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Comparative Theoretical Study of 1,3-Dipolar Cycloadditions of Allyl-Anion Type Dipoles to Free and Pt-Bound Nitriles

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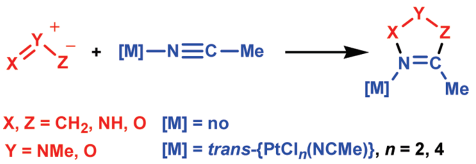

1,3-Dipolar cycloadditions of a series of 12 allyl-anion type 1,3-dipoles $X{=}Y^{+}{-}Z^{-}$ (X, Z = CH_2, NH, O; Y = N(Me), O) to acetonitrile MeC≡N, both free and coordinated to Pt^{II} and Pt^{IV} in the complexes *trans*-$[PtCl_n(NCMe)_2]$ (n = 2, 4), were investigated by theoretical methods. The reactivity increases along the following sequence of dipoles, the first three being inert toward nitriles: ON(Me)O < NHN(Me)O < NHN(Me)NH < $CH_2N(Me)O$ < OOO ≈ NHONH < $CH_2N(Me)NH$ < NHOO < $CH_2N(Me)CH_2$ < CH_2OCH_2 ≈ CH_2ONH < CH_2OO. The thermodynamic stability of the cycloaddition products (reaction energies) inversely correlates with the activation energies with exception of dioxadiazoles $\overline{\mathrm{N{=}C(Me)OON}}\mathrm{H}$ which cannot exist in the uncoordinated state. A complete *ortho* selectivity of these reactions is predicted. Coordination of MeCN to platinum accelerates the reactions of $CH_2N(Me)CH_2$, CH_2ONH, and particularly $CH_2N(Me)O$ and $CH_2N(Me)NH$ and stabilizes the corresponding products. Coordination accelerates the reactions of CH_2OCH_2, CH_2OO, and NHONH only slightly and inhibits the reactions of NHOO and OOO. The cycloadditions of nitrones to nitriles are potentially interesting for dynamic combinatorial chemistry. The details of the reaction mechanisms and correlations of activation and reaction energies, synchronicity, and charge transfer vs dipole nature, FMO energies, atomic charges, HSAB properties, distortion energies, and regioisomeric pathways are discussed.

Introduction

1,3-Dipolar cycloaddition (CA) is a general and extremely effective route for the synthesis of a great variety of heterocyclic systems, many of them with laboratory, industrial, or pharmacological applications.[1] Alkenes and alkynes are the most explored dipolarophiles in the cycloaddition reactions, while heteroatomic dipolarophiles, e.g., organonitriles RC≡N bearing the C≡N triple bond, are investigated scarcely. The most well-studied type of cycloadditions to nitriles is their reaction with azides (Scheme 1).[2−5] This process allows the synthesis of tetrazoles exhibiting important medicinal and industrial properties.[2,6] Reactions of

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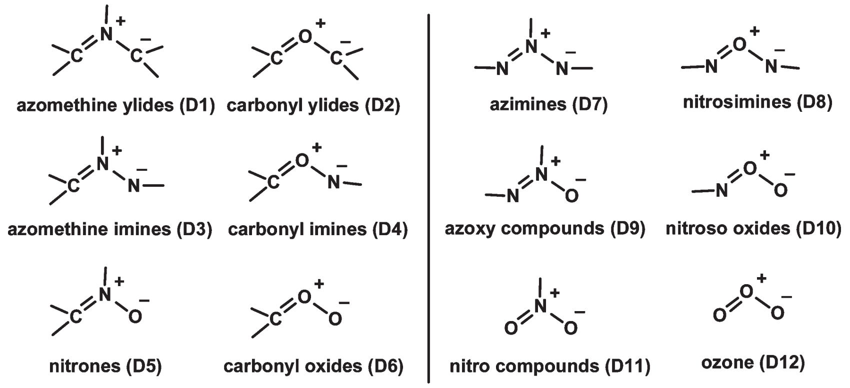
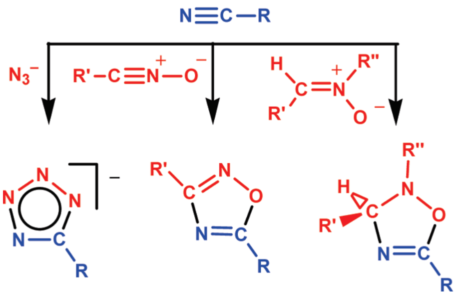


FIGURE 1. 1,3-Dipoles of the allyl-anion type (numbering is given for the dipoles studied in this work).

SCHEME 1. Reactions of Nitriles with Azides, Nitrile Oxides, and Nitrones



RCN with dipoles of two other types, i.e., nitrile oxides[7,8] and nitrones,[9,10] were also investigated, mostly recently, by both experimental[7,9] and theoretical[8,10] methods, and they result in the formation of 1,2,4-oxadiazoles and 2,3-dihydro-1,2,4-oxadiazoles, respectively (Scheme 1).

The considerable chemical inertness of nitriles is one of the main factors restricting their usage in the cycloaddition reactions. This problem was successfully overcome by the application of transition-metal complexes as promoters of the reaction. Rather recently, it was found that the coordination of RCN to platinum in complexes *trans*-$[PtCl_n(N{\equiv}CR)_2]$ ($n = 2, 4$) dramatically enhances the reactivity of nitriles, opening up a facile route for the synthesis (performed under mild conditions) of little explored classes of heterocycles such as 2,3-dihydro-1,2,4-oxadiazoles.[9,10] This metal in the oxidation states +II and, in particular, +IV is among the best activators of RCN, although other metals, e.g., Pd,[7b,11,12] Zn,[4a] Co,[5] and some others,[2] also exhibit an activation effect. The strong effect of platinum on the reactivity of RCN species toward cycloadditions is accounted for by two main factors.[10,13] (i) The high affinity of Pt to nitriles provides the exclusive coordination of RCN but not a dipole to the metal center. The resulting decrease of the $LUMO_{nitrile}$ energy and the $HOMO_{dipole}-LUMO_{nitrile}$ gap leads to facilitation of the normal electron-demand cycloadditions. (ii) The coordination of RCN to a metal in a high oxidation state (e.g., Pt^{IV}) shifts significantly the electron density from the ligand to the metal and enhances the atomic charge on the nitrile carbon atom.[14] This, in turn, facilitates the asynchronous cycloaddition reactions, for which the electrostatic factors play an important role.

Among 12 conventional 1,3-dipoles of the allyl-anion type (Figure 1), only nitrones were systematically studied in the reactions with nitriles, whereas the reactivity of the other 11 dipoles toward the C≡N bond of RCN is almost unexplored by both experimental and theoretical methods. Thus, this work is the first attempt to fill this gap, and its essential goal is a systematic and detailed theoretical study of cycloaddition reactions of nitriles with the whole series of the allyl-anion type 1,3-dipoles. Within this goal the following problems were addressed: first, the investigation and comparison of the reactivity of various dipoles toward nitriles; second, the analysis of how the coordination of RCN to Pt^{II} and Pt^{IV} (which greatly activates nitriles in the reactions with nitrones and nitrile oxides) works for other dipoles;[15] third, the consideration of details of the reaction mechanism and an estimate of the activation and reaction energies of the processes studied; fourth, the analysis of the regio- and stereoselectivity of the cycloadditions to nitriles; fifth, the examination and discussion of various trends and correlations between kinetic and thermodynamic parameters of the reactions (activation, reaction energies, distortion, and interaction energies), features of the reaction mechanisms (synchronicity, nature of transition states, charge transfer), and the electronic structure of dipoles (including the composition and energies of frontier molecular orbitals (FMO), charge distribution, and hard–soft acid–base (HSAB)

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properties). The cycloadditions of 12 dipoles $X{=}Y^{+}{-}Z^{-}$ (X, Z = CH_2, NH, O; Y = O, NMe) (**D1−D12**) (Figure 1) with acetonitrile $MeC{\equiv}N$, free and coordinated to Pt^{II} and Pt^{IV} centers in the complexes *trans*-$[PtCl_n(N{\equiv}CMe)_2]$ [n = 2 (**1**), 4 (**2**)], were studied in this work.

Computational Details

The full geometry optimization of all structures and transition states (TS) has been carried out at the DFT/HF hybrid level of theory using Becke's three-parameter hybrid exchange functional in combination with the gradient-corrected correlation functional of Lee, Yang, and Parr (B3LYP)[16] with the help of the Gaussian-98[17] program package. Restricted approximations for the structures with closed electron shells and unrestricted methods for the structures with open electron shells have been employed. A stability test was carried out using the keyword STABLE in Gaussian-98. As a result, instability of wave functions at the restricted methods was found for CH_2OCH_2, CH_2ONH, NHONH, NHOO, and OOO. Hence, for these structures, unrestricted approximations were used with following reoptimization of the wave functions to achieve a stable solution. For dipoles $CH_2N(Me)NH$, NHN(Me)NH, NHONH, and NHN(Me)O, all possible *syn* and *anti* isomers were calculated, and the activation and reaction energies relative to the most stable ones are discussed. No symmetry operations have been applied. The geometry optimization was carried out using a quasi-relativistic Stuttgart pseudopotential that described 60 core electrons and the appropriate contracted basis set (8s7p6d)/[6s5p3d][18] for the platinum atom and the 6-31G(d) basis set for other atoms. Then, single-point calculations were performed on the basis of the equilibrium geometries found using the 6-311+G(d,p) basis set for nonmetal atoms. The basis set superposition error was not estimated because it weakly affects the activation and reaction energies of cycloadditions to nitriles, as shown previously.[10b,c]

To test the applicability of the used method, the structures of reactants, products, and TSs of all metal-free reactions have also been computed at the CBS-Q level.[19] The difference of the activation energies obtained by the B3LYP and CBS-Q methods is within 3 kcal/mol while that of the reaction energies is higher and in the range of 0.9−10.3 kcal/mol, B3LYP overestimating the exoergic character of the reactions. However, the correlation between the B3LYP and CBS-Q energies for various dipoles is perfect ($R^2 = 0.99$, Figure 1S, Table 1S in Supporting Information) making the B3LYP values to be reliable for the analysis of the *relative* reactivity of various dipoles, the main subject of the present work.

The Hessian matrix was calculated analytically for the optimized structures in order to prove the location of correct minima (no imaginary frequencies) or saddle points (only one negative frequency) and to estimate the thermodynamic parameters, the latter being calculated at 25 °C. For some structures of the complexes, a "wrong" imaginary frequency corresponding to the rotation of the methyl group of the unreacting MeCN ligand was found. However, its value does not exceed 15i cm^{-1} providing no noticeable influence on the total energy. The nature of all transition states was investigated by the analysis of vectors associated with the imaginary frequency and, in some cases, by the calculations of the intrinsic reaction coordinates (IRC) using the Gonzalez−Schlegel method.[20]

Total energies corrected for solvent effects (E_s) were estimated at the single-point calculations on the basis of gas-phase geometries at the CPCM-B3LYP/6-311+G(d,p)//gas-B3LYP/6-31G(d) level of theory using the polarizable continuum model in the CPCM version[21] with CH_2Cl_2 as solvent. The entropic term in CH_2Cl_2 solution (S_s) was calculated according to the procedure described by Wertz[22] and Cooper and Ziegler[23] using eqs 1 − 4

$$\Delta S_1 = R \ln V^{s}{}_{m,\,liq}/V_{m,\,gas} \tag{1}$$

$$\Delta S_2 = R \ln V^{\circ}{}_{m}/V^{s}{}_{m,\,liq} \tag{2}$$

$$\alpha = \frac{S^{\circ,\,s}{}_{liq} - (S^{\circ,\,s}{}_{gas} + R \ln V^{s}{}_{m,\,liq}/V_{m,\,gas})}{(S^{\circ,\,s}{}_{gas} + R \ln V^{s}{}_{m,\,liq}/V_{m,\,gas})} \tag{3}$$

$$\begin{aligned} S_s &= S_g + \Delta S_{sol} = S_g + [\Delta S_1 + \alpha(S_g + \Delta S_1) + \Delta S_2] \\ &= S_g + [(-11.80\ \mathrm{cal/mol{\cdot}K}) - 0.213(S_g - 11.80\ \mathrm{cal/mol{\cdot}K}) \\ &\quad + 5.45\ \mathrm{cal/mol{\cdot}K}] \end{aligned} \tag{4}$$

where S_g is the gas-phase entropy of solute, ΔS_{sol} is the solvation entropy, $S^{\circ,s}{}_{liq}$, $S^{\circ,s}{}_{gas}$, and $V^{s}{}_{m,liq}$ are the standard entropies and molar volume of the solvent in liquid or gas phases (173.84 and 270.28 J/mol·K and 64.15 mL/mol, respectively, for CH_2Cl_2), $V_{m,gas}$ is the molar volume of the ideal gas at 25 °C (24450 mL/mol), and $V^{\circ}{}_{m}$ is the molar volume of the solution corresponding to the standard conditions (1000 mL/mol). The enthalpies and Gibbs free energies in solution (H_s and G_s) were estimated using the expressions 5 and 6

$$H_s = E_s(\text{6-311+}G(\text{d,p})) + H_g(\text{6-31G(d)}) - E_g(\text{6-31G(d)}) \tag{5}$$

$$G_s = H_s - TS_s \tag{6}$$

where E_s, E_g, and H_g are the total energies in solution and gas phase and gas-phase enthalpy calculated at the corresponding level.

