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Nitrous Oxide as a 1,3-Dipole: A Theoretical Study of Its Cycloaddition Mechanism

Loc Thanh Nguyen,[†,‡,§] Frank De Proft,[‡] Asit K. Chandra,[∥] Tadafumi Uchimaru,[∥]
Minh Tho Nguyen,*[,§] and Paul Geerlings*[,‡]

Group of Computational Chemistry, Faculty of Chemical Engineering, HoChiMinh City University of Technology, HoChiMinh City, Vietnam, Eenheid Algemene Chemie, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium, National Institute of Advanced Industrial Science and Technology AIST, Central 5, Tsukuba, 305-8565 Japan, and Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

pgeerlin@vub.ac.be

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The 1,3-dipolar cycloadditions of nitrous oxide and substituted alkynes have been studied at the B3LYP/6-31G(d,p) level. The reaction is controlled by LUMO (dipole) − HOMO (dipolarofile) and involves aromatic transition structures. The shape of the potential energy surface and the regioselectivity are not affected by the polarity of the solvents, except in the case of $N_2O + HC{\equiv}CSiH_3$. Different reactivity criteria including FMO coefficients product *C*, local softness differences Δ, magnetic susceptibility anisotropy χ_{anis}, and nucleus-independent chemical shifts NICS were used to predict the regioselectivity in all studied cases; the *C*, Δ criteria turn out to give the best results among them. The aromaticity of the transition structure is not a factor in determining the regiochemistry of the cycloaddtition reactions.

Introduction

N_2O (nitrous oxide) is a molecule with an abundance of applications in medicine,[1] radiation chemistry,[2] food industry,[3] biology,[4] and catalytic[5] fields. Recently, there has been considerable interest in the reactions of nitrous oxide due to its important impact on the chemistry of the troposphere and stratosphere. N_2O is considered as a strong greenhouse gas because, with its long lifetime and significant IR absorption, a molecule of nitrous oxide is estimated to be about 200−300 times more powerful in warming potential than a molecule of carbon dioxide (CO_2).[6] Thus, although this gas exists only at the trace level in the troposphere, its effect on the atmospheric chemistry is expected to be by far larger than its weights.[7] In addition, N_2O could be transported to the stratosphere where it could be photochemically fragmented yielding the nitric oxide radical (NO).[8] The latter is well-known for its role in destroying the ozone layer, which protects the Earth from harmful ultraviolet radiation.[9]

As a consequence, nitrous oxide concentration is expected to affect global warming and stratospheric ozone loss, so its level should remain as low as possible, and the N_2O emissions should be reduced. The concentration of N_2O in the atmosphere is increasing at an annual rate of about 0.3%.[10] Atmospheric nitrous oxide is derived from natural and anthropogenic sources, but the latter are the main and only ones that can be minimized upon improvements in technology or changes in land use. Several anthropogenic sources of N_2O emissions have been identified, including biomass burning, fossil fuel combustion, industrial production of adipic and nitric acids, nylon manufacturing, and vehicular traffic.[11] Other well-known N_2O sources are wastewater treatment plants, fertilized soils,[12] nitrogen-enriched rivers and estuaries, and nitrogen-enriched groundwater.[13]

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* To whom correspondence should be addressed. E-mail: minh.nguyen@chem.kuleuven.ac.be.

[†] HoChiMinh City University of Technology.

[‡] Vrije Universiteit Brussel.

[§] University of Leuven.

[∥] National Institute of Advanced Industrial Science and Technology AIST.

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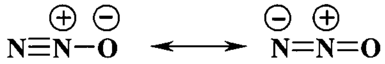
Owing to the high exothermicity and efficiency of the reactions of N_2O with metal atoms giving metal oxides, the addition of metals to combustion systems has been considered as a possible way of reducing the emission of the greenhouse N_2O gas.[14] Another capable interesting solution is to selectively recover N_2O on an adsorbent to produce a concentrated stream of N_2O during desorption and use it as an oxidant for organic chemistry.[15] Oxidations of most organic compounds by nitrous oxide giving N_2, the only byproduct, are thermodynamically favorable but are considered to be extremely slow except at high temperatures.[16] One dramatic procedure proposed by Solutia (formerly Monsanto) is to recover and use N_2O as a selective oxidant to convert benzene to phenol and then hydrogenate phenol to cyclohexanone. The latter is then oxidized by nitric oxide to adipic acid, returning N_2O as a byproduct and thus closing the N_2O cycle.[15] Another possible process is oxidizing phosphines (PR_3) by nitrous oxide at or below 100 °C.[16] The catalytic decomposition of nitrous oxide on various surfaces[5] as well as the dissociative electron attachment have widely been investigated.[17] Reactions of N_2O with radicals giving N_2 has also been studied.[18]

In contrast, relatively little is known about the behavior of nitrous oxide as a 1,3-dipole. In fact, this linear three-atomic species is isoelectronic with fulminic acid (HCNO), diazomethane (H_2CNN), and hydrozoic acid (HNNN), which are the parent molecules of important classes of 1,3-dipoles.[19] The 1,3-dipolar cycloaddition (1,3-DC) of nitrous oxide to alkenes and alkynes was experimentally studied by a group at ICI about half a century ago.[20] These reactions were, however, described by no more than one page[21] in the 1984 comprehensive treatise of the reactions.[19] Subsequently, the dipole reactivity of nitrous oxide has mainly been analyzed by means of quantum chemical methods.[22] In view of the presence of N_2O in different environments where simple dipolarophiles might exist, one may ask the question as to whether nitrous oxide could undergo certain 1,3-DC reactions as a mean of transformation. It is known that the primary five-membered rings are unstable and tend to eliminate molecular nitrogen (N_2) yielding various end products.[21] Therefore, the regioselectivity of the 1,3-DC reaction of NNO will be first determined by ab initio calculations. In general, for asymmetric dipolarophiles the distinct transition structures corresponding to two different approaches to the partners could be located. The energy difference between them allows the regioselectivity to be determined, the approach having the lowest energy gain being expected to yield the regioselective adduct.

