC addition of CH_2=N(CH_3)O to **Pt^{IV}-1**. For the latter process, the detailed search of the potential energy surface resulted in location of a closed-shell zwitterionic intermediate **I(NR-Pt^{IV}-1)CC_M** and two transition states **TS(NR-Pt^{IV}-1)CC_{M1}** and **TS(NR-Pt^{IV}-1)CC_{M2}** corresponding to the stepwise mechanism.[58] The reactant molecules are united in **TS(NR-Pt^{IV}-1)CC_{M1}** and **I(NR-Pt^{IV}-1)CC_M** by the CO bond. The IRC calculations demonstrated the connection along the same reaction path between these TSs and **I(NR-Pt^{IV}-1)CC_M** as well as respective reactants and the product **P(NR-Pt^{IV}-1)CC_M**.

Transition states of the CN and *meta*-CC additions to Pt complexes (except **TS(NR-Pt^{II}-2)CC_{Mex}**) as well as **TS(NR-Pt^{II}-2)CC_{Oen}**, **TS(NR-Pt^{IV}-2)CC_{Oen}**, and **I(NR-Pt^{IV}-1)CC_M** exhibit intramolecular interactions between hydrogens of the CH_2 and/or CH_3 groups of the dipole and the Cl atoms (Figure 2S). The respective Cl···H contacts are within the range of 2.60−3.05 Å. These attractive interactions even result in bending of the PtN(1)C(2) fragment in **TS(NR-Pt^{II}-1)CC_M**, **TS(NR-Pt^{IV}-1)CC_M**, **TS(NR-Pt^{IV}-2)CC_{Men}**, **TS(NR-Pt^{IV}-2)CC_{Mex}**, **TS(NR-Pt^{IV}-1)$CC_{M1(2)}$**, and **I(NR-Pt^{IV}-1)CC_M** with the PtNC angle of 127.6−158.9°, while for other TSs of the CC addition, this fragment is nearly linear. The H-bonding stabilizes the TS and provides the regio- and stereoselectivity of the corresponding reaction, at least in the gas phase (see below). Detailed analysis of the nature of transition states and the intermediate, reaction mechanisms, and synchronicity of the processes is given in the Supporting Information.

Activation Effect and Reactivity. An inspection of the electronic activation energies, enthalpies, and Gibbs free energies of activation for CH_2Cl_2 solution (E_a, $\Delta H_s^{\ddagger}$, and $\Delta G_s^{\ddagger}$, respectively, Tables 1, 2, and 3S) indicates that the cyanoalkyne N≡CC≡CH is more reactive than the cyanoalkene N≡CCH=CH_2 in all CN and CC additions by 2.38−4.13 kcal/mol (by a factor of $5.6 \times 10^1 - 1.1 \times 10^3$). Both N≡CC≡CH and N≡CCH=CH_2 ligands are predicted to be more reactive, by 0.75−3.13 kcal/mol, than N≡CCH_3[30a] toward the CN addition of CH_2=N(CH_3)O, whereas for the CA of nitrile oxide, N≡CCH_3 is slightly (by 0.28 kcal/mol)[31] more reactive than N≡CCH=CH_2.

In the case of *nitrone CAs*, the coordination of N≡CC≡CH and N≡CCH=CH_2 to Pt^{II} and, particularly, to Pt^{IV} results in the significant decrease of the activation barriers. This activation effect is the most pronounced for CA to the CN bond and reaches 18.62 kcal/mol (in terms of $\Delta G_s^{\ddagger}$) corresponding to the reaction acceleration by a factor of 4.5×10^{13} (reaction with complex **Pt^{IV}-2**). Such enhancement of the reaction rate is even higher than that for the CAs to monofunctional nitrile N≡CCH_3 (10.76−17.00 kcal/mol).[30] The *meta*-CC addition is also significantly facilitated on going from free ligands to the Pt^{IV} complexes when the activation barrier is reduced by 8.65−14.75 kcal/mol (by a factor of 2.2×10^6−6.6×10^{10}), despite the fact that the CC bond is not involved directly in a coordination to the metal center. In contrast, for the *ortho*-CC addition, the activation is much smaller, only by 4.26−6.85 kcal/mol, and the reaction rate should increase by a factor of 1.3×10^3−1.1×10^5.

In the reactions with *nitrile oxides*, the activation effect is much smaller. The maximum decrease of the $\Delta G^{\ddagger}$ value is 5.82, 6.10, and 5.08 kcal/mol for the CN, *meta*-, and *ortho*-CC additions, respectively, corresponding to the reaction acceleration by factors of 1.9×10^4, 3.0×10^4, and 5.3×10^3. In contrast to the nitrone CAs, the coordination of the ligands to Pt^{II} affects insignificantly the kinetics of the CN addition. In fact, the

(58) A minimum for the triplet biradical intermediate was also located, but it is 33.29 kcal/mol less stable than the closed-shell zwitterionic structure.