For some structures, the topological analysis of the electron density distribution with the help of the AIM method of Bader[24] was performed using the programs GRIDV, GRDVEC, CONTOR, and EXT94B.[25] The Wiberg bond indices (B_i)[26] and atomic charges were computed by using the natural bond orbital

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(NBO) partitioning scheme.[27] The reaction synchronicity (S_y) was calculated using the formula[28,29]

$$S_y = 1 - (2n-2)^{-1} \sum_{i=1}^{n} \frac{|\delta B_i - \delta B_{av}|}{\delta B_{av}} \qquad (7)$$

where n is the number of bonds directly involved in the reaction ($n = 5$ for 1,3-dipolar cycloadditions). δB_i is the relative variation of a given B_i at the transition state relative to reactants (R) and products (P), and it is calculated as

$$\delta B_i = \frac{B_i^{TS} - B_i^{R}}{B_i^{P} - B_i^{R}} \qquad (8)$$

If the δB_i value is negative it is assumed to be zero. The average value of δB_i (δB_{av}) is defined as

$$\delta B_{av} = n^{-1} \sum_{i=1}^{n} \delta B_i \qquad (9)$$

The local softnesses s^+ and relative electrophilicities s^+/s^- have been calculated using the published formulas.[30]

Results and Discussion

In the present paper, the following naming scheme is used. Each reaction product or transition state is denoted by a name comprised of three to five components: nature of the structure (P, reaction product; TS, transition state; I, intermediate), dipole number (see Figure 1), dipolarophile (L, free MeCN; Pt^{II}, complex **1**; Pt^{IV}, complex **2**), regioselectivity (O, *ortho*; M, *meta*), and stereoselectivity (en, *endo*; ex, *exo*). Thus, for instance, the transition state for the *exo*-*ortho* addition of azomethine imine **D3** to complex **1** is marked as **TS(3-Pt^{II})Oex**.

In sections 1−6, the reactivity of six pairs of the dipoles is discussed, and the dipoles within each pair are distinguished by the central atom/group (NMe or O). The dipoles are considered in the order of the increase of the $HOMO_{dipole}$−$LUMO_{nitrile}$ gap (within the series with the N and O central atoms) which determines the reactivity (see section 11.ii). In sections 7−13, the general correlations of FMO energies, atomic charges, charge transfer, HSAB properties, synchronicity, distortion, activation, and reaction energies are analyzed.

1. Cycloadditions of Azomethine ($CH_2{=}N^+(Me){-}CH_2^-$, D1) and Carbonyl ($CH_2{=}O^+{-}CH_2^-$, D2) Ylides. Azomethine and carbonyl ylides are highly reactive species usually generated in situ that readily undergo cycloaddition, e.g., with alkenes or alkynes.[1,31] Their reactions with organonitriles should result in the formation of 2,5-dihydro-1*H*-imidazoles [**P(1-A)**] and 2,5-dihydro-1,3-oxazoles [**P(2-A)**], respectively, as 1,3-dipolar cycloaddition products (Scheme 2). We were able to find only a few publications on the cycloadditions of azomethine[32] or carbonyl[33] ylides to the C≡N bond of nitriles.[34]

SCHEME 2. Reactions of Azomethine (D1) and Carbonyl (D2) Ylides with Nitriles

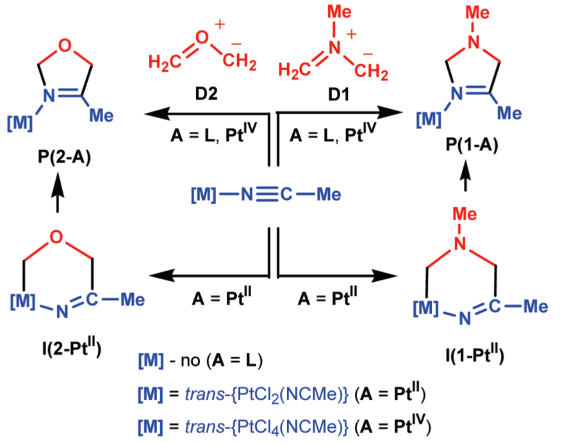

TABLE 1. Activation and Reaction Energies (kcal/mol) of the Reactions of D1 and D2 with Nitriles for the Gas Phase and CH_2Cl_2 Solution (in Parentheses)

reaction	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔG
D1 + **L**	4.7 (9.8)	17.8 (19.0)	−47.7 (−39.4)	−32.9 (−28.8)
D1 + **1**	−6.2 (3.4)	9.0 (14.2)	−60.3 (−49.5)	−41.8 (−36.1)
D1 + **2**	−5.4 (4.3)	8.9 (14.4)	−64.9 (−53.8)	−45.4 (−39.6)
D2 + L	1.5 (5.6)	13.9 (14.2)	−71.8 (−66.8)	−57.7 (−56.8)
D2 + **1**			−82.1 (−74.8)	−66.4 (−63.6)
D2 + **2**	−2.8 (5.0)	8.8 (13.1)	−86.1 (−78.9)	−67.1 (−65.0)

Reactions of the ylides with free MeCN and complex **2** occur via the concerted mechanism while the stepwise mechanism is operating in the case of additions to **1** (Scheme 2, see the Supporting Information for details). Reactions of **D1** and **D2** with MeCN have very small gas-phase activation enthalpies $\Delta H_g^{\ddagger}$ while the $\Delta G_s^{\ddagger}$ values for CH_2Cl_2 solutions are noticeably higher due to an entropic contribution and solvent effects (Table 1). Carbonyl ylide CH_2OCH_2 is more reactive (by 4.8 kcal/mol) than azomethine ylide $CH_2N(Me)CH_2$.

Coordination of MeCN to platinum results in a slight decrease of the activation barriers by 1.1−4.8 kcal/mol. The negative values for the activation enthalpies $\Delta H_g^{\ddagger}$ are accounted for by the formation, on the first step of the process, of molecular van der Waals complexes with energies lower than the sum of energies of separated reactants.[10] In terms of gas-phase $\Delta H_g^{\ddagger}$ values, the cycloadditions to both **1** and **2** have no activation barrier relative to separated reactants. Therefore, the activation effect provided by coordination of nitrile to Pt does not depend on the oxidation state of the metal. The $\Delta G_s^{\ddagger}$ values are much higher than $\Delta H_g^{\ddagger}$ (by 15.9−20.4 kcal/mol), and in the ΔG_s scale, the activation

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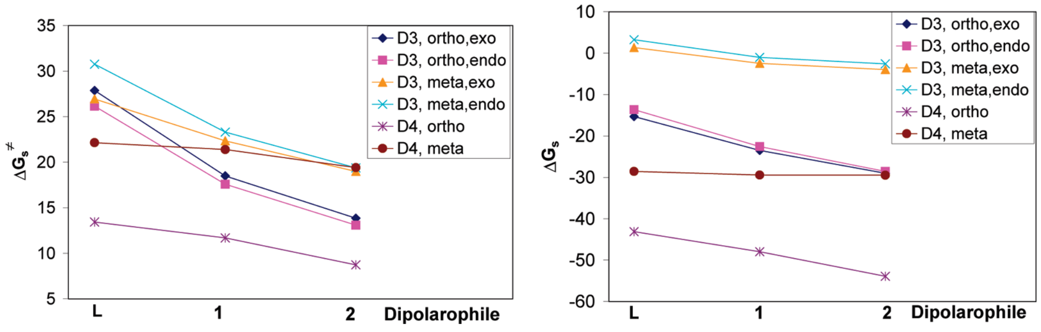


FIGURE 2. Reactivity of **D3** and **D4** toward MeCN, **1**, and **2**

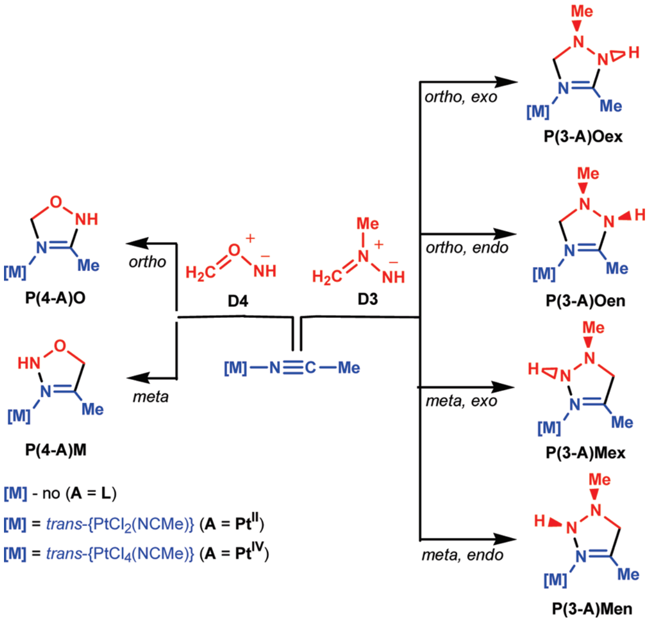
barrier is completely determined by entropic factors and solvent effects but not by the enthalpy term.

All processes have strongly negative reaction enthalpies (ΔH) and Gibbs free energies (ΔG), and the additions of CH_2OCH_2 are significantly more exothermic and exoergonic than the reactions of $CH_2N(Me)CH_2$. The coordination of MeCN to platinum increases the negative values of ΔH and ΔG along the row of dipolarophiles MeCN−**1**−**2**.

Thus, the cycloadditions of *azomethine and carbonyl ylides* to nitriles are favorable from both kinetic and thermodynamic viewpoints. Meanwhile, the $\Delta G_s^{\ddagger}$ value for the reaction **D1** + MeCN (19.0 kcal/mol) indicates that this process should not be very fast. In such a situation, taking into account that ylides of the **D1** type are highly reactive species, some concurrent side reactions are expected. Indeed, the photochemical generation of azomethine ylide from *N*-(silylmethyl)phthalimine in MeCN solution resulted in the isolation of the *N*-methylated product instead of a cycloadduct with nitrile.[35] The ligation of RCN to Pt^{II} or Pt^{IV} may be a way to improve the reactivity of azomethine ylides toward nitriles, but two points should be mentioned in this respect. First, in the case of nitriles activated by Pt^{II}, the easily forming intermediates **I(1-Pt^{II})** and **I(2-Pt^{II})** (Scheme 2) are rather stable [ΔG_s of formation is (−12.3)−(−28.7) kcal/mol]. Their transformation to the final cycloaddition products although being strongly exoergonic requires overcoming a significant activation barrier (14.8−20.7 kcal/mol). Hence, the calculations predict that these intermediates may be easily detected experimentally or even isolated from the reaction mixture, and their formation as side products decreases the reaction selectivity and the yield of the five-membered cycloadducts. Second, when the nitrile is activated by Pt^{IV} in complex **2**, another side reaction is also expected, i.e., an oxidation of ylide by Pt^{IV}.

2. Cycloadditions of Azomethine ($CH_2{=}N^+(Me){-}NH^-$, D3) and Carbonyl ($CH_2{=}O^+{-}NH^-$, D4) Imines. Azomethine imines and, in particular, carbonyl imines are poorly explored 1,3-dipoles. To our knowledge, their cycloaddition reactions with the nitrile function were not studied. The addition of these dipoles to RCN should result in the formation of 2,3(5)-dihydro-1*H*-1,2,4(3)-triazoles [**P(3-A)**] and 2,5-dihydro-1,2,4(3)-oxadiazoles [**P(4-A)**] (Scheme 3). The reactions may occur along two different regioisomeric pathways and, in the case of *C*-unsubstituted azomethine imines, via *exo*- or *endo*-approaching modes.

SCHEME 3. Reactions of Azomethine (D3) and Carbonyl (D4) Imines with Nitriles



The mechanism of the reactions of **D3** and **D4** with MeCN and **2** is concerted. In the cases of *ortho*-*exo*- and *meta*-*endo*-(**D3** + **1**) additions and the *meta*-(**D4** + **1**) addition, both concerted and stepwise mechanisms may be operating, the former being slightly (by 0.7−2.1 kcal/mol) more favorable than the latter. For the *ortho*-*endo*- and *meta*-*exo*-(**D3** + **1**) additions and the *ortho*-(**D4** + **1**) addition, only the stepwise pathway was found.

The reactivity trends for these reactions are shown in Figure 2. The processes are characterized by low to moderate activation barriers (Table 2 and Table 3S, Supporting Information). Carbonyl imine CH_2ONH is significantly more reactive than azomethine imine $CH_2N(Me)NH$. The coordination of MeCN to Pt^{II} and, particularly, to Pt^{IV} provides an activation of nitrile, significant for the *ortho*- and *meta*-,*endo*-cycloadditions of **D3** (by 7.4−14.0 kcal/mol, reaction rate increasing by a factor of 2.9×10^5 to 1.9×10^{10}), moderate for the *meta*-, *exo*-addition of **D3** (by 4.6−6.6 kcal/mol), and weak for the reactions of **D4** (by 0.7−4.7 kcal/mol).