Nitrous oxide is known to belong to the propargyl anion type, which is characterized by a linear structure (for a recent review, see ref 23).



$$N{\equiv}\overset{\oplus}{N}{-}\overset{\ominus}{O} \longleftrightarrow \overset{\ominus}{N}{=}\overset{\oplus}{N}{=}O$$

This type has an extra π orbital located in the plane perpendicular to the propargyl anion type molecular orbital; thus, the former is not directly involved in the resonance structures and reactions of the dipole. The 1,3-DC of a 1,3-dipole with alkynes (or alkenes) comprises 4 π electrons from the dipole and 2 π electrons from the alkynes (or alkenes). There is now a general agreement that the 1,3-DC reaction follows a concerted path;[24] therefore, according to the Woodward−Hoffmann rules,[25a] it is thermally allowed with the description $[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$, in which the three $2p_z$ orbitals of the 1,3-dipole and the two $2p_z$ orbitals of the alkyne both combine suprafacially. The transition structures of the concerted 1,3-DC reaction are thus controlled by the frontier molecular orbitals (FMO) of the reactants. The $LUMO_{dipole}$ can interact with the $HOMO_{alkyne}$ or vice versa. However, the introduction of π-electron-donating or π-electron-withdrawing substituents on the dipole or on the alkyne can vary the relative FMO energies and modify the reaction nature considerably.[23]

In relation to our continuing theoretical interest[26] and in an attempt to gain deeper insight in both the understanding of the mechanism of 1,3-DC reactions, particularly in their regioselectivity, and the use[27a,b] of DFT-based reactivity descriptors[28,29] to probe it and to relate it to aromaticity,[27c] we set out to investigate the 1,3-DC of N_2O with a comprehensive series of dipolarophiles, including acetylene and substituted alkynes. N_2O is also better suited for a study of regioselectivity of dipolarophiles as the behavior of the 1,3-dipole is not affected by substituents. On the other hand, it has been shown that the solvent can influence the regioselectivity on the 1,3-DC reactions (see, for example, refs 30 and 31); therefore, the solvent effect in three typical solvents with strongly different dielectric constants, including water, acetonitrile, and benzene, has also been studied. Our purpose

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is thus two-fold: (i) a determination of the energy barriers for two possible addition approaches in gas phase and in solvents and (ii) a rationalization of the observed regioselectivity making use of a variety of reactivity indices including the local criteria based on the density functional theory (DFT)[27a,28] and the idea of aromaticity of the transition state.[27c,30]

Details of Calculation

Structures and energies calculations were carried out with the aid of the Gaussian 98 set of programs.[32] All geometrical parameters were optimized and the stationary point structures were characterized by harmonic vibrational frequency analyses at the B3LYP/6-31G(d,p) level. The transition structure has only one imaginary vibrational frequency. The normal mode of this vibration corresponds to the reaction coordinate. In the case of the concerted 1,3 dipolar cycloaddition, this mode involves the stretching of two intermolecular distances and the bending of the NNO framework. Distortion of the dipolarophiles also contributes to this mode. The reaction coordinate can clearly be identified by intrinsic reaction coordinate (IRC) computations, and the energy profile is clearly established. For iodine, the effective core potential was used.[33a−c] Zero-point vibrational energies (ZPEs) were calculated at the B3LYP/6-31G(d,p) level and were scaled down by a factor of 0.9806.[33d] In the simplest case, the relative energies were further refined by single-point electronic energy computations at the coupled-cluster level with the larger basis sets (CCSD(T)/6-311++G(d,p) and CCSD(T)/6-311++G(2df,2p)). It is obvious that the B3LYP geometries do not correspond to the exact parameters of the stationary points at the CCSD(T) level if the latter could be performed. Nevertheless, recent studies[35b] involving complete optimization at the CCSD(T) level for the analogous HCNO + HCCH reaction showed that the potential energy surface in the saddle region is quite shallow and that a large fluctuation of the geometries induces only a small change in the electronic energy. Thus, the energy barrier varies only by at most 0.4 kJ/mol in going from HF to B3LYP- to CCSD(T)-optimized geometries at a certain level of theory.

Atomic charges were obtained via natural population analysis by using the NPA option in the Gaussian program. The solvent effect has been examined with the polarizable continuum model (PCM)[34] using the SCRF keyword in the Gaussian program. The dielectric constants were taken equal to 78.39 corresponding to water, 36.64 (acetonitrile), and 2.247 (benzene). The nucleus-independent chemical shifts (NICS) values were derived from magnetic shieldings computed using the gauge-independent atomic orbital (GIAO)[35] method and using the NMR option in the Gaussian program. Magnetic susceptibility anisotropies (χ_{ani}) have been calculated according to the following equation

$$\chi_{ani} = \chi_{zz} - \frac{1}{2}[\chi_{xx} + \chi_{yy}] \quad (1)$$

where χ_{zz} is the out-of-plane component and χ_{xx} and χ_{yy} are the in-plane components of the magnetic susceptibility tensor, which were computed using the continuous set of gauge transformations (CSGT)[36] method. In this paper, bond distances are given in angstroms, bond angles in degrees, total energies in hartrees, zero-point and relative energies in kilojoules per mole.

Results and Discussion

Frontier Molecular Orbital Analysis. Table 1 presents the LUMO − HOMO energy gaps and the differences in vertical ionization energies (IE) and electron affinities (EA) derived from B3LYP/6-31G(d,p) calculations for N_2O, acetylene, and substituted alkynes (RC≡CR′).