TABLE 2. Energetic Characteristics (in kcal/mol) of the Cycloadditions of $CH_3C{\equiv}NO$ to Cyanoalkenes and Cyanoalkynes at the B3LYP/6-31G* Level[a]

dipolarophile	type of addition	E_{ag} (E_{as})	$\Delta G_g^{\ddagger}$ ($\Delta G_s^{\ddagger}$)	ΔE_g (ΔE_s)	ΔG_g (ΔG_s)
N≡CC≡CH	to CN	13.90 (15.95)	24.55 (26.60)	−51.08 (−50.15)	−35.58 (−34.65)
	to CC, *meta*	11.15 (13.15)	22.36 (24.36)	−79.97 (−80.39)	−63.68 (−64.10)
	to CC, *ortho*	12.25 (12.12)	22.65 (22.52)	−76.64 (−76.93)	−60.49 (−60.78)
Pt^{II}-1	to CN	12.66 (17.61)	25.42 (30.37)	−57.70 (−52.77)	−40.33 (−35.40)
	to CC, *meta*	6.04 (9.90)	18.37 (22.23)	−82.37 (−81.24)	−65.49 (−64.36)
	to CC, *ortho*	9.61 (9.50)	19.58 (19.47)	−76.69 (−76.21)	−60.11 (−59.63)
Pt^{IV}-1	to CN	6.98 (11.86)	20.33 (25.21)	−57.55 (−53.04)	−39.22 (−34.71)
	to CC, *meta*	3.56 (8.34)	16.27 (21.05)	−83.77 (−81.93)	−65.37 (−63.53)
	to CC, *ortho*	8.58 (8.66)	21.29 (21.37)	−76.99 (−76.12)	−60.60 (−59.73)
N≡CCH=CH_2	to CN	13.50 (16.32)	26.35 (29.17)	−55.20 (−53.52)	−37.95 (−36.27)
	to CC, *meta*	12.12 (13.97)	25.21 (27.06)	−36.30 (−37.66)	−19.37 (−20.73)
	to CC, *ortho*	11.75 (12.31)	24.36 (24.92)	−36.49 (−38.57)	−19.82 (−21.90)
Pt^{II}-2	to CN	12.22 (17.82)	25.90 (31.50)	−61.37 (−55.69)	−42.43 (−36.75)
	to CC, *meta*	8.40 (11.93)	22.58 (26.11)	−35.66 (−35.90)	−18.17 (−18.41)
	to CC, *ortho*	9.46 (10.70)	22.36 (23.60)	−35.67 (−36.67)	−19.21 (−20.21)
Pt^{IV}-2	to CN	6.05 (11.69)	17.71 (23.35)	−61.24 (−55.78)	−44.86 (−39.40)
	to CC, *meta*	6.88 (10.18)	17.66 (20.96)	−35.81 (−35.36)	−18.26 (−17.81)
	to CC, *ortho*	8.69 (10.35)	18.18 (19.84)	−35.57 (−36.33)	−18.35 (−19.11)

[a] Energies corrected on the solvent effects in parentheses (CH_2Cl_2 as a solvent).

ligation of N≡CC≡CH and N≡CCH=CH_2 in complexes **Pt^{II}-1** and **Pt^{II}-2** even inhibits the reaction by 2.33−3.77 kcal/mol! It is also worthwhile to mention that **Pt^{II}-1** is predicted to be more reactive toward the *ortho*-CC addition than **Pt^{IV}-1**.

For some reactions of the complexes, the negative E_a and $\Delta H^{\ddagger}$ values relative to reactants have been obtained. Such situation was described previously for the nitrone addition to the activated acetonitrile,[30] and it is caused by formation, on the first step of the process, a molecular van der Waals complex with a total energy lower than the sum of the total energies of separated reactants. The consideration of the entropic factor for these bimolecular reactions increases the activation barriers, and the $\Delta G^{\ddagger}$ values become positive.

Reaction Energies. The calculations of the reaction energies ΔE_s, ΔH_s, and ΔG_s (Tables 1, 2, and 3S) indicate the following. First, all reactions are exothermic and exoergonic. Second, the alkenyl oxadiazolines **P(NR-X-2)CN** (X = L, Pt^{II}, Pt^{IV}) and alkenyl oxadiazoles **P(NO-X-2)CN** appear to be more stable, by 1−5 kcal/mol (in terms of ΔG_s), than the corresponding alkynyl heterocycles **P(NR-X-1)CN** and **P(NR-X-1)CN**. Third, the products of the nitrile oxide additions are more stable than those of the nitrone additions especially in case of oxadiazoles **P(NO-X-1)CN** and **P(NO-X-2)CN** and isoxazoles **P(NO-X-1)CC**, reflecting their aromatic character. Thus, the thermodynamic stability of the cycloaddition products generally increases along the following sequence: isoxazolidines **P(NR-X-2)CC** < alkynyl oxadiazolines **P(NR-X-1)CN** < alkenyl oxadiazolines **P(NR-X-2)CN** ≪ isoxazolines **P(NO-X-2)CC** ≪ isoxazole **P-(NR-X-1)CC** ≈ alkynyl oxadiazoles **P(NO-X-1)CN** < alkenyl oxadiazoles **P(NO-X-2)CN)** ≪ isoxazole **P(NO-X-1)CC**. Fourth, coordination of the ligands to Pt^{II} and, particularly, to Pt^{IV} increases the relative stability of the oxadiazolines **P(NR-X-1)CN** and **P(NR-X-2)CN** and, in smaller degree, of the *meta*-isoxazole **P(NR-X-1)CC_M** but weakly affects the stability of isoxazolidines **P(NR-X-2)CC** and products of the nitrile oxide additions.