Reaction energies strongly depend on the regioisomeric pathways (Figure 2). *Meta*-additions are much less thermodynamically favorable than the *ortho* ones. *Meta*-additions of **D3** have small negative or even positive ΔG_s values, while the other reactions are clearly exoergonic. In general, the

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TABLE 2. Activation and Reaction Energies (kcal/mol) of the *Ortho*-Additions of D3 and D4 to Nitriles for the Gas Phase and CH_2Cl_2 Solution (in Parentheses)

reaction	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔG
D3 + L, *exo*	12.4 (18.6)	25.6 (27.9)	−32.4 (−25.3)	−18.3 (−15.3)
D3 + L, *endo*	12.2 (16.8)	25.5 (26.1)	−30.1 (−24.0)	−15.5 (−13.6)
D3 + **1**, *exo*	0.2 (8.9)	13.8 (18.5)	−46.7 (−36.6)	−28.6 (−23.5)
D3 + **1**, *endo*	−2.8 (6.0)	13.3 (17.6)	−45.3 (−36.1)	−26.8 (−22.6)
D3 + **2**, *exo*	−7.0 (3.2)	7.9 (13.9)	−52.6 (−42.7)	−33.9 (−29.0)
D3 + **2**, *endo*	−6.1 (2.3)	9.0 (13.1)	−51.9 (−42.4)	−33.0 (−28.6)
D4 + L	0.7 (5.0)	12.9 (13.4)	−56.8 (−52.5)	−43.5 (−43.1)
D4 + **1**	−5.6 (2.0)	8.2 (11.7)	−68.1 (−60.6)	−50.6 (−48.0)
D4 + **2**	−6.7 (0.4)	5.4 (8.7)	−72.6 (−65.2)	−56.8 (−53.9)

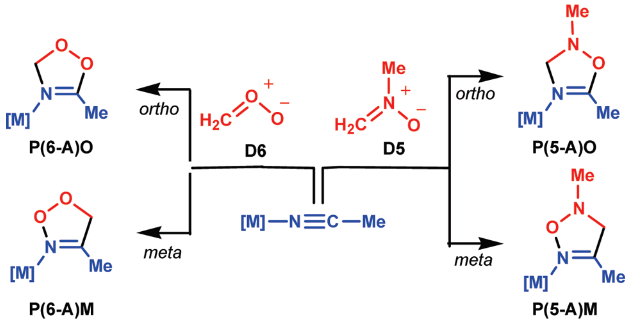
products derived from $CH_2N(Me)NH$ are less stable than those obtained from CH_2ONH, and all of them are less stable than the products derived from $CH_2N(Me)CH_2$ and CH_2OCH_2, respectively. Coordination of the nitrile increases the exoergonic character of the reactions by 0.9−14.9 kcal/mol.

The reaction **D3** + MeCN has a similar activation barrier for both *ortho*- and *meta*-channels. However, the *meta*-additions are reversible while the *ortho*-additions are irreversible providing the complete *ortho*-selectivity controlled by thermodynamic rather than kinetic factors. Coordination of MeCN to Pt makes the *ortho*-pathways to be even more favorable, and all the other reactions also exhibit complete *ortho*-selectivity from both kinetic and thermodynamic viewpoints.

Thus, the reactions of *carbonyl imines* with nitriles may easily lead to 2,5-dihydro-1,2,4-oxadiazoles. The coordination of RCN to platinum facilitates the reaction, but such an activation effect is not high. Taking into account the low activation barrier of the metal-free process, this way of activation of the dipolarophile is not crucial. In contrast, the ligation of RCN to platinum should provide a good way, from both kinetic and thermodynamic points of view, to accelerate the reaction of *azomethine imines* with nitriles and to facilitate the formation of 2,3-dihydro-1*H*-1,2,4-triazoles opening up a possible route for the synthesis of these rare heterocycles. Meanwhile, the cycloadditions of both azomethine and carbonyl imines to nitriles cannot be an effective way for the synthesis of other regioisomers, i.e., 2,5-dihydro-1*H*-1,2,3-triazoles and 2,5-dihydro-1,2,3-oxadiazoles. It is also important that the six-membered metallaorganic intermediates of the stepwise mechanisms **I(3-Pt^{II})** and **I(4-Pt^{II})** are less stable than the initial compounds, and their plausible formation during the reaction should not affect the yield of the cycloaddition product as expected in the case of ylides (see section 1).

3. Cycloadditions of Nitrones ($CH_2{=}N^+(Me){-}O^-$, D5) and Carbonyl Oxides ($CH_2{=}O^+{-}O^-$, D6). Nitrones, being the most important and well-studied dipoles of the allyl-anion type, are involved in reactions with a great number of various dipolarophiles[1] including nitriles.[2,9] In contrast, carbonyl oxides are highly reactive species usually obtained in situ by ozonolysis of alkenes or by reactions of diazo compounds with singlet oxygen, and only a limited number of their [3 + 2]-cycloadditions (e.g., to carbonyl compounds,[36,37] alkenes,[38] imines,[39] isocyanate,[40] and sulfoxides[41]) are known. The reactions of these dipoles with nitriles may occur via two regioisomeric pathways and should lead to the formation of 2,3-dihydro-1,2,4(5)-oxadiazoles [**P(5-A)**] and 3(5)*H*-1,2,4(3)-dioxazoles [**P(6-A)**] (Scheme 4). The *ortho*-additions of nitrones to RCN have been extensively studied recently,[10] and here they are discussed briefly for comparison purposes.

SCHEME 4. Reactions of Nitrones (D5) and Carbonyl Oxides (D6) with Nitriles



[M] - no (**A = L**)
[M] = *trans*-{$PtCl_2(NCMe)$} (**A = Pt^{II}**)
[M] = *trans*-{$PtCl_4(NCMe)$} (**A = Pt^{IV}**)

All reactions of **D5** and **D6** with MeCN, **1**, and **2** occur via the concerted mechanism. The reactivity trends for these processes are shown in Figure 3. The *ortho*-(**D6** + MeCN) addition has a small activation barrier (11.6 kcal/mol), while the *meta*-(**D6** + MeCN) and (**D5** + MeCN) additions exhibit rather high activation energies (28.2−38.4 kcal/mol) (Table 3). The coordination of MeCN to Pt^{II} and Pt^{IV} greatly accelerates the cycloadditions of nitrones, but the reactions of CH_2OO are inhibited or only slightly accelerated. In fact, $CH_2N(Me)O$ in the reaction with **2** has a reactivity comparable with that of CH_2OO. Thus, the activation of nitriles by Pt affects the reactivity of nitrones and carbonyl oxides very differently.

The ΔG_s value of the reaction $CH_2N(Me)O$ + MeCN is either slightly negative (−1.8 kcal/mol for the *ortho*-approach) or strongly positive (26.1 kcal/mol for the *meta*-approach). In contrast, the reaction of CH_2OO is clearly exoergonic, especially along the *ortho*-channel (ΔG_s = −35.8 kcal/mol). Ligation of the nitrile to Pt makes the *ortho*-addition of $CH_2N(Me)O$ noticeably more exoergonic but the reaction energies of other processes either not change significantly or even increase. The *ortho*-additions of both dipoles appear to be much more plausible than the *meta*-additions.

Thus, reactions of *nitrones* with free alkyl nitriles are not favorable from both kinetic (high activation barrier) and

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(39) McCullough, K. J.; Mori, M.; Tabuchi, T.; Yamakoshi, H.; Kusabayashi, S.; Nojima, M. *J. Chem. Soc., Prekin Trans. 1* **1995**, 41.

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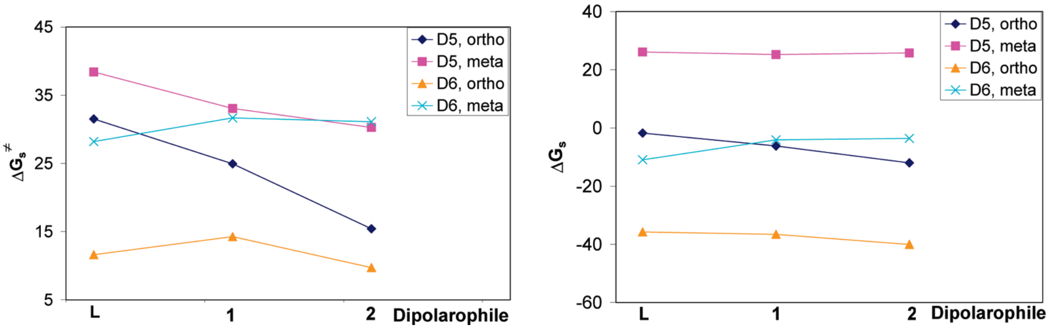

FIGURE 3. Reactivity of **D5** and **D6** toward MeCN, **1**, and **2**.

TABLE 3. Activation and Reaction Energies (kcal/mol) of the *Ortho*-Additions of D5 and D6 to Nitriles for the Gas Phase and CH_2Cl_2 Solution (in Parentheses)

reaction	$\Delta H^\ddagger$	$\Delta G^\ddagger$	ΔH	ΔG
D5 + L	14.9 (22.6)	27.6 (31.5)	−21.1 (−11.3)	−7.6 (−1.8)
D5 + **1**	3.3 (13.1)	19.7 (25.0)	−32.8 (−19.0)	−15.2 (−6.2)
D5 + **2**	−3.9 (7.1)	8.0 (15.4)	−37.1 (−22.6)	−22.2 (−12.0)
D6 + L	−2.8 (3.1)	9.4 (11.6)	−54.5 (−44.6)	−41.9 (−35.8)
D6 + **1**	−6.7 (3.5)	7.7 (13.7)	−62.6 (−49.2)	−45.1 (−36.6)
D6 + **2**	−10.4 (0.3)	3.0 (9.7)	−67.2 (−53.1)	−49.2 (−40.0)

thermodynamic (low stability of the products) points of view. However, the activation of the dipolarophile by its coordination to Pt allows the facile synthesis of 2,3-dihydro-1,2,4-oxadiazoles which are sufficiently stable when they are bound with metal. This is in agreement with recent results of a series of experimental works on this subject.[9] In contrast, the low activation barriers and high relative stability of 3*H*-1,2,4-dioxazoles should allow an easy reaction between *carbonyl oxides* and nitriles. However, a number of side reactions, including radical ones, are expected[42] due to the high reactivity of these dipoles. Coordination of RCN to Pt in this case is expected to be not only helpless but may even inhibit the process. The cycloadditions of nitrones and carbonyl oxides to nitriles cannot serve as a synthetic route to 2,3-dihydro-1,2,5-oxadiazoles and 5*H*-1,2,3-dioxazoles.

4. Cycloadditions of Azimines ($NH{=}N^+(Me){-}NH^-$, **D7**) **and Nitrosimines** ($NH{=}O^+{-}NH^-$, **D8**). Examples of cycloadditions of azimines are rare,[43] while to our knowledge, nitrosimines in the form RNONR′ are still hypothetical compounds. The expected products of cycloadditions of azimines and nitrosimines to nitriles are 2,3-dihydro-1*H*-tetrazoles [**P(7-A)**] and 2,5-dihydro-1,2,3,5-oxatriazoles [**P(8-A)**] (Scheme 5). These reactions may occur via several stereoisomeric paths, i.e., *exo*-,*exo*-, *exo*-,*endo*-, and *endo*-,*endo*-approaches for **D7** and *exo*- and *endo*-approaches for **D8**.

For all reactions of **D7** and **D8** with MeCN, **1**, and **2**, the concerted mechanism is realized. The calculated activation and reaction energies and their trends are schematically presented in Figure 4. The activation barriers are high for the reaction NHN(Me)NH + MeCN ($\Delta G_s^\ddagger$ = 41.2−43.3 kcal/mol) and moderate in the case of NHONH + MeCN ($\Delta G_s^\ddagger$ = 25.7−27.3 kcal/mol) (Table 4). Thus, the nitrosimine **D8** is significantly more reactive than azimine **D7**. The coordination of MeCN to Pt greatly decreases the activation barrier of NHN(Me)NH cycloadditions by 16.0 kcal/mol that corresponds to the reaction acceleration by a factor of 5.4×10^{11}. In contrast, the activation of the reactions of NHONH is small and does not exceed 3.9 kcal/mol. As a result, the reactivity of both dipoles toward **2** is similar. Azimines are the least reactive dipoles among all those discussed above, while nitrosimines should have a reactivity comparable with $CH_2N(Me)NH$ and $CH_2N(Me)O$ (addition to MeCN) or even lower (additions to **1** and **2**).

The reaction of NHN(Me)NH is clearly endoergonic, although the ligation of MeCN to Pt decreases the ΔG_s values from 13.7 to 6.2 kcal/mol. The additions of NHONH are exoergonic, and the coordination does not affect the reaction energies.

Thus, the calculations predict that the cycloadditions of *azimines* to nitriles are not effective. Indeed, even when nitrile is activated by Pt^{IV} and the activation barrier is sufficiently moderate to permit the process from kinetic viewpoints, the low thermodynamic stability of the products does not allow their isolation. The cycloadditions of *nitrosimines* have the activation barrier comparable to that for the reactions of nitrones with **1**. The available experimental data[44,45] indicate that the latter process occurs if nitriles with electron-withdrawing substituents or/and cyclic nitrones are used. Thus, it is expected that the nitrosimines also might react with nitriles, at least if the appropriate substituents are applied. It is important that the coordination of RCN to Pt is not an effective way to accelerate the reaction with NHONH.