It turns out that, for acetylene, π-electron-donating substituted alkynes, and some π-electron-withdrawing substituted alkynes such as HC≡CCHO, CH_3C≡CCHO, and HC≡CCOOH, named hereafter as the group R^1 (cases 2−15 in Table 1), the energy gaps of $LUMO_{NNO}$ − $HOMO_R$ are smaller than those of $LUMO_R$ − $HOMO_{NNO}$, as also confirmed by the differences between vertical IE and EA's. As such, according to the frontier orbital theory, the N_2O moiety behaves as an electrophilic reagent and the alkyne R^1 as a nucleophilic reagent. On the contrary, for other π-electron-withdrawing substituted alkynes such as HC≡CNO_2 and CH_3C≡CNO_2, called hereafter the group R^3 (cases 17 and 18 in Table 1), the situation is reversed and N_2O becomes a nucleophilic reagent and the alkyne R^3 an electrophilic one. It is interesting to note that there is one borderline case, HC≡CCN, named the group R^2 (case 16 in Table 1) in which both energy gaps are not much different from each other (both LUMO − HOMO and IE − EA gaps).

The 1,3-DC of N_2O to Acetylene. It is well-known that two different mechanisms for the dipolar cycloadditions have been proposed, one is a concerted approach and the other involves a biradical intermediate.[19] It is not our intention to make any additional comment on the concerted-stepwise debate, but we rather confine ourselves in the concerted approach. A large body of experimental results[19] appear to favor the concertedness of the addition. For a lucid discussion of the problem, we refer to Chapter 2 of ref 19. Figure 1 displays the relative energies and the main geometrical parameters of the equilibrium and transition structures, computed at B3LYP/6-31G(d,p) level for the addition of N_2O to HC≡CH. The relative energies obtained by single-point electronic energy computations at CCSD(T)/6-311++G(d,p) and CCSD(T)/6-311++G(2df,2p) are also presented in Figure 1.

Accordingly, the reaction path takes place via the transition structure for addition to form the 1,2,3-oxadiazole cycloadduct (Prod1) followed by a transition structure for ring-opening to yield finally the formyldiazomethane (Prod2). The schematic energy profile in Figure 1 indicates that the energy gap between the reactants and other points along the reaction path seems to be reduced at the CCSD(T) levels as compared with those obtained from B3LYP method. The B3LYP method

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Table 1. Differences (in eV) in LUMO − HOMO Energies and (IE − EA) of NNO and Related Structures

no.	structure	E_{HOMO}[a] (*IE*[b])	$\mathbf{E_{LUMO}}$[a] (*EA*[b])	$\mathbf{E_{LUMO}}$**(NNO)** − E_{HOMO}(R)[a] [*IE*(*R*) − EA(NNO)[b]]	$\mathbf{E_{LUMO}}$**(R)** − E_{HOMO}(NNO)[a] [*IE*(*NNO*) − EA(R)[b]]
1	N_2O	−9.31 (*12.83*)	−0.52 (*−3.01*)		
2	HC≡CH	−7.68 (*11.11*)	1.38 (*−4.38*)	7.16 (*14.12*)	10.69 (*17.21*)
3	$HC{\equiv}CCH_3$	−7.06 (*10.06*)	1.67 (*−4.22*)	6.54 (*13.07*)	10.98 (*17.05*)
4	HC≡CF	−7.63 (*11.01*)	1.92 (*−4.98*)	7.11 (*14.02*)	11.23 (*17.81*)
5	HC≡CCl	−7.45 (*10.36*)	0.72 (*−3.29*)	6.93 (*13.36*)	10.04 (*16.12*)
6	HC≡CBr	−7.25 (*10.01*)	0.10 (*−2.63*)	6.73 (*13.01*)	9.41 (*15.46*)
7	HC≡CI	−7.06 (*9.61*)	−1.07 (*−1.29*)	6.54 (*12.61*)	8.24 (*14.11*)
8	HC≡COH	−6.61 (*9.77*)	1.09 (*−3.55*)	6.08 (*12.77*)	10.40 (*16.38*)
9	$HC{\equiv}CNH_2$	−5.87 (*8.80*)	1.69 (*−4.34*)	5.35 (*11.80*)	11.00 (*17.17*)
10	$HC{\equiv}CPH_2$	−6.81 (*9.34*)	0.00 (*−2.28*)	6.29 (*12.35*)	9.31 (*15.10*)
11	HC≡CSH	−6.50 (*9.15*)	−0.10 (*−2.28*)	5.97 (*12.16*)	9.21 (*15.11*)
12	$HC{\equiv}CSiH_3$	−7.69 (*10.39*)	0.17 (*−7.87*)	7.17 (*13.40*)	9.48 (*20.70*)
13	HC≡CCOOH	−7.80 (*10.54*)	−1.39 (*−1.18*)	7.28 (*13.55*)	7.92 (*14.01*)
14	$CH_3C{\equiv}CCHO$	−7.20 (*9.85*)	−1.66 (*−0.82*)	6.68 (*12.85*)	7.65 (*13.65*)
15	HC≡CCHO	−7.57 (*10.40*)	−2.05 (*−0.61*)	7.05 (*13.40*)	7.26 (*13.44*)
16	HC≡CCN	−8.41 (*11.20*)	−1.50 (*−1.15*)	7.88 (*14.21*)	7.81 (*13.97*)
17	$HC{\equiv}CNO_2$	−8.21 (*11.01*)	−3.07 (*0.31*)	7.69 (*14.01*)	6.24 (*12.52*)
18	$CH_3C{\equiv}CNO_2$	−7.68 (*10.25*)	−2.67 (*0.07*)	7.16 (*13.25*)	6.64 (*12.76*)

[a] Frontier orbital energies taken from B3LYP/6-31G(d,p) wave functions (in bold). [b] Vertical ionization energies and electron affinities obtained from B3LYP/6-31G(d,p) computations (in italic).