Chemoselectivity. The 1,3-DCAs to bifunctional dipolarophiles such as cyanoalkenes and cyanoalkynes may occur either to the CN bond or to the CC bond or concurrently to both of them. The reactions of *free N≡CC≡CH and N≡CCH=CH_2* exhibit clear CC chemoselectivity (Tables 1, 2, and 3S). The additions to the CC bond (along the least energetic channel) are by 4.08−8.24 kcal/mol (in terns of $\Delta G_s^{\ddagger}$) more energetically favorable than the CN additions. Thus, the exclusive formation of CC addition products rather than oxadiazolines and oxadiazoles is expected, and this conclusion is in agreement with experimental data for the reactions of nitrones with N≡CCH=CH_2[7a,54b,59] and of mesitonitrile oxide with cyanoacetylene.[29a] The chemoselectivity is similar for the reactions of both NCCCH and N≡CCH=CH_2 with each particular dipole, while the CAs of nitrone are twice more selective (in terms of the activation barriers) in comparison with CAs of nitrile oxide.

The coordination of the ligands to Pt^{II} results in a decrease of the CC chemoselectivity for the nitrone CAs but a significant increase for the nitrile oxide CAs, and the latter reactions become more selective than the former ones. The coordination of the ligands also causes the reactions of cyanoalkynes to be more selective than those of the cyanoalkenes. Meanwhile all of the reactions of platinum(II) complexes **Pt^{II}-1** and **Pt^{II}-2** should lead exclusively to formation of the CC addition products. This is in contradiction with experimental observations on the formation of oxadiazoline as the only product in the reaction of PhCH=$N(CH_3)O$ with *trans*-[$PtCl_2${N≡CCH=CHPh}$_2$].[60] The reasons for this disagreement are discussed below (see Substituent Effects section).

The coordination of the ligands to the Pt^{IV} center leads to a decrease of the CC chemoselectivity. As a result, the difference of the activation barriers for the CN and *meta*-CC additions of CH_2=$N(CH_3)O$ reduces to 1.36 kcal/mol (**Pt^{IV}-1**) and 2.69 kcal/mol (**Pt^{IV}-2**), corresponding to the isomeric ratios of 1:10 and 1:94, respectively. The selectivity of nitrile oxide additions to **Pt^{IV}-1** and **Pt^{IV}-2** becomes comparable to that of the free ligands. Nevertheless, the ligation of N≡CC≡CH and N≡CCH=CH_2 to platinum—even in its high oxidation state—is not

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sufficient to switch chemoselectivity in the reactions with CH_2═$N(CH_3)O$ and CH_3C≡NO because of intramolecular interactions and solvent effect which make the CC pathways more preferable than the CN ones (see below).

Regio- and Stereoselectivity. The CC addition of CH_2═$N(CH_3)O$ to *free N≡CC≡CH* is predicted to have no regioselectivity (Tables 1, 2, and 3S) and should afford **P(NR-L-1)CC$_M$** and **P(NR-L-1)CC$_O$** in ratio of 47:53. For other reactions with *free N≡CC≡CH and N≡CCH═CH$_2$*, the CC addition along the *ortho* pathway is more favorable (by 1.60−2.14 kcal/mol) in comparison to the *meta* pathways, and formation of the *meta*-cycloadducts is expected only in a small amount. These results are consistent with the experimental[7a,54b,61] and theoretical[6c,10,29c] data on the reactions of PhCH═$N(CH_2CH_2CN)O$, cyclic nitrones, and HC≡NO with N≡CCH═CH_2 and of RC≡NO (R = H, 2,4,6-$(CH_3)_3C_6H_2$) with N≡CC≡CH. At the same time, no regioselectivity is predicted theoretically for the CA of CH_2═$N(H)O$[10] and CH_3CH═$N(H)O$[11] to N≡CCH═CH_2, while R_2C═$N(R')O$ (R = *cyclo*-C_3H_5, R′ = Me; R = Ph, R′ = Me, Ph)[59,62] and *N*-methylfluorenoneimine-*N*-oxide[63] react with acrylonitrile to give the *meta*-isomer as the dominant or the sole product. This demonstrates that the substituent nature may significantly affect the reaction course (see Substitution Effects section).