5. Cycloadditions of Azoxy Compounds ($NH{=}N^+(Me){-}O^-$, **D9**) **and Nitroso Oxides** ($NH{=}O^+{-}O^-$, **D10**). The cycloadditions of azoxy compounds[46] and nitroso oxides[47] are very

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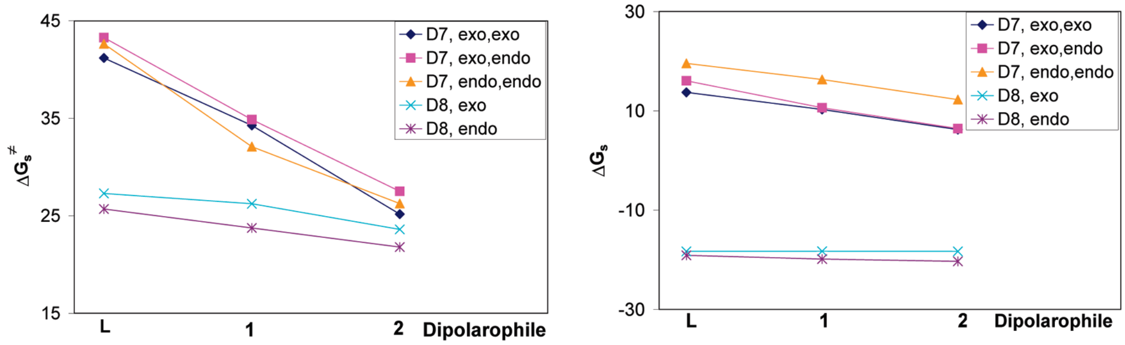

FIGURE 4. Reactivity of **D7** and **D8** toward MeCN, **1**, and **2**.

SCHEME 5. Reactions of Azimines (D7) and Nitrosimines (D8) with Nitriles

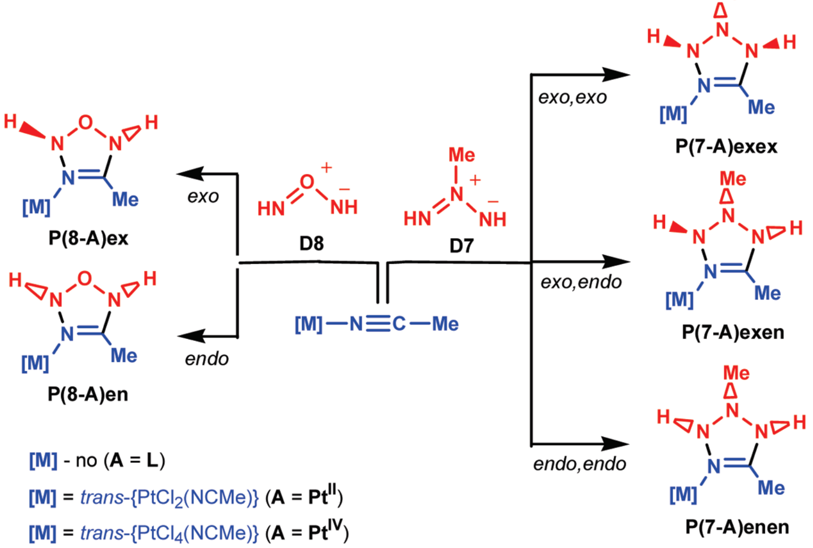

TABLE 4. Activation and Reaction Energies (kcal/mol) of the Reactions of D5 and D6 with Nitriles along the Most Favorable Stereoisomeric Channels for the Gas Phase and CH_2Cl_2 Solution (in Parentheses)

reaction	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔG
D7 + **L**, *exo,exo*	26.2 (31.8)	39.6 (41.2)	−3.5 (+3.5)	+10.8 (+13.7)
D7 + **1**, *exo,exo*	13.5 (22.3)	30.2 (34.3)	−14.7 (−2.9)	+3.4 (+10.3)
D7 + **1**, *endo,endo*	14.8 (21.8)	29.3 (32.1)	−7.5 (+2.7)	+11.2 (+16.3)
D7 + **2**, *exo,exo*	6.5 (14.3)	21.6 (25.2)	−17.5 (−7.3)	+1.1 (+6.2)
D8 + L, *endo*	11.7 (17.1)	24.1 (25.7)	−33.7 (−28.5)	−20.4 (−19.1)
D8 + **1**, *endo*	4.6 (13.9)	18.5 (23.8)	−39.4 (−30.6)	−24.4 (−19.9)
D8 + **2**, *endo*	2.8 (12.3)	16.4 (21.8)	−40.9 (−33.2)	−23.1 (−20.3)

poorly explored even with common dipolarophiles such as olefins and acetylenes due to the low stability of the expected heterocyclic products[48] and the low stability of nitroso oxides. Their additions to nitriles should lead to the formation of 2,3-dihydro-1,2,3,4(5)-oxatriazoles [**P(9-A)**] and 3*H*-1,2,3,4(5)-dioxadiazoles [**P(10-A)**] (Scheme 6). The reactions may occur via two regioisomeric paths and, in the case of **D9**, along either the *exo*- or the *endo*-approach. However, there are no experimental X-ray structural data for heterocycles of these types. The geometry optimization resulted in the location of the cyclic products **P(9-A)O/Men/ex**, but no minima corresponding to cyclic products of the **D10** + MeCN addition were found. Instead, the cleavage of the OO bond occurs during the optimization and acyclic products **P(10-L)O/M$_{\mathbf{acyc}}$** are formed (Scheme 6). For the reactions of NHOO with **1** and **2**, the structures of both cyclic (**P(10-Pt$^{\mathbf{II}}$)O/M**, **P(10-Pt$^{\mathbf{IV}}$)O/M**) and acyclic (**P(10-Pt$^{\mathbf{II}}$)O$_{\mathbf{acyc}}$**, **P(10-Pt$^{\mathbf{IV}}$)O$_{\mathbf{acyc}}$**) products were obtained, and the species of the latter type are much more stable than those of the former (see below).

For all the reactions examined in this section, cyclic TSs of the concerted mechanism were found. The cycloadditions of **D9** to free MeCN are characterized by high activation barriers (47.8−54.3 kcal/mol), while those of the reactions of **D10** are moderate (23.7−29.7 kcal/mol) (Figure 5, Table 5). The coordination of MeCN to Pt affects noticeably only the former processes, lowering the $\Delta G_s^{\ddagger}$ value by 8.1−12.0 kcal/mol (increase of the reaction rate by a factor of 8.7×10^5−6.3×10^8). However, despite such an acceleration, the activation barrier still remains very high and comparable with that of the reaction **D7** + MeCN. Thus, azoxy compounds are predicted to be even less reactive toward nitriles than azimines. The ligation of nitrile to Pt slightly inhibits the NHOO cycloadditions rather than accelerates them. Meanwhile, the activation barrier of the reaction NHOO + MeCN is comparable with that of the reaction $CH_2N(Me)O$ + **1**, and therefore, the process is possible from

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[48] Jursic, B. S. *J. Heterocycl. Chem.* **1997**, *34*, 1383.

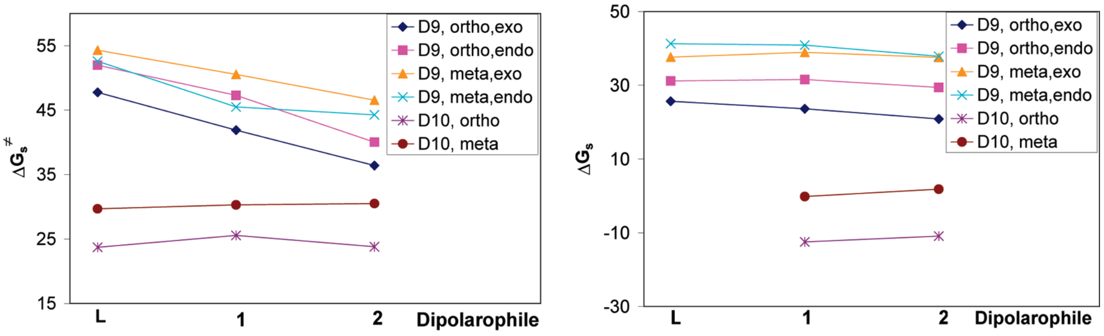


FIGURE 5. Reactivity of **D9** and **D10** toward MeCN, **1**, and **2**.

SCHEME 6. **Reactions of Azoxy Compounds (D9) and Nitroso Oxides (D10) with Nitriles**

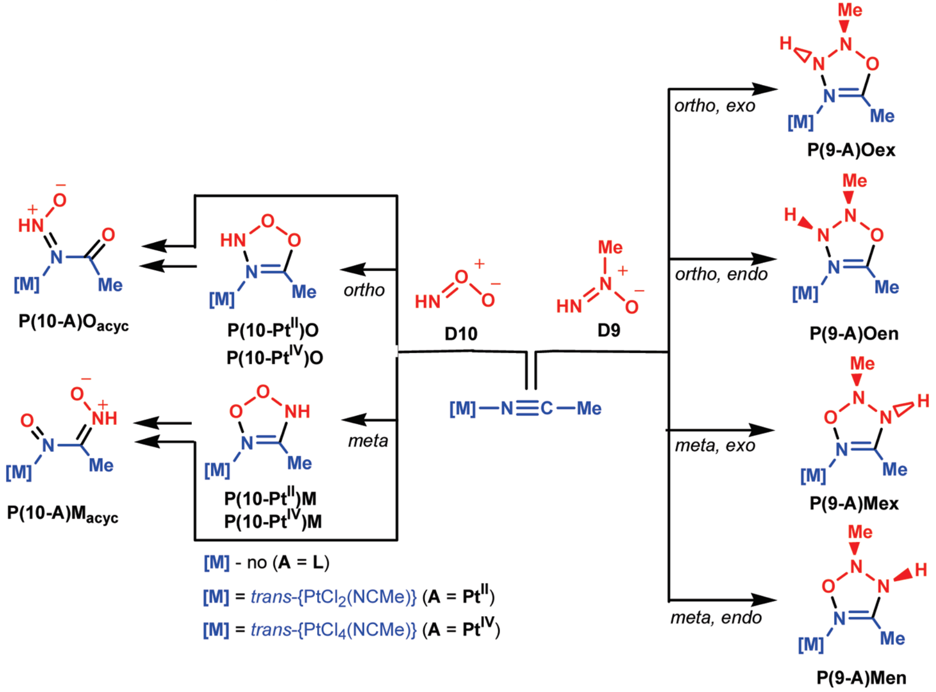


TABLE 5. **Activation and Reaction Energies (kcal/mol) of the *Ortho* Additions of D9 and D10 to Nitriles for the Gas Phase and CH_2Cl_2 Solution (in Parentheses)**

reaction	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔG
D9 + L, *exo*	31.3 (38.5)	44.5 (47.8)	+7.4 (+15.9)	+21.2 (+25.7)
D9 + **1**, *exo*	21.5 (31.9)	35.7 (41.9)	−2.4 (+10.9)	+15.1 (+23.6)
D9 + **2**, *exo*	15.3 (25.4)	30.7 (36.4)	−5.3 (+7.8)	+12.6 (+20.8)
D10 + L	8.6 (15.0)	21.1 (23.7)	-86.2^a $(-84.2)^a$	-74.3^a $(-76.0)^a$
D10 + **1**	2.7 (13.7)	19.2 (25.6)	−37.1 (−23.2) -93.5^a $(-84.1)^a$	−22.1 (−12.5) -76.9^a $(-72.2)^a$
D10 + **2**	1.7 (12.8)	17.1 (23.8)	−39.0 (−23.6) -94.7^a $(-84.0)^a$	−21.5 (−10.9) -79.0^a $(-72.8)^a$

[a] Reaction energies corresponding to the formation of acyclic products.

the kinetic point of view depending on the substituents (see section 4).

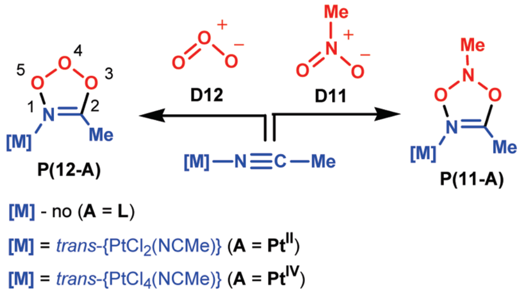
The additions of NHN(Me)O are highly endothermic and endoergonic indicating that 2,3-dihydro-1,2,3,4(5)-oxatriazoles thermodynamically are not stable. The ΔG_s values of reactions of NHOO with **1** and **2** are close to zero (*meta*-additions) or negative (*ortho*-additions). The complexation of the nitrile does not affect significantly the reaction energies.

In all cases, the *ortho*-additions are kinetically and thermodynamically more favorable than the *meta*-additions.