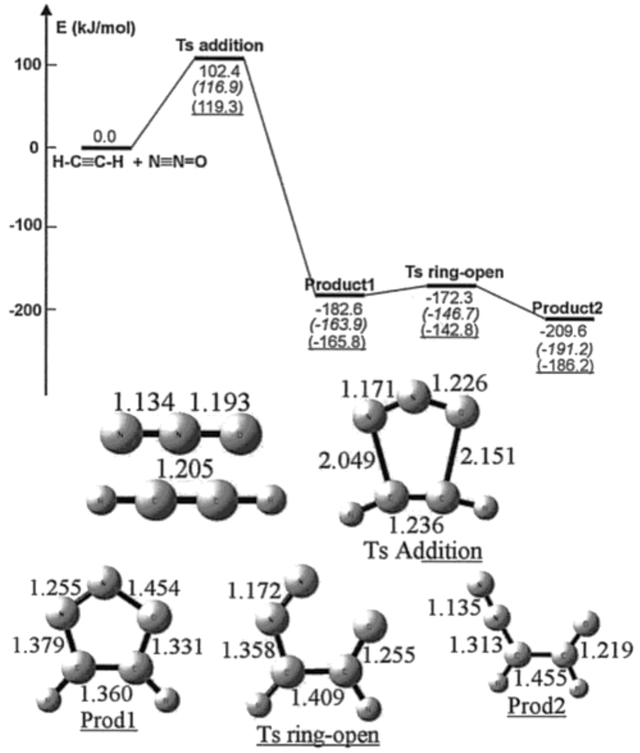

Figure 1. Schematic potential energy profiles and geometries along the reaction path in the reaction of HC≡CH + N_2O. Relative energies obtained at B3LYP/6-31G(d,p), CCSD(T)/6-311++G(d,p) (in parentheses, italic), and CCSD(T)/6-311++G-(2df,2p) (in parentheses, underline) using B3LYP/6-31G(d,p) optimized geometries and corrected for zero-point contributions.

tends to suggest an earlier transition structure and thereby to underestimate the energy barriers relative to the results derived from coupled cluster methods.[31,37−b] Nevertheless the B3LYP still provides the most reasonable tool at present as far as the reliability and computational time are concerned,[37] showing moreover low sensitivity to further extension of the basis set.[37b]

Table 2. Relative Energies (kJ/mol) of Related Structures in the Additions of N_2O to Acetylene in Gas Phase and in Solution Using the PCM at B3LYP/6-31G(d,p)

structure	gas phase	benzene $\epsilon = 2.247$	acetonitrile $\epsilon = 36.64$	water $\epsilon = 78.39$
HC≡CH + $\mathbf{N_2O}$	0.0	0.0	0.0	0.0
Ts addition	102.4	93.2	93.6	96.8
Prod1	−182.6	−216.2	−221.9	−225.2
Ts ring-open	−172.3	−197.4	−202.8	−206.8
Prod2	−209.6	−231.9	−235.0	−238.2

In addition, to estimate the solvent effect on the 1,3-DC of N_2O to HC≡CH, we also calculated the single point electronic energies of all points along the reaction path in the presence of a solvent continuum. Table 2 lists all the results performed at the B3LYP/6-31G(d,p) level and using the PCM model for three continua including benzene, acetonitrile and water. When increasing the polarity of the solvent, all structures tend to increase their stabilization, but the shape of the potential energy surface is not basically affected, irrespective of the polarity of the solvent.

Another question is as to whether 1,2,3-oxadiazole (Prod1) can be stable although it was originally postulated as an intermediate in the 1,3-DC of N_2O to alkynes.[20c] This problem has previously been studied by one of us[38] using the modest HF/3-21G optimizations and single-point energy calculations at some higher levels up to the MP4SDQ/6-31G(d,p). In the present study, higher levels of calculations (B3LYP/6-31G(d,p) optimization and CCSD(T) single-point energy calculations) have been carried out and their results together with the best values of ref 38 are listed in Table 3.

As can be seen, the activation energy for the ring-opening appears to increase whereas the energy gap between Prod1 and Prod2 tends to decrease at higher levels. A similar trend is also observed upon increase of the solvent polarity in going from benzene to water if we take into account only the values from B3LYP method. Accordingly, the present study performed at higher levels of calculations comes to the same conclusion suggested

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Table 3. Stability of 1,2,3-Oxadiazole (Prod1) Compared to Formyldiazomethane (Prod2) and the Ts for Ring Opening at Different Levels and in Different Solvents (in kJ/mol)

structure	gas phase *a*	*b*	*c*	*d*	benzene[e] $\epsilon = 2.247$	acetonitrile[e] $\epsilon = 36.64$	water[e] $\epsilon = 78.39$
Prod1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ts ring-opening	15.9	10.3	17.2	23.0	18.8	19.1	18.4
Prod2	−37.2	−27.0	−27.3	−20.4	−15.7	−13.1	−13.0

[a] Best values obtained from ref 9a. [b] Values at B3LYP/6-31G(d,p) level (this work). [c] Values at CCSD(T)/ 6-311++G(d,p) level (this work). [d] Values at CCSD(T)/ 6-311++G(2df,2p) level (this work). [e] Values derived from Table 2.

in the previous work[38b] that the unsubstituted 1,2,3-oxadiazole is not stable as a discrete species.

Moreover, to have an additional idea about the feasibility of a 1,3-DC of N_2O to acetylene, we also take note here of the activation energies of the 1,3-DC of acetylene with different 1,3-dipoles. A large number of studies have been reported on the reactions of fulminic acid ($HC\equiv N^+O^-$) and nitrone ($H_2C{=}N^+HO^-$) with acetylene, but we choose one reported in ref 30, as it used a comparable level (B3LYP/6-31+G(d)) as our level of calculation (B3LYP/6-31G(d,p)). Accordingly, the activation energy amounts to 83 kJ/mol for the addition of nitrone to acetylene and 63 kJ/mol for that of fulminic acid to acetylene. Compared to the present value of 102 kJ/mol for the addition of N_2O to acetylene, it turns out to be about 20 kJ/mol higher in energy than that to nitrone and 40 kJ/mol higher than that to fulminic acid. As such, the 1,3-DC of N_2O to acetylene could reasonably occur under mild thermal conditions.