The additions to *the Pt^{II} complexes* exhibit even higher *ortho*-selectivity except the reaction of CH_2═$CN(CH_3)O$ with **Pt^{II}-1** which becomes clearly *meta*-selective. Finally, the *coordination of N≡CC≡CH and N≡CCH═CH$_2$ to the Pt^{IV}* center results in significant facilitation of the *meta* approaches. The reactions of the nitrone are completely *meta*-selective, while the interactions of CH_3C≡NO with **Pt^{IV}-1** and **Pt^{IV}-2** should lead to the mixture of the *meta*- and *ortho*-isomers in the ratios of 63:37 and 13:87, correspondingly. The previous theoretical studies of the reaction of CH_2═N(H)O with another electron-deficient alkene (e.g., acrolein CH_2═CHCHO) also demonstrated the great increase of the *meta*-selectivity upon interaction of the dipolarophile with such Lewis acid as BH_3.[64]

The reaction of CH_2═$N(CH_3)O$ with N≡CCH═CH_2 is not stereoselective. The products of this process are formed in the isomeric ratio **P(NR-L-2)CC$_{Men}$/P(NR-L-2)CC$_{Mex}$/P(NR-L-2)CC$_{Oen}$/P(NR-L-2)CC$_{Oex}$** ≈ 3:3:48:46. For the nitrone additions to **Pt^{II}-2** and **Pt^{IV}-2**, the *exo* approaches become more favorable, by 0.84 kcal/mol (**Pt^{II}-2**, *ortho* channel) and 3.68 kcal/mol (**Pt^{IV}-2**, *meta* channel) in comparison with the *endo* approaches. In fact, in the latter reaction, the almost exclusive formation of *exo-meta*-isoxazolidine is predicted. Thus, the coordination of cyanoalkenes and cyanoalkynes to Pt^{II} and Pt^{IV} is a promising and effective way to control regio- and stereoselectivity of 1,3-DCA to the CC multiple bonds.

Another important factor which greatly affects the electronic activation energies and, therefore, determines the regio- and stereoselectivity is the intramolecular interactions in the transition states. Indeed, for the metal-mediated CC additions, TSs bearing the stabilizing H-bonding (**TS(X-Y-Z)CC$_{M(en)}$**, **TS(NR-Pt^{IV}-2)CC$_{Mex}$**, and **TS(NR-Y-2)CC$_{Oen}$**; X = NR, NO; Y = Pt^{II}, Pt^{IV}; Z = 1, 2, see above) *always* have lower total energy than the TSs of other regio- and stereoisomeric routes with no intramolecular interactions (**TS(X-Y-Z)CC$_{O(ex)}$**, **TS(NR-Pt^{II}-2)CC$_{Mex}$**). TSs with the H-bonding sufficiently strong to distort the structure (**TS(NR-Y-1)CC$_M$** and **TS(NR-Pt^{IV}-2)CC$_{M(en,ex)}$**) have the lowest relative energies. Hence, a modification of reactants' molecules leading to formation of H-bonds in the TS, for example, by introducing appropriate substituents, should reduce the energy of this particular TS, and it is another way to control the selectivity. The structures of TSs with the intramolecular H-bonds are rigid enough to preserve this bonding in solutions. Indeed, the full geometry optimization of, for instance, **TS(NO-Pt^{II}-1)CC$_M$** at the CPCM level does not result in any changes of the intramolecular H-bonding.

TABLE 3. Activation Energies (E_{as}) and Gibbs Free Energies of Activation ($\Delta G_s^{\ddagger}$) in Solutions (in kcal/mol) for the Reaction of CH_2═$N(CH_3)O$ with Pt^{IV}-2 Calculated at the B3LYP/6-31G* Level

type of addition	solvent	E_{as}	$\Delta G_s^{\ddagger}$	solvent	E_{as}	$\Delta G_s^{\ddagger}$
to CN	heptane	−2.59	9.06	C_2H_5OH	0.91	12.56
to CC, *meta*, *endo*		−1.16	11.05		0.49	12.70
to CC, *meta*, *exo*		−1.82	10.80		−1.46	11.16
to CC, *ortho*, *endo*		2.81	14.24		3.13	14.56
to CC, *ortho*, *exo*		3.83	16.17		2.05	14.39
to CN	C_6H_6	−2.94	8.71	CH_3CN	−1.70	9.95
to CC, *meta*, *endo*		−1.53	10.68		−1.29	10.92
to CC, *meta*, *exo*		−2.76	9.86		−6.16	6.46
to CC, *ortho*, *endo*		2.60	14.03		2.12	13.55
to CC, *ortho*, *exo*		3.36	15.70		1.75	14.09
to CN	$CHCl_3$	−1.82	9.83	H_2O	1.08	12.73
to CC, *meta*, *endo*		−1.08	11.13		0.11	12.32
to CC, *meta*, *exo*		−4.27	8.35		−2.26	10.36
to CC, *ortho*, *endo*		2.48	13.91		3.06	14.49
to CC, *ortho*, *exo*		2.70	15.04		1.51	13.85
to CN	CH_2Cl_2	−0.50	11.15			
to CC, *meta*, *endo*		−0.07	12.14			
to CC, *meta*, *exo*		−4.16	8.46			
to CC, *ortho*, *endo*		3.33	14.76			
to CC, *ortho*, *exo*		3.17	15.51			