Thus, the calculations predict that *azoxy compounds* cannot be involved in cycloadditions with nitriles due to high activation barriers and positive reaction energies. The coordination of the nitrile to Pt cannot facilitate sufficiently the reactions of this type. The additions of *nitroso oxides* with free MeCN should result in the formation of an acyclic product; i.e., azoxy compounds (Scheme 6) or derived species, instead of a cyclic product, the latter does not exist. Oxygen-transfer reactions with a rupture of the OO bond are well-known for nitroso oxides.[47b] Ligation to platinum stabilizes 3*H*-1,2,3,4-dioxadiazoles and the reactions of NHOO with **1** and **2** are exoergonic. However, the acyclic products **P(10-Pt^{II})$_{Oacyc}$** and **P(10-Pt^{IV})$_{Oacyc}$** are much more stable (by 59.7−61.9 kcal/mol) than dioxadiazoles **P(10-Pt^{II})O** and **P(10-Pt^{IV})O**. Thus, a rapid conversion of the cyclic adducts to acyclic species is expected.

6. Cycloadditions of Nitro Compounds (O═N$^+$(Me)−O$^-$, D11) and Ozone (O═O$^+$−O$^-$, D12). Nitro compounds are known to be involved in reactions with alkenes to give isoxazoles via formation of intermediate nitrile oxides upon

SCHEME 7. Reactions of Nitro Compounds (D11) and Ozone (D12) with Nitriles



dehydratation.[49] Examples of a direct cycloaddition of nitro compounds through two oxygen atoms are rare.[50] The cycloaddition of ozone to dipolarophiles is the first and rate-limiting stage of the ozonolysis leading to the formation of the *O*-transfer products.[51] The expected products of the direct cycloadditions of these dipoles to nitriles are 1,3,2,4-dioxadiazoles [**P(11-A)**] and 1,2,3,4-trioxazoles [**P(12-A)**] (Scheme 7). No X-ray structural data for the species of these types are known. Analysis of the calculated structural parameters suggests that at least the noncoordinated trioxazole **P(12-L)** should undergo an easy decomposition as a result of the O(4)O(5) bond cleavage. Indeed, in **P(12-L),** the O(4)O(5) bond is significantly longer than the O(3)O(4) bond (1.548 and 1.446 Å, respectively). The Wiberg bond indices of the O(4)O(5), O(3)O(4), and N(1)O(5) bonds are 0.86, 0.99, and 1.10, correspondingly, indicating that the O(4)O(5) bond is weakened while the N(1)O(5) bond has a partially double character.

All reactions of **D11** and **D12** with the nitriles occur via the concerted mechanism. The cycloaddition of nitromethane ON(Me)O to MeCN has a very high activation energy ($\Delta G_s^{\ddagger}$ = 60.7 kcal/mol) and positive reaction energy (ΔG_s = 47.7 kcal/mol) (Table 6). The coordination of MeCN to Pt only slightly accelerates this reaction (by 3.8 kcal/mol) but increases the ΔG_s value. The activation barrier of the reaction OOO + MeCN is significantly lower ($\Delta G_s^{\ddagger}$ = 28.0 kcal/mol), and the process is exothermic and exoergonic (ΔG_s = −8.6 kcal/mol). The ligation of the nitrile to platinum clearly inhibits this process (by 5.3 kcal/mol) and enhances the reaction energy (by 9.6 kcal/mol).

Thus, the calculations indicate that nitro compounds are unreactive for the direct cycloadditions to nitriles. In fact, these dipoles are the most inert ones among all the 1,3-dipoles of the allyl-anion type. The reactivity of ozone toward MeCN is predicted to be comparable to the reactivity of nitrones. However, the reaction $CH_2N(Me)O$ + MeCN belongs to the normal electron demand type, whereas the reaction OOO + MeCN is an inverse electron demand process (see section 7). Hence, the modes of the activation of these systems should be different, i.e., coordination of dipolarophile to a Lewis acid in the case of nitrones and coordination of dipole to a Lewis acid in the case of ozone (consideration of the latter activation type is not a subject of the present article).

TABLE 6. Activation and Reaction Energies (kcal/mol) of Additions of D11 and D12 to Nitriles for the Gas Phase and CH_2Cl_2 Solution (in Parentheses)

reaction	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔG
D11 + L	41.4 (50.3)	56.0 (60.7)	+25.5 (+37.0)	+40.6 (+47.7)
D11 + **1**	33.2 (46.1)	48.9 (57.3)	+22.3 (+37.5)	+41.2 (+51.3)
D11 + **2**	31.0 (44.5)	48.2 (56.9)	+20.8 (+36.2)	+39.9 (+50.1)
D12 + L	14.1 (19.3)	26.5 (28.0)	−24.8 (−16.9)	−12.8 (−8.6)
D12 + **1**	13.7 (20.5)	27.6 (30.4)	−21.7 (−11.4)	−4.9 (+0.7)
D12 + **2**	14.8 (22.3)	30.0 (33.2)	−22.0 (−11.5)	−4.9 (+0.9)

In this work, the reactivity of a series of 12 1,3-dipoles of allyl-anion type was studied allowing the elucidation of some general correlations and relationships of fundamental and practical interest which are examined in the following sections.

7. Frontier Molecular Orbitals. The correlation of FMO energies with the dipole nature was previously examined by Houk et al. for some 1,3-dipoles.[52] The results of our DFT calculations for the whole series of 1,3-dipoles of the allyl-anion type are plotted in Figure 6 and Figure 5S (Supporting Information) and their inspection indicates that (i) both HOMO and LUMO energies of dipoles bearing a central O atom are lower than those of analogous dipoles bearing a central N atom;[53] (ii) the FMO energies decrease along the row of the terminal atoms C > N > O; (iii) the reactions of $CH_2N(Me)CH_2$, CH_2OCH_2, and $CH_2N(Me)NH$ (electron-deficient dipoles) with free MeCN are clearly normal electron demand (NED) processes ($\Delta\Delta E = |E(\text{HOMO}_{\text{dipole}}) - E(\text{LUMO}_{\text{nitrile}})| - |E(\text{HOMO}_{\text{nitrile}} - E(\text{LUMO}_{\text{dipole}})| < -2$ eV), the cycloadditions of HNOO, ON(Me)O and OOO (electron-rich dipoles) are inverse electron demand (IED) reactions ($\Delta\Delta E > 2$ eV), while the reactions of other dipoles with MeCN are ambiphilic (Figure 6B); (iv) the coordination of MeCN to Pt shifts the $\Delta\Delta E$ plot down toward the normal electron demand processes, majority of reactions becomes NED and only one (with ozone) remains to be IED; (v) the coordination of MeCN to Pt^{II} decreases the narrowest HOMO−LUMO gap for all dipoles (even ozone) while the ligation to Pt^{IV} increases this gap for HNOO, ON(Me)O, and OOO and decreases for other dipoles (Figure 6C).

8. Effective Atomic Charges. Another factor that may affect the reactivity, in particular in asynchronous cycloadditions, is the atomic charge on the reacting atoms.[10c] The NBO atomic charge on the X atom of a dipole $X{=}Y^+{-}Z^-$ increases within the four triads of dipoles **D1** < **D3** < **D5** (triad A), **D2** < **D4** < **D6** (triad B), **D7** < **D9** < **D11** (triad C), and **D8** < **D10** < **D12** (triad D) (Figure 7A). This charge is higher in dipoles bearing the central O atom compared to the analogous N-centered dipoles. There is no clear correlation between the charge and FMOs energies along the whole sequence of dipoles. However, within the triads the trend is obvious; i.e., the lower the HOMO or LUMO energy (the lower the NED character of a reaction), the higher the

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[49] Cecchi, L.; De Sarlo, F.; Machetti, F. *Chem.—Eur. J.* **2008**, *14*, 7903.

[50] For example: (a) Okada, K.; Saito, Y.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1731. (b) Butts, C. P.; Calvert, J. L.; Eberson, L.; Hartshorn, M. P.; Robinson, W. T. *J. Chem. Soc., Chem. Commun.* **1993**, 1513. (c) Leitich, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 372.

[51] (a) Johnson, D.; Marston, G. *Chem. Soc. Rev.* **2008**, *37*, 699. (b) Horie, O.; Moortgat, G. K. *Acc. Chem. Res.* **1998**, *31*, 387. (c) Cremer, D.; Crehuet, R.; Anglada, J. *J. Am. Chem. Soc.* **2001**, *123*, 6127. (d) Wheeler, S. E.; Ess, D. H.; Houk, K. N. *J. Phys. Chem. A* **2008**, *112*, 1798.

[52] (a) Houk, K. N.; Sims, J.; Duke, R. E. Jr; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

[53] For some dipoles, the highest occupied interacting MO of π-symmetry is HOMO-1 (**D6** and **D10**) or HOMO-2 (**D11** and **D12**).

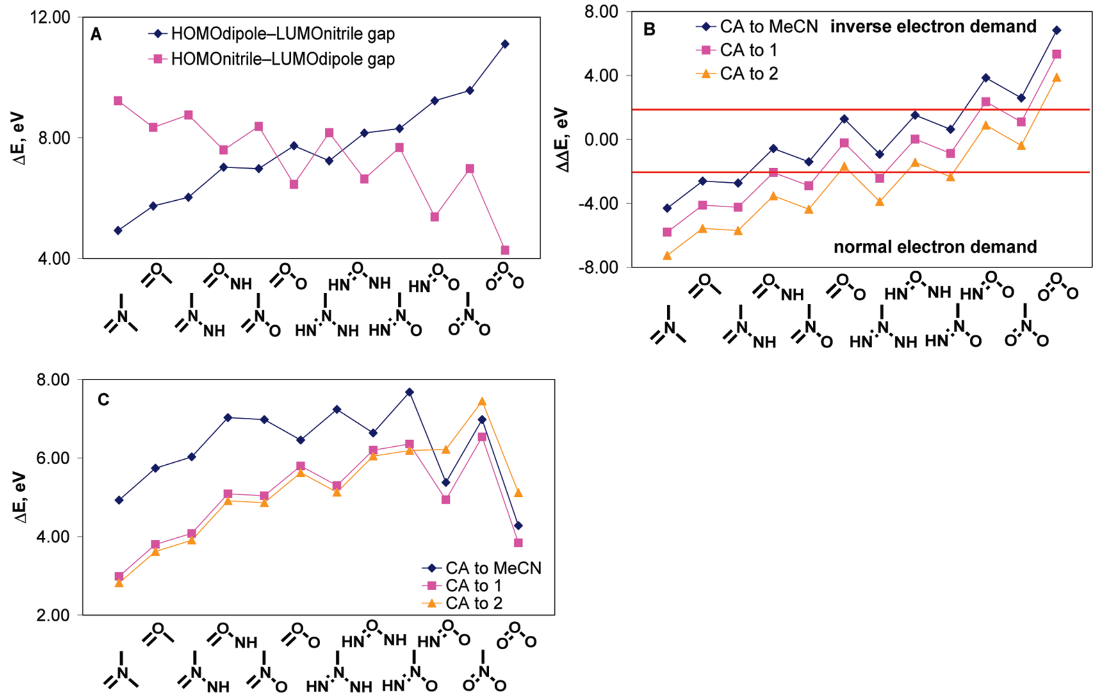

FIGURE 6. HOMO−LUMO energy gaps for the additions to MeCN (A), the ΔΔ*E* parameter (see text) (B), and the narrowest HOMO−LUMO gap (C) for additions to MeCN, **1**, and **2**.

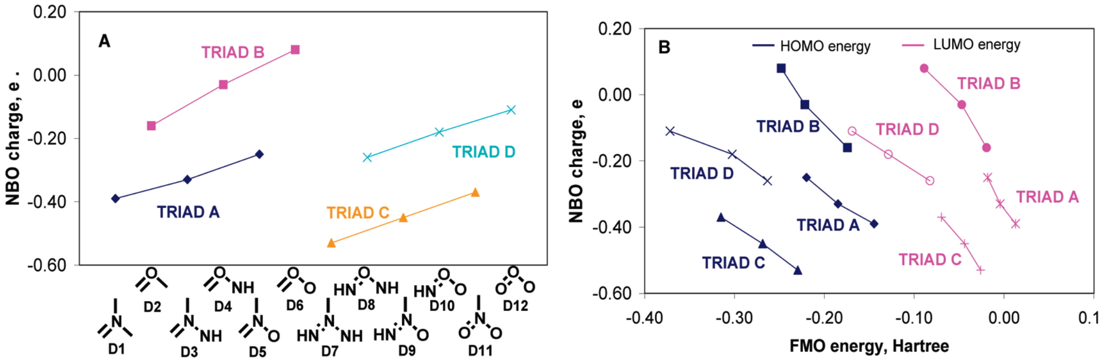

FIGURE 7. Plots of the NBO atomic charge on the X atom of dipole X=Y$^+$−Z$^-$ vs dipole nature (A) and dipole FMO energies (B).

atomic charge (Figure 7B). The charges on the Z atom obey the same general trends with exception of **D1** and **D2** (Figure 6S, Supporting Information).

9. Charge Transfer. NBO charge transfer (CT) from the dipole to the acetonitrile molecule occurring upon the formation of TS decreases within the triads A−D along the row of the terminal atoms C > N > O (Figure 8A). In fact, for dipoles **D6** and **D9**−**D12**, a "back" charge transfer from MeCN to the dipole takes place. There is a clear and expected correlation between CT and the HOMO/LUMO energies: when the FMO energy decreases, the dipole-to-nitrile charge transfer also decreases (Figure 8B).