The 1,3-DC of N_2O to Substituted Alkynes. Geometries. To obtain more details about the 1,3-DC of N_2O to alkynes, we have investigated this reaction with a series of substituents including π-electron-donating group such as CH_3, the halogens, OH, NH_2, PH_2, etc. and π-electron-withdrawing group such as CHO, CN, and NO_2. A combination of substituent groups is also considered in the cases of $CH_3C\equiv CCHO$ and $CH_3C\equiv CNO_2$. When the two carbon atoms of alkynes and the terminal N and O atoms of N_2O approach to each other, two cycloadducts are in principle possible; but in many cases, the reaction proceeds predominantly through one transition state (Ts) and thus introduces a regioselectivity. Normally, the lower energy Ts of the two is defined as Ts_n (normal) and the other one as Ts_r (reverse). However, considering the large number of transition structures investigated in our study and their identity, the terms Ts_n and Ts_r do not allow the attack site in the transition state to be clearly defined. Therefore, in the relevant Tables 4 and S1−S3 (Supporting Information), the Ts' are defined rather as Ts-O-to-C(R) (referred to hereafter as Ts-OCR) which stands for an attack of the N_2O oxygen to the substituted carbon, or Ts-O-to-C(H) (named Ts-OCH) standing for an attack of N_2O oxygen atom to the unsubstituted carbon of alkynes. As a consequence the N_2O nitrogen atom will attack the other carbon of alkynes. Moreover, for the sake of simplicity, we only plot the two general Ts's, in which H stands for hydrogen (or the CH_3 group in the cases of substituent combination) and R for substituents.

Table S1 (Supporting Information) presents both schematic transition structures and a selection of geometrical parameters of all Ts's in the 1,3-DC of N_2O to alkynes. The local softness differences D_1 and D_2 are also included in Table S1. Those quantities will be defined and discussed in the regioselectivity section. According to Table S1, the least variable bonds in the Ts's are then N−N, N−O, and C−C; their average lengths of 1.17 ± 0.01, 1.22 ± 0.01, and 1.24 ± 0.01 Å, respectively do not differ significantly from those in the separated reactants. The lengths of the two newly forming bonds, C−N (R_1) and C−O (R_2), differ in going from the unsubstituted to the substituted cases. ΔR_1 stands for the differences between the C−N bond distances in the Ts's of unsubstituted and substituted cases. Similarly, ΔR_2 stands for the differences in the C−O bond distances. Generally, it is clear that the forming bonds undergo small opposite changes, therefore the average lengths of the forming bonds are not significantly affected by the presence of substituents on the acetylene species. This trend has also been observed in the 1,3-DC of diazomethane and formonitrile oxide with substituted ethylene.[37a] It can be ascribed to the competition of the reacting system between maintaining bonding as strong as possible and leaving room for an asynchronicity demanded by the asymmetry of the reactants.

Energy Barriers and Solvent Effect. The gas-phase calculated dipole moments (DPM) and the relative energies of all Ts's in the 1,3-DC of N_2O to substituted alkynes in gas phase and in different solvents are given in Table S2 of the Supporting Information.

In referring to our classification above derived from the frontier molecular orbital (FMO) interactions, in the group R^1 and R^2, the Ts_n (Ts normal) is Ts-OCR except for the case of $CH_3C\equiv CCHO$. This Ts-OCR is characterized by the attack of N_2O oxygen to the alkyne unsubstituted carbon and N_2O nitrogen to the substituted carbon. On the contrary, in the group R^3, the Ts_n is Ts-OCH in which oxygen is attached to C(−H) (or C(−CH_3) in $CH_3C\equiv CNO_2$) while nitrogen is attached to C(−NO_2). These observations confirm that the substituents can change the relative FMO energies and thereby the way of interaction in the 1,3-DC reactions. In summary, the activation energies corresponding to Ts_n increase in the following order: $NH_2 < H < NO_2 \approx F < SiH_3 = CHO \approx CH_3 < PH_2 < OH < SH <$ CH_3 and CHO $<$ CH_3 and NO_2 $< Br < I < COOH < Cl < CN$.

As in the unsubstituted case, we have also investigated the solvent effect using the PCM in three continua with different dielectric constants ϵ corresponding to the benzene, acetonitrile and water values. Due to the lack of analytical gradients, only single-point SCRF calculations were done at the B3LYP/6-31G(d,p) level, with the gas-phase geometries optimized at the same level. Table S2 emphasizes that, except for the case of SiH_3, the regioselectivity in the 1,3-DC of N_2O to alkynes is not affected by the polarity of the solvent. For the case of $HCCSiH_3$, the large difference of 261 kJ/mol in going from $\epsilon = 2.25$ to $\epsilon = 78$ seems suspectly large. Presumably this comes from a not correct charge distribution or a difficulty in defining the cavity and the related parameters for Si; similarly the large changes in some systems (148 and 111 kJ/mol) should be regarded with much caution. In general when going from low ϵ (corresponding to benzene) to high ϵ (corresponding to water), the activation energy of all Ts's tends to increase, but the amplitude of such change is rather small (less than 5 kJ/mol). In the SiH_3 case, it is interesting to see that the activation energy of the Ts for high ϵ is very high as compared with the corresponding ones low ϵ solvents. Moreover, the regioselectivity in this case is effectively changed in high ϵ (aqueous) solution, in which the Ts-OCR being the Ts normal in the gas phase becomes the Ts reverse. The results of our calculations (not presented here) show that the stabilization of most of the structures is increased in water, but the stability variation in the reactants and Ts are approximately in the same order of magnitude; therefore the regioselectivity is not affected. In contrast, due to the highly polar nature of the $H-C\equiv C-SiH_3$ moiety, its energy in high ϵ media lies 261 kJ/mol lower than that in benzene. The energies of Ts-OCH and Ts-OCR in a high ϵ solvent are situated 148 and 111 kJ/mol, respectively, lower than those in a low ϵ solvent. Consequently, the order of regioselectivity is changed upon solvation as mentioned above.