Solvent Effects. In the previous sections, the reactivity and selectivity of the processes studied were analyzed in terms of the Gibbs free energy in only CH_2Cl_2 solution. In the current part of the article, we attempt to verify how the solvation and solvent nature affect the reaction course. Comparison of the $\Delta G_g^{\ddagger}$ and $\Delta G_s^{\ddagger}$ values and also the $\Delta G_s^{\ddagger}$ magnitudes for different solvents reveals the following (Tables 1−4, 3S, and 4S). First, solvation by any of the solvents listed in Tables 3, 4, and 4S leads to a growth of activation barriers of the CN and (*endo*)-*meta*-CC additions by 0.53−5.64 kcal/mol, and such inhibition increases on going from the free ligands N≡CC≡CH and N≡CCH═CH_2 to the Pt^{IV} complexes. Second, the different situation was found for the *ortho*-CC and *exo-meta*-CC additions, that is, the solvent effects result in acceleration or only weak inhibition of the reactions along these channels. For CAs to the free dipolarophiles, there is a general correlation between the relative solvent effect and dipole moment of the TS, that is, the higher the dipole moment, the lower the solvent effect (Tables 1, 2, 3S, and 5S). However, this trend is not always fulfilled for CAs to the Pt complexes, indicating the importance of the nonelectrostatic component in the total solvent effect.[30b]

Third, solvation is a key factor determining, in some cases, direction of the process. Indeed, for the reactions of CH_2═$N(CH_3)O$ with cyanoalkenes, the change of chemoselectivity from the CC- to CN-type is predicted for the gas phase upon coordination of N≡CCH═CH_2 to Pt^{II} and Pt^{IV}, but solvation prevents such a switch due to a higher inhibition of the CN

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TABLE 4. Activation Energies (E_{as}) and Gibbs Free Energies of Activation ($\Delta G_s^{\ddagger}$) in Solutions (in kcal/mol) for the Reactions of CH_2═$N(CH_3)O$ with Pt^{IV}-1 and N≡CCH═CH_2 Calculated at the B3LYP/6-31G* Level

type of addition	solvent	E_{as}	$\Delta G_s^{\ddagger}$
Reaction: CH_2═$N(CH_3)O$ + **Pt^{IV}-1**			
to CN	heptane	−2.75	10.48
to CC, *meta*		−4.58	8.76
to CN	C_6H_6	−3.20	10.03
to CC, *meta*		−5.04	8.30
to CN	$CHCl_3$	−2.52	10.71
to CC, *meta*		−3.65	9.69
to CN	CH_2Cl_2	−1.31	11.92
to CC, *meta*		−2.78	10.56
to CN	C_2H_5OH	−1.14	12.09
to CC, *meta*		−2.40	10.94
to CN	CH_3CN	−2.68	10.55
to CC, *meta*		−3.97	9.37
to CN	H_2O	−0.55	12.68
to CC, *meta*		−2.07	11.27
Reaction: CH_2═$N(CH_3)O$ + N≡CCH═CH_2			
to CN	heptane	14.73	28.23
to CC, *meta*, *exo*		9.10	23.11
to CN	C_6H_6	14.38	27.88
to CC, *meta*, *exo*		8.65	22.66

addition than the CC ones. The change of regio- and/or stereoselectivity (from the *meta* to *ortho* channel and from the *endo* to *exo* approach) is also found for the reactions of CH_2═$N(CH_3)O$ with N≡CC≡CH, **Pt^{II}-2**, and **Pt^{IV}-2** and of CH_3C≡NO with N≡CC≡CH, **Pt^{II}-1**, and **Pt^{IV}-2** on going from the gas phase to the solution.

Fourth, variation of the solvent provides significant changes of the reactivity and even selectivity. The reaction of CH_2═$N(CH_3)O$ with **Pt^{IV}-2** should occur at the CC bond with solvents of high and medium polarity, but it proceeds in another direction, namely, at the CN bond in benzene and heptane solutions, that is, with the most nonpolar solvents of the selected series. In the latter cases, the predicted CN/*exo*-*meta*-CC isomeric ratio reaches 19:1, while for the CH_2Cl_2 solution, this ratio is 1:94. Thus, the solvent nature is among the most important factors, which allows the control of selectivity in the reactions studied. In contrast to **Pt^{IV}-2**, for additions of CH_2═$N(CH_3)O$ to the free N≡CCH═CH_2, a variation of the solvent does not lead to the switch of the selectivity. The same holds true also for the nitrone CA to **Pt^{IV}-1**; CC selectivity in heptane and benzene becomes even higher in comparison to that of other solvents.

Fifth, for the reactions of CH_2═$N(CH_3)O$ with **Pt^{IV}-1** and **Pt^{IV}-2**, the CN and (*endo*)-*meta*-CC additions are facilitated on going from the polar to low-polar solvents, with the exception of acetonitrile, for which the comparatively low activation barriers were obtained (Tables 3, 4, and 4S and Figure 1). This finding is similar to that for the reactions of cyclic nitrones with coordinated acetonitrile.[30b] Surprisingly, the *exo*-*meta*-CC addition of CH_2═$N(CH_3)O$ to **Pt^{IV}-2** in heptane and benzene is characterized by a relatively high activation barrier, close to that for water or ethanol solutions. This is because of the relatively small stabilizing electrostatic component in the total solvent effect for this reaction in the nonpolar solvents. The *endo*-*ortho*-CC addition is only weakly affected by the solvent nature, while the reaction along the *exo*-*ortho*-CC route is inhibited from the polar to nonpolar solvents.