The coordination of nitrile enhances CT in most of the cases due to the more electron-deficient character of MeCN in the complexes than in the free state. However, for reactions of ylides CH_2YCH_2 (**D1**, **D2**) and imines CH_2YNH (**D3**, **D4**), the dipole-to-**2** charge transfer is similar or even *lower* than that of the dipole-to-MeCN (Figure 7SA, Supporting Information). Such a situation is accounted for by the fact that **TS(1-Pt^{IV})**, **TS(2-Pt^{IV})**, **TS(3-Pt^{IV})**, and **TS(4-Pt^{IV})** are very "early" on the reaction path and the reactants' molecules interact only weakly with each other in these TSs. Finally, the *ortho*-TSs exhibit lower dipole-to-nitrile CTs than the *meta*-TSs (Figure 7SB, Supporting Information).

10. Synchronicity. Considering the trends of the reaction synchronicity along the series of dipoles, the following conclusions can be drawn. (i) The reactions of dipoles with the central N atom are generally more synchronous compared to dipoles with the central O atom (Figure 9A). (ii) The synchronicity increases along the sequences ylides < imines < oxides. (iii) Nitrile coordination decreases the synchronicity for all dipoles, and such a trend is clear for the *ortho*-additions although much smaller for the *meta*-ones (Table 2S, Figure 8S, Supporting Information). (iv) There is a correlation between the HOMO or LUMO energy of the dipole and the synchronicity within the triads A and B; i.e., the lower the FMO energy (the lower the NED character), the higher the synchronicity (Figure 9B). (v) For cycloadditions to

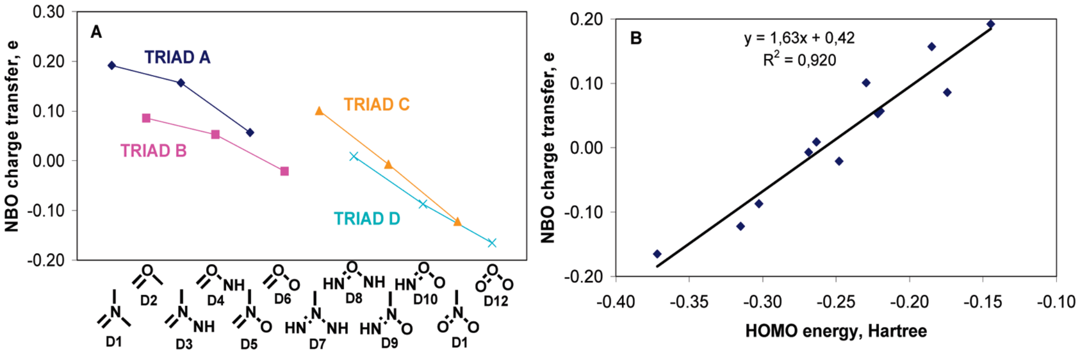

FIGURE 8. Plots of the dipole-to-nitrile NBO charge transfer vs dipole nature (A) and dipole HOMO energy (B) for cycloadditions to MeCN (only the most favorable regio- and stereoisomeric pathways are considered).

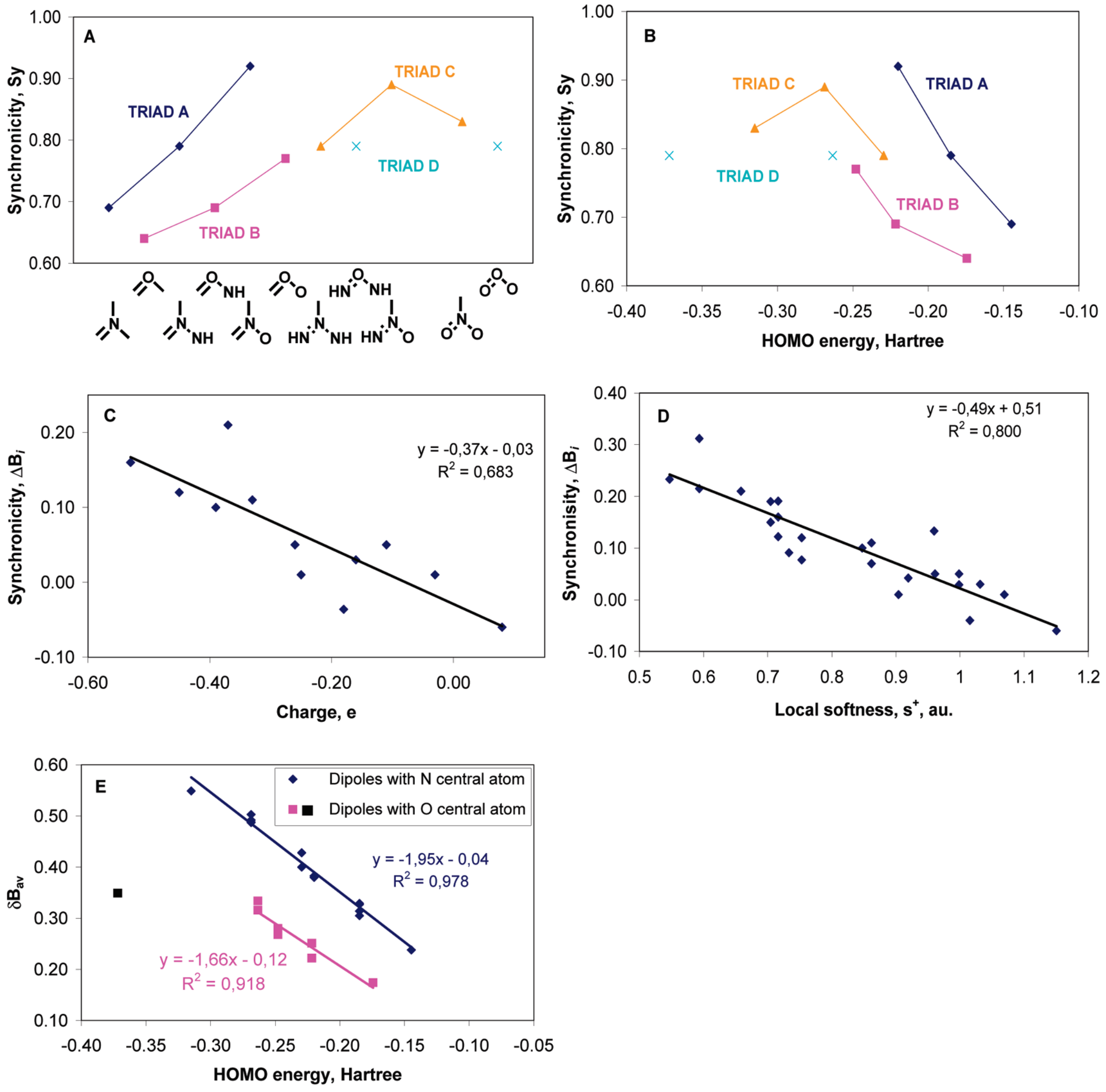

FIGURE 9. Plots of synchronicity in terms of S_y vs dipole nature and dipole HOMO energy (A, B), synchronicity in terms of $\Delta B_i = B_{C(2)Z(3)} - B_{N(1)X(5)}$ in TS vs NBO charge and local softness s^+ on the atom X(5) of dipole XYZ (C, D) and parameter δB_{av} vs dipole HOMO energy (*E*) for additions to MeCN. All regio- and stereoisomeric pathways are included in the plots D and E.

free MeCN, there is some, although far from perfect, correlation between synchronicity (in terms of ΔB_i) and charge on the X atom of the dipole $X{=}Y^+{-}Z^-$: the lower the negative charge, the higher the synchronicity (Figure 9C). However, no clear dependence of S_y or ΔB_i on the charge on the Z atom or on combinations of the charges was found. (vi) There is a relationship between the synchronicity (ΔB_i) and the local softness s^+ or the relative electrophilicity s^+/s^- of the X(5)

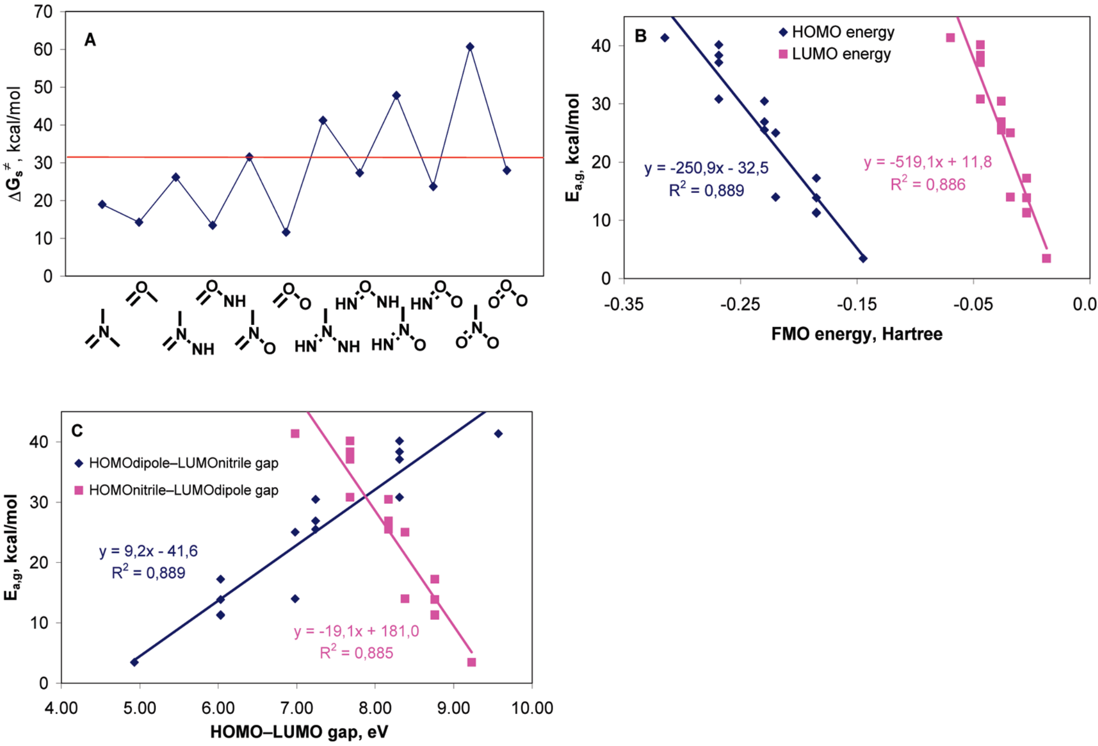

FIGURE 10. Plots of activation energies ($\Delta G_s^{\ddagger}$ or $E_{a,g}$) vs dipole nature (A), FMO energies (B), and HOMO−LUMO gaps (C) for dipoles with the central N atom and additions to MeCN.

atom of the dipole XYZ, interacting with the N atom of nitrile; i.e., the higher softness (relative electrophilicity) provides the higher synchronicity (Figure 9D). At the same time, no correlation with the HSAB properties of another atom Z(3) was found. Thus, it seems that the nature of the atom X(5) interacting with the nitrile nitrogen is one of the main factors determining the synchronicity. (vii) Within two series of dipoles with O or N central atoms, the "advancement" of a transition state along the reaction path (parameter δB_{av}, formula 9) obeys a clear trend (except ozone). The "later" transition states correspond to dipoles bearing more electronegative terminal atoms and, hence, having lower FMO energies (Figure 9E). (viii) Finally, the synchronicity depends on the regioisomeric pathway. In the case of reactions with free MeCN, the *ortho*-additions are usually more synchronous than the *meta*-ones while for the reactions with **2** the opposite trend takes place (Figure 10S, Supporting Information).

11. Activation Energy. i. Activation Energy and Dipole Nature. The activation barrier of the reactions with free MeCN increases along the following series of dipoles: $CH_2OO <$ $CH_2ONH \approx CH_2OCH_2 < CH_2N(Me)CH_2 < NHOO < CH_2N(Me)NH < NHONH \approx OOO < CH_2N(Me)O < NHN(Me)NH < NHN(Me)O < ON(Me)O$. Reactions of dipoles bearing the central N atom have significantly higher activation energies compared to analogous O-centered dipoles (Figure 10A). The reactivity of dipoles of the former type decreases along the sequence ylides > imines > oxides, the order known for cycloadditions to alkenes and alkynes.[52,54] The activation barriers of the *meta*-additions are always higher than those of the *ortho*-additions.