Regioselectivity. As discussed in previous sections, the 1,3-DC of N_2O to alkynes passes preferentially through the Ts-OCR in the groups R^1 and R^2, whereas it takes place via the Ts-OCH in the group R^3. The calculated activation energy differences are small (typical about 1 kcal/mol). To check whether the calculated regioselectivity might be influenced by entropy factors when considering $e^{-\Delta G^{\ddagger}RT}$ instead of $e^{-E_A/RT}$ where $\Delta G^{\ddagger}$ is the Gibbs free energy of activation, we evaluated the corresponding activation entropies $\Delta S^{\ddagger}$ for the two Ts's and calculated the difference in their contribution to $\Delta G^{\ddagger}$ at 298.15 K. The typical order of magnitude of $T\Delta S^{\ddagger}$ was between − 40 and − 50 kJ/mol, the differences between the two Ts's being in almost all cases much smaller than 1 kJ/mol. Exceptions were $HC\equiv CNH_2$ (4.5 kJ/mol) and $HC\equiv CCHO$ (7.3 kJ/mol), only the latter case leading to a reversal of the $\Delta G^{\ddagger}$ sequence as compared to E_A.

In an attempt to explain such regioselectivity, we have used DFT-based reactivity descriptors such as Fukui functions and local softness, which have been found to be very useful for interpreting the regiochemistry in addition reactions.[26a−b,39] Detailed discussion and commonly used formulas of the DFT-based reactivity descriptors can be found elsewhere (see for example ref 27a and references therein). A comparison of this analysis with the classical FMO is also made.

Besides, we also analyze the regioselectivity by utilizing other criteria based on the aromaticity of the Ts. Cossío et al.[30] found that even though all the Ts in the 1,3-DC of nitrile oxides or nitrones with carbon−carbon multiple bond are aromatic, such Ts aromaticity is important but not determinant for the regioselectivity in this kind of reaction. However, in a recent study,[40] we found that the aromaticity (NICS(1) values) of the transition state together with the local softness constitutes the good criteria in predicting the regioselectivity in the [2 + 1] cycloaddition of CX (X = O, S) to substituted alkynes. To figure out if there is any generality in this concept, we have also calculated the NICS values at 1 Å above the center of the five-membered Ts. Furthermore, another index for the aromaticity, namely the magnetic susceptibility of all Ts's, was also evaluated.

In addition, as mentioned in the Introduction, the nature and height of the Ts of the concerted 1,3-DC can chemically be rationalized by the FMO of the reactants. In fact, those FMO interactions are already expressed in the local softness differences, but in order to make a more detailed comparison of both criteria we also consider the FMO coefficients as a regioselectivity criterion. From a simple view of second-order perturbation theory for orbital controlled reactions, the interaction energy at an initial stage of the reaction of the 1,3-dipole with an alkyne can be described in the following equation[25b,c]

$$\Delta E \propto \frac{(\Sigma C^{i}_{\mathrm{HOMO}} C^{j}_{\mathrm{LUMO}})^2}{E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}}} \qquad (2)$$

where C^{i}_{HOMO} and C^{j}_{LUMO} are the orbital coefficients at the reacting atoms in the HOMO and LUMO, respectively. The $E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}}$ is the difference of the HOMO and LUMO energies. Because the $E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}}$ difference is the same in both Ts_n and Ts_r in the 1,3-DC reactions, the product $C_{\mathrm{HOMO}}C_{\mathrm{LUMO}}$ foreshadows the regioselectivity: the larger the $C_{\mathrm{HOMO}}C_{\mathrm{LUMO}}$ product, the larger the stabilizing interaction energy between both partners and the more favored the reaction. We define C as the product of FMO coefficients and it has the expression in (3) if N_2O acts as an electrophile corresponding to the Ts-OCH:

$$C = (C_{\mathrm{N}}^{\mathrm{LUMO}} C_{\mathrm{C(-R)}}^{\mathrm{HOMO}} + C_{\mathrm{O}}^{\mathrm{LUMO}} C_{\mathrm{C-(-H)}}^{\mathrm{HOMO}})^2 \qquad (3)$$

When the Ts-OCR is involved, C becomes

$$C = (C_{\mathrm{N}}^{\mathrm{LUMO}} C_{\mathrm{C(-H)}}^{\mathrm{HOMO}} + C_{\mathrm{O}}^{\mathrm{LUMO}} C_{\mathrm{C-(-R)}}^{\mathrm{HOMO}})^2 \qquad (4)$$

If N_2O acts as a nucleophile, C will have the forms similar to (3) and (4), but we then need to consider the HOMO coefficients of N and O in N_2O and the LUMO coefficients of the carbon atoms in alkynes. For the sake of simplicity, the evaluation of the product C has been done by HF/STO-3G orbital coefficients.