Substituent Effects. The calculations predict that the reaction of nitrone CH_2═$N(CH_3)O$ with complex **Pt^{II}-2** occurs preferably at the CC bond rather than at the CN one. However, the

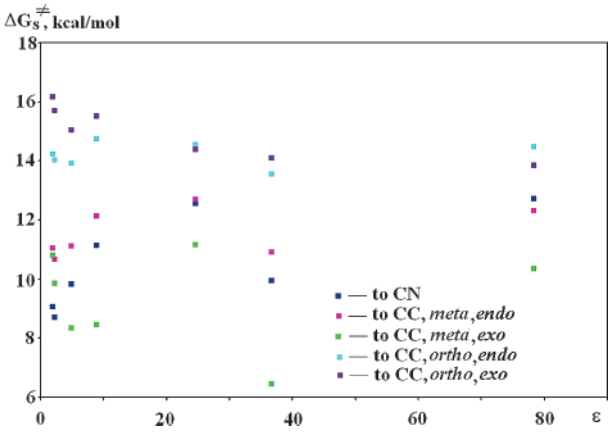

FIGURE 1. Dependence of the $\Delta G_s^{\ddagger}$ values on the dielectric constant (ϵ) of the solvent for the reaction of CH_2═$N(CH_3)O$ with **Pt^{IV}-2**.

TABLE 5. Activation Parameters (in kcal/mol) of the Cycloaddition Reactions of Phenyl-Substituted Reactants Calculated at the B3LYP/6-31G* Level[a]

dipolarophile	type of addition	E_{ag} (E_{as})	$\Delta H_g^{\ddagger}$	$\Delta G_g^{\ddagger}$ ($\Delta G_s^{\ddagger}$)
	Dipole − CH_2═$N(CH_3)O$			
Pt^{II}-2Ph	to CN	3.57 (9.57)	4.40	18.23 (24.23)
	to CC, *meta*, *endo*	8.39 (13.52)	9.04	23.15 (28.28)
	to CC, *meta*, *exo*	11.87 (15.67)	12.66	25.80 (29.60)
	to CC, *ortho*, *endo*	9.72 (13.42)	10.40	24.47 (28.17)
	to CC, *ortho*, *exo*	12.82 (14.74)	13.52	26.15 (28.07)
Pt^{IV}-1Ph	to CN	−2.59 (3.23)	-2.02	10.86 (16.68)
	to CC, *meta*	−1.84 (2.01)	-1.45	12.37 (16.22)
	Dipole − PhCH═$N(CH_3)O$			
Pt^{II}-2	to CN	5.31 (12.72)	5.94	20.76 (28.17)
	to CC, *meta*, *endo*	7.06 (11.24)	7.87	22.03 (26.21)
	to CC, *meta*, *exo*	9.80 (13.30)	10.47	24.70 (28.20)
	to CC, *ortho*, *endo*	10.40 (12.32)	11.04	25.05 (26.97)
	to CC, *ortho*, *exo*	13.44 (14.95)	14.04	27.89 (29.40)
Pt^{II}-2Ph	to CN	6.88 (15.93)	7.49	22.24 (31.29)
	to CC, *meta*, *endo*	14.72 (22.00)	15.13	29.84 (37.12)
	to CC, *meta*, *exo*	18.06 (25.32)	18.39	33.25 (40.51)
	to CC, *ortho*, *endo*	20.84 (27.59)	21.11	35.90 (42.65)
	to CC, *ortho*, *exo*	22.20 (27.83)	22.60	37.35 (42.98)
Pt^{II}-1Ph	to CN	8.36 (15.80)	8.69	22.99 (30.43)
	to CC, *meta*	5.89 (12.62)	6.29	21.50 (28.23)

[a] Energies corrected on the solvent effects in parentheses (CH_2Cl_2 as a solvent).

experimental data suggest that the reaction of PhCH═$N(CH_3)O$ with *trans*-[$PtCl_2${N≡CCH═CHPh}$_2$] leads to exclusive formation of CN addition products.[60] We proposed that such disagreement is accounted for by the substituents (phenyl groups) at the nitrone and dipolarophile molecules, which affect the chemoselectivity of the reaction. In order to prove this hypothesis, theoretical studies of the reactions of RCH═$N(CH_3)O$ (R = H, Ph) with *trans*-[$PtCl_2${N≡CCH═CH_2}{N≡CCH═CHR′}] (R′ = H, **Pt^{II}-2**; Ph, **Pt^{II}-2Ph**), *trans*-[$PtCl_2${N≡CC≡CH}{N≡CC≡CPh}] (**Pt^{II}-1Ph**), and *trans*-[$PtCl_4${N≡CC≡CH}{N≡CC≡CPh}] (**Pt^{IV}-1Ph**) have been undertaken (Schemes 1 and 2).