As was mentioned above, in accord with experimental studies, the effectiveness of cycloadditions of nitrones $CHR'{=}N(R'')O$ to free RCN depends on the nature of substituents in dipole and dipolarophile molecules. The reaction occurs only when a strong electron-acceptor group R and/or cyclic nitrone are used.[44,45] This allows the consideration of the activation barrier of the reaction $CH_2{=}N(Me)O + MeCN$ as a boundary line ($\Delta G_s^{\ddagger} \approx 32$ kcal/mol), i.e. the processes with higher activation barrier should not take place while those with lower $\Delta G_s^{\ddagger}$ values are kinetically possible. The analysis of the activation energies calculated in this work indicates that three dipoles of the triad C (NHN(Me)NH, NHN(Me)O, and ON(Me)O) are more inert than the nitrone toward MeCN, whereas the other dipoles are more reactive (Figure 10A). When nitrile is coordinated to the Pt^{IV} center in **2**, azimine $NH{=}N(Me)NH$ exhibits an activation barrier lower than 32 kcal/mol.

ii. Activation Energy vs FMO Energy. For dipoles with the central N atom (**D1**, **D3**, **D5**, **D7**, **D9**, **D11**), there is a clear correlation between the activation barrier and FMO energies: the lower the FMO energies, the higher the activation barrier (Figure 10B). It is interesting that this relationship is fulfilled also for the $LUMO_{dipole}$ along the whole above-mentioned row including $NH{=}N(Me)O$ (**D9**) and $O{=}N(Me)O$ (**D11**). The dependence of E_a on the $HOMO_{dipole}-LUMO_{nitrile}$ gap is symbate while that between E_a and the $HOMO_{nitrile}-LUMO_{dipole}$ gap is antibate (Figure 10C). It indicates that all these reactions are controlled by the $HOMO_{dipole}-LUMO_{nitrile}$ interaction (NED processes) even when the $HOMO_{dipole}-LUMO_{nitrile}$ gap is wider than the $HOMO_{nitrile}-LUMO_{dipole}$ gap. There is no clear dependence of the activation energy on FMO energies for dipoles with the central O atom (Figure 11S, Supporting Information).

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(54) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646.

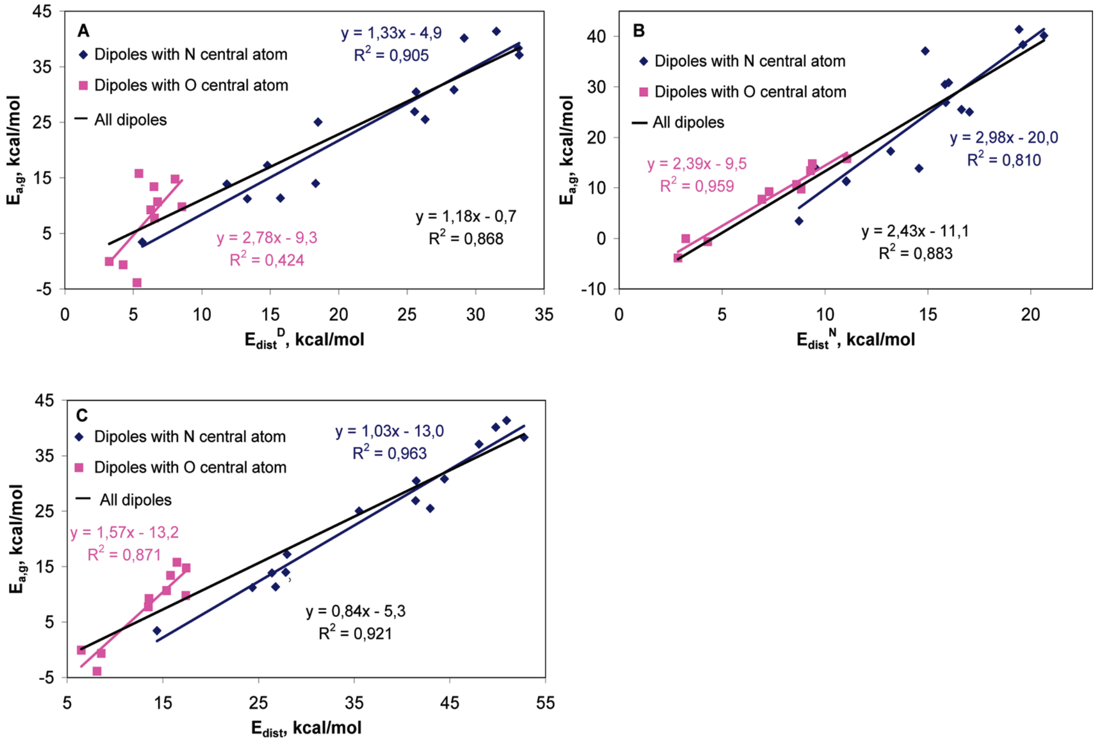

FIGURE 11. Plots of activation energy $E_{a,g}$ vs distortion energies E_{dist}^{D} (A), E_{dist}^{N} (B), and E_{dist} (C) of additions to MeCN for all regio- and stereoisomeric pathways.

iii. Activation Energy vs Distortion Energy. The energy decomposition analysis[55] is a powerful tool for the investigation of factors affecting the reactivity. The activation energy of a reaction may be decomposed onto two main components, i.e., distortion energy E_{dist} (overall energy required to distort the reactants' molecules to the geometry of a transition state) and interaction energy E_{int} (energy evolved upon interaction of the distorted fragments to give the TS). The E_{dist} term, in turn, is a sum of the distortion energies of the individual reactants (e.g., dipole E_{dist}^{D} and nitrile E_{dist}^{N}). Such an energy decomposition scheme was used to clarify the origin of the chemo- and stereoselectivity of some cycloaddition reactions,[10a,54,56] including those with nitriles.[10a] As was shown recently by Ess and Houk,[56b] for a number of cycloadditions, there is a linear correlation between the activation barrier and E_{dist}, and namely the latter determines the relative reactivity of reactants in these processes.

For the reactions of dipoles bearing a central N atom with MeCN, there are clear linear trends between E_a and E_{dist}^{D}, E_{dist}^{N}, or total E_{dist} (Figure 11). In the case of dipoles with a central O atom, there is no clear relationship between E_a and E_{dist}^{D}, although the $E_a-E_{dist}^{N}$ and E_a-E_{dist} correlations are obvious. It is interesting that if we consider all the dipoles altogether, the correlations between E_a and all the distortion energies are also satisfactory. Finally, the activation energy does not depend on the interaction energy (Figure 12S, Supporting Information), and the reasons were discussed by Hayden and Houk on the basis of analysis of the E_{dist} and E_{int} evolution along the reaction path for some dihydrogenation and Diels−Alder reactions.[57] It was shown that E_{int} is close to zero at the point corresponding to the TS and, hence, weakly changed from the reactants to the TS. In contrast, E_{dist} has a high value at the TS giving the main contribution to the total activation barrier. In the case of the additions to nitriles, E_{int} is noticeably below zero although usually significantly lower, in absolute value, than E_{dist} (except addition of **D2** and *ortho*-additions of **D4** and **D6**).

iv. Activation Energy vs Charges. No clear relationship between the activation energy and atomic charges or charge transfer was found (Figure 13S, Supporting Information). Therefore, the orbital factors play a more important role than the electrostatic ones even in the case of the additions to the Pt^{IV} complex **2**. At the same time, there is some, although far from perfect, correlation between E_a and the local softness of the X(5) and Z(3) atoms of the dipole XYZ (or sum of the softnesses) (Figure 14S, Supporting Information); i.e., the higher softness generally corresponds to the lower activation barrier.

v. Activation Energy and TS Nature. An interesting behavior of the activation energy versus geometrical parameters of TSs was found. First, the E_a values increase with the shortening of the $C(2)_{nitrile}\cdots Z(3)_{dipole}$ and $N(1)_{nitrile}\cdots X(5)_{dipole}$ contacts in the TS (an increase of the corresponding Wiberg bond indices). This trend is very clear for the $C(2)\cdots Z(3)$ contact and less obvious but observable for the $N(1)\cdots X(5)$ contact (Figure 12A and Figure 15S, Supporting Information). Second, an even better symbate correlation was found between E_a and the relative variation of Wiberg bond indices $\delta B_{C\cdots Z}$ and $\delta B_{N\cdots X}$ along the reaction

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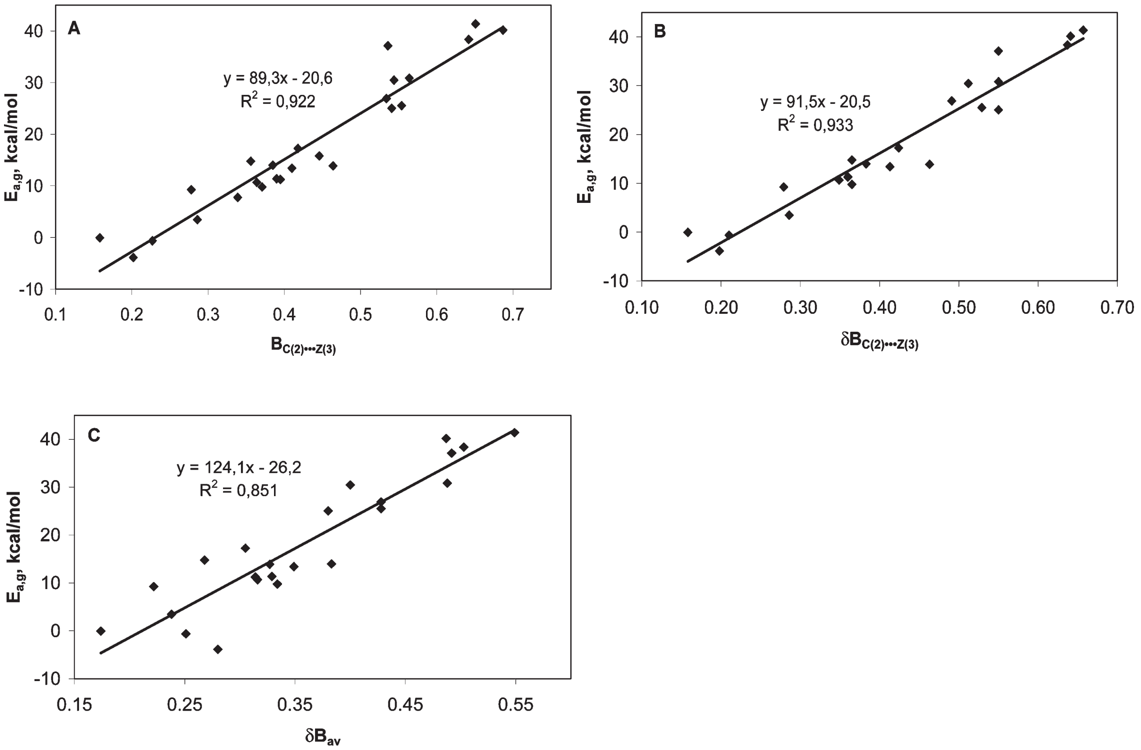

FIGURE 12. Plots of activation energy $E_{a,g}$ vs Wiberg bond index in TS (A) and its variation along the reaction path (B) for the C(2)···Z(3) contact and δB_{av} parameter (C) for all regio- and stereoisomeric pathways and additions to MeCN.

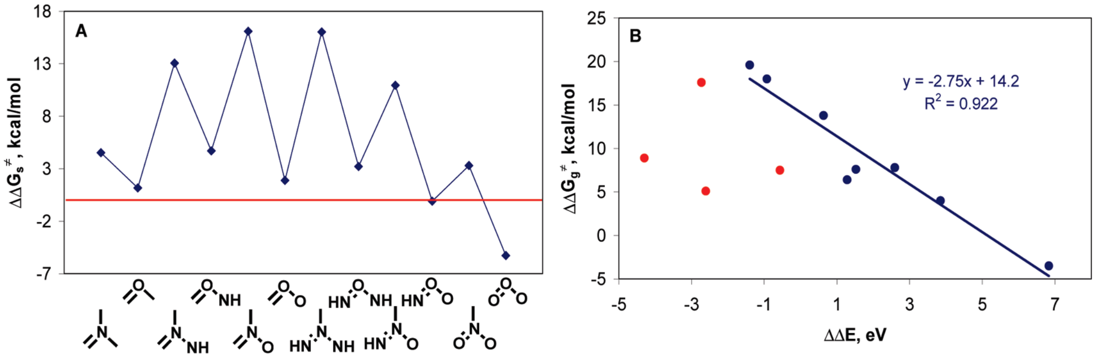

FIGURE 13. Plots of the activation effect $\Delta\Delta G^{\ddagger}$ vs the dipole nature (A) and the difference of the HOMO−LUMO gaps $\Delta\Delta E = |E(\mathrm{HOMO_{dipole}}) - E(\mathrm{LUMO_{nitrile}})| - |E(\mathrm{HOMO_{nitrile}} - E(\mathrm{LUMO_{dipole}})|$ (B).

course [formula 8] (Figure 12B and Figure 15S, Supporting Information). Third, the correlation between E_a and synchronicity is subtle, and in general, a more synchronous TS corresponds to a lower activation barrier (Figure 15S, Supporting Information). Fourth, there is a rather good symbate trend of the activation energy and "advancement" of TS along the reaction path (parameter δB_{av}): the "later" the TS, the higher the barrier (Figure 12C). The same trend was recently found by Hayden and Houk for dihydrogenation and Diels−Alder reactions with polycyclic aromatic hydrocarbons, and it is in agreement with the Hammond−Leffler postulate.[58] The reasons for such a relationship become clear if one takes into account that the activation barrier depends on the distortion energy and a "later" TS corresponds to a greater distortion of the reactants.