As pointed out in the first part, N_2O acts as an electrophile and a substituted alkyne of the group R^1 as a nucleophile. Therefore, within this group, we consider the local softness for nucleophilic attack ($s_k{}^+$) of O and N in N_2O, and for electrophilic attack ($s_k{}^-$) of the carbon atoms in substituted acetylenes. We define D_1 (in Table S1) as the square of softness differences between the alkyne carbon atom and the N_2O nitrogen atom, D_2 (in Table S1) as the one between the alkyne carbon atom and the N_2O oxygen atom, and Δ (in Table 4) as the sum of D_1 and D_2. Those quantities will have the form described in eq 5 if Δ corresponds to the approach in Ts-OCH.

$$\Delta = D_1 + D_2 = (s^{-}_{\mathrm{C(-R)}} - s^{+}_{\mathrm{N}})^2 + (s^{-}_{\mathrm{C(-H)}} - s^{+}_{\mathrm{O}})^2 \qquad (5)$$

When Δ corresponds to the approach in Ts-OCR, (5) becomes

$$\Delta = D_1 + D_2 = (s^{-}_{\mathrm{C(-H)}} - s^{+}_{\mathrm{N}})^2 + (s^{-}_{\mathrm{C(-R)}} - s^{+}_{\mathrm{O}})^2 \qquad (6)$$

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Table 4. Criteria (Activation Energies E_{act} (kJ/mol), Local Softness Differences Δ, Magnetic Susceptibilities χ_{anis} (cgs-ppm), and NICS Values (ppm)) Used in Explaining the Regioselectivity of the 1,3-DC of N_2O and HC≡CR

no.	structure	site attack in TS	E_{act}	Δ[a]	C[b]	χ_{anis}[c]	NICS(1)
1	$HC{\equiv}CCH_3$	O-to-C(−H)	110.9	0.143	0.551	−23.05	−18.32
		O-to-C(−CH_3)	**105.2**[d]	**0.023**	**0.565**	**−19.18**	**−16.61**
2	HC≡CF	O-to-C(−H)	109.7	0.262	0.503	−19.15	−17.03
		O-to-C(−F)	**104.1**	**0.000**	**0.547**	**−16.06**	**−15.57**
3	HC≡CCl	O-to-C(−H)	117.1	0.386	0.452	−22.75	−18.11
		O-to-C(−Cl)	**112.8**	**0.029**	**0.478**	**−19.21**	**−16.58**
4	HC≡CBr	O-to-C(−H)	115.0	0.480	0.313	−22.11	−18.37
		O-to-C(−Br)	**111.0**	**0.068**	**0.351**	**−17.88**	**−16.66**
5	HC≡CI	O-to-C(−H)	112.4	0.670	0.194	−22.58	−18.69
		O-to-C(−I)	**111.4**	**0.150**	**0.224**	**−19.61**	**−17.58**
6	HC≡COH	O-to-C(−H)	114.4	0.469	0.436	−19.03	−17.47
		O-to-C(−OH)	**108.2**	**0.030**	**0.511**	**−15.87**	**−16.14**
7	$HC{\equiv}CNH_2$	O-to-C(−H)	103.7	0.625	0.375	−20.63	−17.84
		O-to-C(−NH_2)	**94.4**	**0.092**	**0.462**	**−9.42**	**−10.62**
8	$HC{\equiv}CPH_2$	O-to-C(−H)	107.5	0.593	0.259	−24.46	−18.80
		O-to-C(−PH_2)	**106.5**	**0.130**	**0.294**	**−39.35**	**−17.76**
9	HC≡CSH	O-to-C(−H)	111.0	0.790	0.235	−19.29	−18.62
		O-to-C(−SH)	**109.4**	**0.192**	**0.294**	**−15.79**	**−17.64**
10	$HC{\equiv}CSiH_3$	O-to-C(−H)	106.7	0.157	0.353	−28.36	−19.18
		O-to-C(−SiH_3)	**105.0**	**0.118**	**0.358**	**−26.48**	**−18.20**
11	HC≡CCOOH	O-to-C(−H)	114.1	0.498	0.349	−32.08	−17.96
		O-to-C(−COOH)	**111.7**	**0.102**	**0.359**	**−31.52**	**−17.33**
12	$CH_3C{\equiv}CCHO$	O-to-C(−CH_3)	**109.9**	**0.744**	**0.491**	**−28.31**	**−15.61**
		O-to-C(−CHO)	114.1	0.266	0.485	−31.02	−16.70
13	HC≡CCHO	O-to-C(−H)	107.0	0.766	0.494	−38.34	−17.83
		O-to-C(−CHO)	**105.0**	**0.249**	**0.504**	**−36.87**	**−17.21**
14	$HC{\equiv}CNO_2$	O-to-C(−H)	**104.0**	**0.748**	**0.225**	**−15.31**	**−17.34**
		O-to-C(−NO_2)	106.1	0.819	0.184	−36.16	−17.33
15	$CH_3C{\equiv}CNO_2$	O-to-C(−CH_3)	**110.7**	**0.760**	**0.220**	**1.67**	**−15.56**
		O-to-C(−NO_2)	119.8	0.826	0.177	−6.99	−16.66

[a] Δ: differences in local softness (see text for definitions). [b] C: FMO coefficients product (see text). [c] χ_{ani}: magnetic susceptibility anisotropies of the transition structures for addition. [d] In bold: the favored reaction path via the Ts normal.

where s^+_N, s^+_O are the local softness values of the N^1 and O^3 atoms in $N^1N^2O^3$, and $s^-_{C(-H)}$ and $s^-_{C(-R)}$ represent the local softness of C(−H) and C(−R) in HC≡CR.

In the case of $CH_3C{\equiv}CCHO$, C(−H) also stands for C(−CH_3) and C(−R) for C(−CHO).

These quantities, derived from HSAB considerations,[25b] can be seen as orbital-free generalizations of expressions (3) and (4). The validity of the expressions has been demonstrated in a very recent paper by Ponti.[41]

On the contrary, within the group R^3, N_2O acts as a nucleophile and the corresponding substituted alkyne as an electrophile. Therefore, in this case we will consider the local softness for electrophilic attack (s_k^-) of O, N in N_2O, and for nucleophilic attack (s_k^+) of carbon atoms in substituted acetylenes. As a consequence, Δ will have the form expressed in eq 7 if it corresponds to the Ts-OCH.

$$\Delta = D_1 + D_2 = (s^+_{C(-R)} - s^-_N)^2 + (s^+_{C(-H)} - s^-_O)^2 \quad (7)$$

When Δ corresponds to the Ts-OCR, (7) becomes

$$\Delta = D_1 + D_2 = (s^+_{C(-H)} - s^-_N)^2 + (s^+_{C(-R)} - s^-_O)^2 \quad (8)$$

In the case of $CH_3C{\equiv}CNO_2$, C(−H) also stands for C(−CH_3) and C(−R) for C(−NO_2).