The introduction of the Ph group either to the dipole or to the dipolarophile or to both of them results in the enhancement of the activation barriers in comparison with nonsubstituted reactants (Table 5). For the reaction of C-phenylnitrone PhCH═$N(CH_3)O$ with the cyanoalkene complex **Pt^{II}-2**, the CC additions remain more favorable than the CN addition, while the reactions

TABLE 6. Decomposition of the Activation Energy (E_a) onto the Distortion Energy of Dipolarophile (E_{dist}^{DF}), Distortion Energy of Nitrone (E_{dist}^{NR}), and Interaction Energy (E_{int}) (in kcal/mol)

dipolarophile	type of addition	E_{dist}^{DF}	E_{dist}^{NR}	E_{int}
	Dipole − CH_2═$N(CH_3)O$			
Pt^{II}-2	to CN	20.50	9.33	−27.72
	to CC, *meta*, *endo*	12.74	11.38	−21.81
	to CC, *meta*, *exo*	11.50	11.09	−17.32
	to CC, *ortho*, *endo*	8.23	10.55	−16.36
	to CC, *ortho*, *exo*	7.46	10.26	−12.61
Pt^{II}-2Ph	to CN	21.02	9.51	−26.96
	to CC, *meta*, *endo*	13.25	14.21	−19.07
	to CC, *meta*, *exo*	14.45	14.60	−17.18
	to CC, *ortho*, *endo*	13.30	14.53	−18.11
	to CC, *ortho*, *exo*	14.27	15.25	−16.70
	Dipole − PhCH═$N(CH_3)O$			
Pt^{II}-2	to CN	23.53	13.36	−31.58
	to CC, *meta*, *endo*	16.28	15.54	−24.76
	to CC, *meta*, *exo*	16.68	15.53	−22.41
	to CC, *ortho*, *endo*	11.16	17.87	−18.63
	to CC, *ortho*, *exo*	10.55	18.36	−15.47
Pt^{II}-2Ph	to CN	24.05	13.42	−30.59
	to CC, *meta*, *endo*	17.45	19.05	−21.78
	to CC, *meta*, *exo*	21.53	18.31	−21.78
	to CC, *ortho*, *endo*	17.89	22.62	−19.67
	to CC, *ortho*, *exo*	17.05	23.40	−18.25

of CH_2═$N(CH_3)O$ with **Pt^{II}-2Ph** and, particularly, of PhCH═$N(CH_3)O$ with **Pt^{II}-2Ph** become completely CN chemoselective, consistent with the experimental data. Thus, the variation of substituents, especially at the dipolarophile molecule, allows the modification of the reaction selectivity.

It is interesting to note that, for the reactions between PhCH═$N(CH_3)O$ and **Pt^{II}-1Ph** and between CH_2═$N(CH_3)O$ and **Pt^{IV}-1Ph**, a switch of the chemoselectivity is not predicted although the difference of the $\Delta G_s^{\ddagger}$ values of the CN and *meta*-CC channels becomes smaller than that for the reaction of unsubstituted reactants.

The switch of the selectivity upon introduction of the Ph groups into the cyanoalkene molecule may be determined by several factors such as steric repulsions imposed by the Ph groups, the electronic factors caused by the electron acceptor character of the phenyl group, and the additional H-bonding emerging when new substituents are inserted. In order to analyze the first of these factors, we decomposed the gas-phase activation energies E_a onto three components. The formation of a transition state may be represented as the sum of the following processes: (1) distortion of the dipolarophile molecule from the equilibrium geometry to the geometry corresponding to the TS [dipolarophile^{eq} → dipolarophile*, $E_{dist}^{DF} = E$(dipolarophile*) − E(dipolarophile^{eq})]; (2) distortion of the nitrone molecule from the equilibrium geometry to the geometry corresponding to the TS [nitrone^{eq} → nitrone*, $E_{dist}^{NR} = E$(nitrone*) − E(nitrone^{eq})]; (3) interaction of the distorted fragments to form the TS [dipolarophile* + nitrone* → TS, $E_{int} = E$(TS) − (E(dipolarophile*) + E(nitrone*))] (Table 6). Therefore, $E_a = E_{dist}^{DF} + E_{dist}^{NR} + E_{int}$.

For the reaction of unsubstituted reactants CH_2═$N(CH_3)O$ and **Pt^{II}-2**, the distortion energy, E_{dist}^{DF}, and interaction energy, E_{int}, are similar for the CN addition and also for the CC additions providing similarity of E_a for all processes. The introduction of the Ph group into reactant(s) leads to an increase of E_{dist}^{DF} and E_{dist}^{NR}, while the E_{int} term varies much less. This enhancement (i.e., relative reactants' destabilization) is higher for CC additions in comparison to the CN addition—somewhat in case of the reaction PhCH═$N(CH_3)O$ + **Pt^{II}-2**, noticeably for CH_2═$N(CH_3)O$ + **Pt^{II}-2Ph**, and very significantly for PhCH═$N(CH_3)O$ + **Pt^{II}-2Ph**. Thus, the substituent effect on the chemoselectivity is accounted for by the greater increase of the E_{dist} terms for CC additions than for the CN ones upon insertion of the Ph group(s).

Such growth of the E_{dist} values from unsubstituted to substituted reactants is determined by two main factors: First, steric repulsion imposed by the bulky Ph groups in the TSs and, second, the loss of a conjugation in phenylnitrone and phenylcyanoalkene molecules at the TS formation.[65] Both of these reasons are more pronounced for CC than for CN additions.