12. Effect of Ligation of Nitrile to Pt on the Reactivity. The greatest activation effect due to coordination of nitriles to Pt is predicted for the cycloadditions of $CH_2N(Me)NH$, $CH_2N(Me)O$, and NHN(Me)NH ($\Delta\Delta G_s^{\ddagger} = \Delta G_s^{\ddagger}$(metal-free reaction) − $\Delta G_s^{\ddagger}$(metal-assisted reaction) = 13.1−16.1 kcal/mol). The activation is moderate for the reactions of $CH_2N(Me)CH_2$, CH_2ONH, and NHN(Me)O ($\Delta\Delta G_s^{\ddagger}$ = 4.7−11.0 kcal/mol), low for the additions of CH_2OCH_2, NHONH, CH_2OO, and ON(Me)O ($\Delta\Delta G_s^{\ddagger}$ = 1.2−3.9 kcal/mol), and negative (corresponding to inhibition) for the reactions of NHOO, and OOO (Figure 13A). The Pt^{IV} usually is a better activator compared to Pt^{II}. The activation effect is usually higher for the *ortho*-additions compared to the *meta*-additions.

In terms of the FMO theory, the effect of nitrile coordination to a Lewis acid on the activation barrier is related with the predominant HOMO−LUMO interaction type. Indeed, there is a good correlation between the activation effect

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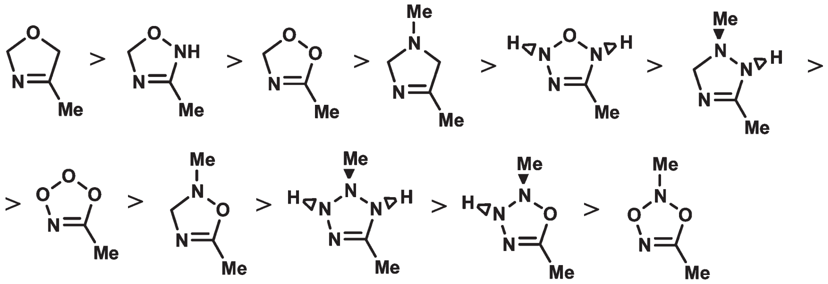

FIGURE 14. Sequence of the cycloaddition products in order of the decrease of their thermodynamic stability relative to reactants (only the products of the most favorable pathways are shown).

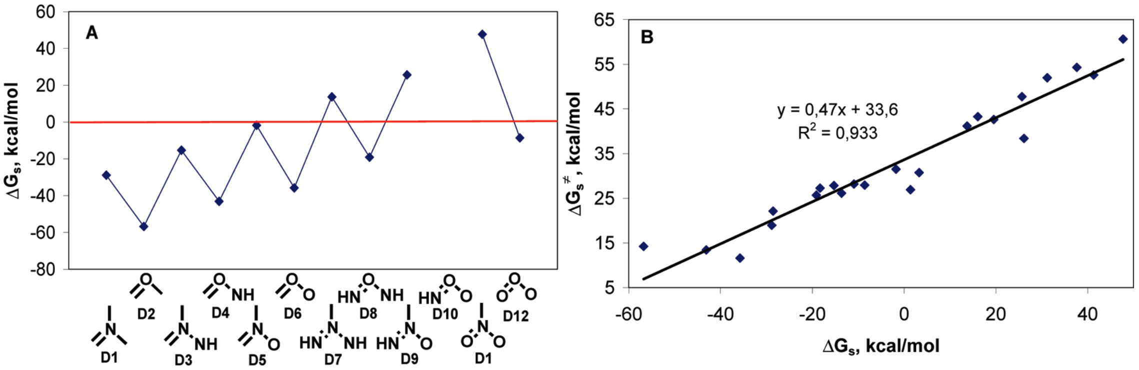

FIGURE 15. Plots of the reaction energy, ΔG_s vs the dipole nature (A) and of activation energy, $\Delta G_s^{\ddagger}$, vs the reaction energy (B) for additions to MeCN.

$\Delta\Delta G_g^{\ddagger}$ and the degree of normal (inverse) electron demand character $\Delta\Delta E$ for the reactions of **D5**−**D12** (the higher the NED character, the higher the activation effect) (Figure 13B, blue dots). However, the dipoles **D1**−**D4** do not obey this trend (Figure 13B, red dots). The activation effect for their reactions is low despite the processes exhibit a high NED character. The explanations of this peculiarity are the following. The reactions of **D1**−**D4** occur via very early TSs with very flat surrounding potential energy surface. In these TSs, the reagents' molecules are bound mainly by the weak dipole−dipole interaction while a strong covalent bonding is not realized yet. Thus, the relative energies of these TSs and, hence, the activation barriers are mostly determined not by orbital factors (FMO energies) but by electrostatic factors and weak van der Waals forces. Moreover, the enthalpic activation barrier of the reactions of **D1**−**D4** with MeCN is already low. Therefore, the acceleration of these processes also cannot be significant (only until the barrier disappears at all).

13. Reaction Energy, Reversibility and Irreversibility of the Reactions. The thermodynamic stability of the cyclic reaction products relative to the reactants decreases along the row, as shown in Figure 14. Reactions of the four dipoles (NHN(Me)NH, NHN(Me)O, NHOO, and ON(Me)O) with free MeCN are not possible or favorable thermodynamically (Figure 15A), but coordination of nitrile to Pt provides a negative ΔG_s value for the reaction of NHOO. The trends found and discussed above for the activation energies are fulfilled also for the reaction energies, i.e., the correlations between ΔE (ΔG_s) and the dipole nature, regioisomeric pathway, FMO energies, HSAB parameters, and nature of TS (Figure 17S, Supporting Information). Additionally, a good trend of the activation energy vs the reaction energy was found: the reactions with higher E_a ($\Delta G_s^{\ddagger}$) values are more endothermic and endoergonic (less exothermic and exoergonic) (Figure 15B). The linear fit of this correlation gives the equations $\Delta G_s^{\ddagger} = 0.47\Delta G_s + 33.6$ ($R^2 = 0.93$), $\Delta G_s^{\ddagger} = 0.44\Delta G_s + 30.2$ ($R^2 = 0.91$), and $\Delta G_s^{\ddagger} = 0.38\Delta G_s + 28.2$ ($R^2 = 0.84$) for additions to MeCN, **1**, and **2**, respectively. The slope for the metal-free reactions is close to 0.5, the value accepted in a number of reactivity models,[58] whereas that for the metal-assisted processes is clearly lower. These relationships are of interest because they allow the approximate express-estimate of activation barriers of cycloadditions to nitriles without the knowledge of the reaction mechanism and calculations of transition states.

The thermodynamic stability of the reaction products and the kinetic selectivity of processes form a basis for several synthetic approaches developed recently, i.e., "click" chemistry[59] and dynamic combinatorial chemistry (DCC).[60] The first approach requires a high thermodynamic stability of the products and reaction selectivity, whereas the second approach deals with reversible thermodynamically controlled processes with activation barriers sufficiently low for the rapid achievement of equilibrium. Although the analysis of applicability of the studied reactions for the "click" chemistry and DCC was not a goal of this work, some very

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preliminary comments in this respect may be outlined. The reactions of the most active 1,3-dipoles (**D1**−**D4**, and **D6**) as well as **D8** are completely irreversible and occur with small or moderate activation barriers. However, the applications of these processes in the "click" chemistry is conceivably hampered by their poor selectivity and low availability of some of these dipoles. The formation of cycloaddition products along the reactions of nitroso oxide **D10** with Pt-bound nitriles is reversible at the micromolar concentrations of reactants. Meanwhile, this process obviously should go further to acyclic products of the O-transfer (**P(10-A)O$_{\mathbf{acyc}}$**) with very negative ΔG values. The reaction of ozone (**D12**) with free MeCN is reversible at the millimolar concentrations but has a too high activation barrier for the DCC application.[61] A similar situation is found for the reaction of nitrone **D5** with MeCN. However, when the nitrile is highly activated (e.g., in complex **2**), $\Delta G_s^{\ddagger}$ is sufficiently low to reach fast the equilibrium, and the process is still reversible at the micromolar concentrations. Thus, the reactions of nitrones with activated nitriles are of a potential interest for DCC.

Final Remarks

In the present work, a systematic and detailed theoretical study of 1,3-dipolar cycloadditions of the series of the allyl-anion type 1,3-dipoles $X{=}Y^{+}{-}Z^{-}$ (X, Z = CH_2, NH, O; Y = N(Me), O) to acetonitrile MeCN has been undertaken including the comparative analysis of the effects of the dipole nature and coordination of MeCN to Pt^{II} and Pt^{IV} on the reactivity. It was found that three types of dipoles, i.e., azimines (NHN(Me)NH), azoxy compounds (NHN(Me)O), and nitro compounds (ON(Me)O), unlikely react with free nitriles due to kinetic and thermodynamic reasons. Nitroso oxides (NHOO), nitrosimines (NHONH), azomethine imines ($CH_2N(Me)NH$), ozone (OOO), and nitrones ($CH_2N(Me)O$) have moderate or low reactivities ($\Delta G_s^{\ddagger}$ = 23.7−31.5 kcal/mol), whereas carbonyl oxides (CH_2OO), carbonyl imines (CH_2ONH), carbonyl and azomethine ylides (CH_2OCH_2 and $CH_2N(Me)CH_2$) are predicted to be the most reactive dipoles in these reactions ($\Delta G_s^{\ddagger}$ = 11.6−19.0 kcal/mol).

The cyclic products of addition of CH_2OCH_2, CH_2ONH, CH_2OO, and $CH_2N(Me)CH_2$ to MeCN exhibit the highest thermodynamic stability relative to the reactants (ΔG_s = (−28.8) − (−56.87) kcal/mol), while the reactions of NHONH, $CH_2N(Me)NH$, OOO, and $CH_2N(Me)O$ have moderate or low negative ΔG_s values (ΔG_s = (−1.8)−(−19.1) kcal/mol). Dioxadiazoles, hypothetical products of cycloaddition of nitroso oxides (NHOO) to nitriles, cannot exist when uncomplexed, and the reaction could proceed further to furnish acyclic azoxy compounds. Similar O-transfer processes are expected also in the case of OOO and CH_2OO. For the reactions of some 1,3-dipoles with nitriles, two regioisomeric pathways are possible, in principle. However, the formation of *ortho*-isomers is kinetically and thermodynamically preferable over the formation of the corresponding *meta*-isomers. Thus, a complete *ortho*-selectivity of these reactions is predicted.

The coordination of a nitrile to a Lewis acid (e.g., Pt^{II} or Pt^{IV}) may significantly affect the reaction rates and stability of cycloaddition products. The calculations predict that this type of reactant modification should greatly accelerate the reactions of $CH_2N(Me)O$ and $CH_2N(Me)NH$ with a nitrile (by a factor of 3.4×10^{9}−6.4×10^{11}) providing, at the same time, a significant stabilization of the cycloaddition products. Thus, this opens up a facile route for the synthesis of poorly explored types of five-membered heterocycles such as 2,3-dihydro-1,2,4-oxadiazoles and 2,3-dihydro-1*H*-1,2,4-triazoles. Additionally, the reaction of $CH_2N(Me)O$ with complex **2** is reversible at the micromolar concentrations and has a rather low activation barrier (15.4 kcal/mol), which indicates that the cycloadditions of nitrones to nitriles are potentially interesting for dynamic combinatorial chemistry.

The reactivity of $CH_2N(Me)CH_2$ and CH_2ONH in the reactions with nitriles may also be enhanced by this way (acceleration by a factor of (2.8−3.3) × 10^{3}), although in the latter case this activation is not crucial due to the high reactivity of carbonyl imines toward free nitriles. The acceleration of the reactions of CH_2OCH_2, CH_2OO, and NHONH upon MeCN coordination is much lower (by a factor of 7−230) and is not important in the first two cases due to the high reactivity of these dipoles. Nevertheless, in the case of nitrosimines, such a moderate lowering of the activation barrier may be helpful allowing the reduction of the reaction time by a factor of 230. The cycloadditions of NHOO and OOO are inhibited by complexation of MeCN and the activation of the dipoles rather than the dipolarophiles is necessary for these processes, consistent with their strong inverse electron demand character. Finally, despite the significant decrease of the activation barriers, NHN(Me)NH, NHN(Me)O, and ON(Me)O remain inert even toward the metal-bound nitriles due to the very low stability of the cycloadducts and the still too high activation energies (in the case of azoxy and nitro compounds).

For the majority of the studied reactions, the concerted mechanism was found to be the most favorable one. Meanwhile, the cycloadditions of $CH_2N(Me)CH_2$, CH_2OCH_2, and CH_2ONH to the complex *trans*-$[PtCl_2(NCMe)_2]$ occur via a stepwise pathway due to the easy formation of six-membered intermediates. A number of correlations, i.e., activation barriers, reaction energies, reaction synchronicity, charge transfer vs dipole nature, FMO energies, atomic charges, HSAB properties of the reacting atoms, distortion energies, and regioisomeric pathways, were found and discussed.

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Supporting Information Available: Discussion of the equilibrium structures of cycloaddition products and details of the reaction mechanism. Figures with equilibrium structures of acyclic intermediates and some TSs, Laplacian distribution in some TSs, and plots demonstrating correlations of various properties (FMO energies, atomic charges, charge transfer, HSAB properties, synchronicity, activation and reaction energies, etc.) with each other. Tables with absolute and relative energies, properties of TSs, FMO energies, atomic charges, charge transfer, HSAB properties, distortion and interaction energies, Cartesian atomic coordinates for equilibrium structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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