To verify further the group classification derived from Table 1, we also calculated the charge transfer from or to the NNO group in all Ts's. Table S3 records the sums of NNO group charges in all Ts's of the 1,3-DC of N_2O and alkynes.

With the group R^1, the sum values are high and negative, which indicates that N_2O actually receives electrons from alkynes and thus behaves as an electrophile. The sum in the group R^3 is also negative but its value is considerably smaller, even equal to zero in the $HC{\equiv}CNO_2$ case. Those observations are in line with what discussed in previous sections from other properties.

In the borderline case (HC≡CCN), from either the view of FMO theory or the charge transfer, it is hard to classify N_2O as electrophile or nucleophile, therefore we cannot apply those above criteria for this case.

All the calculated results using different criteria are summarized in Table 4 and they emphasize a few interesting points. In the first place and, except for the case of $CH_3C{\equiv}CCHO$, the local softness difference Δ and the FMO coefficients product C are successful in explaining the regioselectivity found by the explicit computations of the Ts's. This observation confirms that the studied 1,3-DC reactions are orbital-controlled as expected. It is also interesting to note that those criteria can well predict the preferred site of the initial attack, even though the calculated activation energy differences are nearly always very small (typically of 1 kcal/mol). In most cases, the softness differences D_1 and D_2 (Table S1) associated with the lowest energy Ts (Ts-normal) are found to be the smallest. Moreover, in the majority of those cases, D_1, the softness difference corresponding to the C−N bond is lower than that of D_2. In addition the R_1 value of the C−N bond distance in the Ts_n is, except for some cases, the smallest one out of the four R_1, R_2 possibilities (Table S1). The whole of these data indicate that the 1,3-DC is a concerted but asynchronous process. The correspondence between the smallest local softness difference and the shortest forming bond distance is also remarked in another study of one of the present authors.[39a]

The criteria based on the Ts aromaticity (χ_{anis} and NICS

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(41) Ponti, A. *J. Phys. Chem. A* **2000**, *104*, 8843.

values) fail in the prediction of the correct regioselectivity in all cases, even though all of the Ts's can be considered as aromatic. This finding is in contrast with the results recently obtained for the [2 + 1] additions,[40] but agrees with the conclusion drawn by Cossío et al.,[30] where it was shown that for the 1,3-DC of fulminic acid with 1,3-butadiene, the Ts-normal is the less aromatic, more polar and less synchronous Ts.

To assess the Ts's polarity, we calculated the dipole moments of all Ts's listed in Table S2. It is clear that, for the majority of cases, the Ts_n is more polar than the Ts-reverse (Ts_r). This is probably due to the larger polarization of the N^2-O^3 bond in the $N^1N^2O^3$ group of the Ts_n compared to that of Ts_r, as can be seen in Table S3. Moreover, the C−O bond distance of the Ts_n is longer than that of the Ts_r in most cases (see Table S1). The longer C−O bond distance in the Ts_n leads to poor overlap and covalency between both atoms, resulting in a lower aromaticity of the Ts_n as compared to that of Ts_r. Overall, in this study, the lower activation energy of the Ts corresponds to the more polar, more asynchronous and less aromatic Ts. This is in line with the remarks obtained from the work of Cossío et al.[30]

Concluding Remarks

From the present theoretical study, the following conclusions can be deduced:

(a) The 1,3-DC reactions of N_2O to alkynes are orbital controlled. In the addition to acetylene, π-electron-donating substituted alkynes, and some π-electron-withdrawing substituted alkynes such as HC≡CCHO, $CH_3C{\equiv}CCHO$, and HC≡CCOOH (group R^1), nitrous oxide behaves as an electrophilic reagent and the alkyne as nucleophilic counterpart. On the contrary, in the addition to $HC{\equiv}CNO_2$ and $CH_3C{\equiv}CNO_2$ (group R^3), N_2O acts as a nucleophilic reagent and alkyne as an electrophile. HC≡CCN is a borderline case in which we cannot specify N_2O as nucleophilic or electrophilic reagent; therefore, both interactions are apparently competitive.

(b) The Ts-normal, being the Ts with lower activation energy for the initial attack of N_2O to the group R^1, is the transition structure in which the N_2O oxygen is attached to the alkyne substituted carbon and N_2O nitrogen to the unsubstituted carbon. In the group R^3, a reverse selectivity is operative and it is the Ts in which the N_2O oxygen attached to the unsubstituted carbon of alkyne.

(c) The solvent seems to stabilize all structures almost uniformly but can alter the regioselectivity of the reaction between N_2O and $HC{\equiv}CSiH_3$. For other studied reactions, the shape of the potential energy surface seems to be not affected by the polarity of the solvent.

(d) The local softness differences and the FMO coefficients product are good criteria in predicting the site of the initial attack. It has been shown that the 1,3-DC of N_2O to alkynes is a concerted but asynchronous process. Although all Ts's are aromatic, their aromaticity does not influence the regioselectivity of the reactions. In this study the less aromatic, more polar and more asynchronous Ts is the Ts-normal.

(e) After all, in view of the relatively low energy barriers for 1,3-DC of N_2O, this mode of reaction might be involved as a way of transforming nitrous oxide in various environments under mild conditions.

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Supporting Information Available: *Z*-matrixes or Cartesian coordinates with the computed total energies for all studied structures are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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