Other possible reasons for the substituent effect, such as the relative change of the HOMO and LUMO energies of the reactants due to electron acceptor character of the Ph group and additional attractive intramolecular interactions in TSs, are not effective for the reactions studied. Indeed, the alteration of the reactivity upon the variation of the substituents does not correlate with the FMO energies (Tables 1, 5, 1S, and 3S), and the insertion of the Ph group does not provide any new intramolecular Cl···H interactions (Figure 2S).

Final Remarks

The intentional regulation of chemo-, regio-, and stereoselectivity of 1,3-DCA is an important problem of synthetic organic chemistry. In the present work, extensive theoretical study of the cycloaddition reactions of nitrones and nitrile oxides (dipoles of allyl and propargyl/allenyl anion types, respectively) to bifunctional dipolarophiles bearing both C≡N and C═C/C≡C dipolarophilic groups has been undertaken. It was shown that the selectivities of these processes depend on a delicate balance between different factors such as electronic structure of reactants and transition states, steric repulsive interactions, intramolecular attractive interactions, and solvent effects; all of these factors were investigated, and certain well-defined trends were verified and discussed in detail. The modification of selectivity may be reached by three main ways (or by their combinations), that is, coordination of a dipolarophile to a Lewis acid (e.g., platinum center selected for this study), variation of substituents, and usage of the appropriate solvent.

The CAs to *uncoordinated* N≡CC≡CH and N≡CCH═CH_2 species occur exclusively at the CC bonds. For the reactions of nitrone, *ligation* of the dipolarophiles to Pt^{II} and, particularly, to Pt^{IV} via the N atom results in (i) their great activation toward the CN and *meta*-CC additions and (ii) significant facilitation of the CN versus CC additions. Nevertheless, the application of platinum as a Lewis acid even in its high oxidation state (Pt^{IV}) is not sufficient to switch the chemoselectivity from the CC- to the CN-type. In the case of the nitrile oxide CAs, the situation is more complex: only a weak activation or even inhibition of the processes is predicted on going from the free ligands to the complexes.

Coordination of the dipolarophiles to Pt also affects the regio- and stereoselectivity; that is, it usually favors the *meta* versus *ortho* pathways and *endo* versus *exo* pathways that sometimes

(65) A conjugation between the CC and CN bonds in N≡CCH═CH_2 also takes place. However, upon its breaking, the destabilization of N≡CCH═CHPh is stronger than that of N≡CCH═CH_2 because of more extended conjugated system in the former case involving also the phenyl group.

lead to a switch of the reaction direction. One of the main factors determining this influence is intramolecular interactions between hydrogen and chlorine atoms of reactants usually stabilizing the *meta* and *endo* approaches.

Variation of the substituents at the dipole and dipolarophile molecules, namely, an introduction of the phenyl groups, facilitates the CN versus the CC additions. This effect is the most significant for the reaction $PhCH{=}N(CH_3)O$ + **Pt^{II}-2Ph**, and the switch of the chemoselectivity from the CC to CN cycloaddition takes place. The substituent effect is caused by two main reasons: steric repulsion imposed by the bulky Ph groups in TSs and the loss of conjugation in phenylnitrone and phenylcyanoalkene molecules upon the TS formation.

Solvation results in significant inhibition of the CN and (*endo*)-*meta*-CC additions in comparison to the gas phase but in weak inhibition or even acceleration of the *ortho*-CC and *exo*-*meta*-CC additions (for the reactions of $CH_2{=}N(CH_3)O$ with cyanoalkenes). Furthermore, solvation generally favors CC rather than CN addition, *ortho* rather than *meta* addition, and *exo* rather than *endo* addition, the effects opposite to those induced by the platinum center. The usage of a low polar solvent (such as heptane or benzene) promotes the addition at the CN bond, whereas solvents of high or medium polarity relatively facilitate the *meta*-CC addition. Thus, the best conditions for the switch of the chemoselectivity are the usage of the coordinated phenyl-substituted dipolarophiles and performance of the reaction in low polar solvents.

The mechanistic studies revealed that all reactions apart from one ($CH_2{=}N(CH_3)O$ + **Pt^{IV}-1**) proceed via a concerted mechanism, nearly synchronous for the CN and *meta*-CC additions to free ligands and asynchronous for the other processes (particularly for CAs to Pt^{IV}-bound dipolarophiles). Transition states of all of these reactions have a five-membered cyclic nature. In the case of the reaction of $CH_2{=}N(CH_3)O$ with the complex **Pt^{IV}-1**, a stepwise mechanism (involving the formation of two TSs and a zwitterionic intermediate) is realized instead of concerted one.

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Supporting Information Available: Discussions of the influence of the method and basis set on the energetic characteristics of the processes, of the FMO composition, of the nature of the transition states, plots of selected FMOs, general view of all equilibrium structures, contour line diagrams of the Laplacian distribution, bond paths and selected zero-flux surfaces for **TS-(NR-Pt^{IV}-1)CC_{M1}** and **TS(NR-Pt^{IV}-1)CC_{M2}**, tables with Cartesian coordinates, calculated bond lengths, energies of frontier molecular orbitals, total energies, enthalpies, Gibbs free energies, most important characteristics of TSs, effective NBO atomic charges of reactants, complete versions of Tables 1−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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