Mechanism of $[3+2]$ Cycloaddition of Alkynes to the $[Mo_3S_4(acac)_3(py)_3][PF_6]$ Cluster**


Abstract: A study, involving kinetic measurements on the stopped-flow and conventional UV/Vis timescales, ESI-MS, NMR spectroscopy and DFT calculations, has been carried out to understand the mechanism of the reaction of $[Mo_3S_4(acac)_3(py)_3][PF_6]$ (acac = acetylacetonate, py = pyridine) with two RC≡CR alkynes (R = CH₂CH₂O (btd), COOH (adc)) in CH₃CN. Both reactions show polyphasic kinetics, but experimental and computational data indicate that alkyne activation occurs in a single kinetic step through a concerted mechanism similar to that of organic $[3+2]$ cycloaddition reactions, in this case through the interaction with one Mo($\mu$-$S$) moiety of $[1]^+$. The rate of this step is three orders of magnitude faster for adc than that for btd, and the products initially formed evolve in subsequent steps into compounds that result from substitution of py ligands or from reorganization to give species with different structures. Activation strain analysis of the $[3+2]$ cycloaddition step reveals that the deformation of the two reactants has a small contribution to the difference in the computed activation barriers, which is mainly associated with the change in the extent of their interaction at the transition-state structures. Subsequent frontier molecular orbital analysis shows that the carboxylic acid substituents on adc stabilize its HOMO and LUMO orbitals with respect to those on btd due to better electron-withdrawing properties. As a result, the frontier molecular orbitals of the cluster and alkyne become closer in energy; this allows a stronger interaction.

Introduction

The scope and applications of organosulfur chemistry have increased significantly in recent decades. Compounds with C–S bonds are not only present in a large number of biological molecules, some of them with pharmaceutical properties, but are also nowadays used as auxiliary functions in synthetic sequences.[11] Thus, efforts from the synthetic chemistry community have blossomed into the development of a number of catalytic protocols, most of them involving transition-metal complexes, to form C–S bonds.[12] Conversely, examples of carbon-bridging-sulfur bond formation through the reaction of alkynes with sulfur-bridged metal compounds are scarce. For many years, these were limited to dinuclear complexes,[13] however, in the last 20 years, several reports of trinuclear $[M_3(\mu_3-S)(\mu_3-O)]^{2+}$ clusters ($M = Mo, W; Q = O, S$) that form C–S bonds by reacting with alkynes have appeared.[14] In this way, $[Mo_3(\mu_3-S)(\mu_3-X)(\mu_3-O)]^{2+}$ ($X = O, S$) clusters have been shown to react with acetylene to yield $[Mo_3(\mu_3-S)(\mu_3-X)(\mu_3-O)]^{2+}$ ($X = O, S$) clusters with bridging alkenedithiolate ligands,[15] but the reaction is not limited to the aqua cluster and also occurs for substituted clusters as $[Mo_3(\mu_3-S)(\mu_3-X)(Hnta)]^{2+}$ (Hnta = nitrioltriaacetic acid),[16] $[W_3(\mu_3-S)(\mu_3-X)(NCS)]^{3-}$ ($X = Q, S$),[17] and $[W_3(\mu_3-S)(\mu_3-OAC)(dtp)]^{2+}$ (dtp = diethylidithiophosphate).[18] The reaction products have a variety of structures that have been classified according to the three structural types in Figure 1,[19] although type I compounds are the most common and always appear to be the initial product of the re-
action. A recent kinetic and computational mechanistic study on the reaction of the [Mo₃(S)(μ-S)(H₂O)]⁴⁺ cluster with the alkynes 2-butyne-1,4-diol (btd) and acetylenedicarboxylic acid (adc) in acidic aqueous solutions confirmed previous mechanistic proposals by Shibahara and Ide, in the sense that the initial reaction led to the cycloaddition product labeled as type I through a concerted mechanism in which two C=S o bonds formed through a single five-membered-ring transition state. To obtain additional mechanistic information on this process, we decided to explore the reaction of the same alkynes by using an aprotic solvent and selected the [Mo₃S₄(acac)(py)]PF₆ (I)PF₆; acac = acetylacetonate, py = pyridine) cluster, which was previously shown to be soluble in acetonitrile. The use of this system presents two major advantages from a mechanistic point of view: 1) it avoids some of the complications found in previous work associated with the existence of acid–base equilibria that involve both the cluster and adc, as well as the possibility of the formation of chloro complexes by substitution of coordinated water in [Mo₃S₄(H₂O)]⁴⁺; and 2) unlike the [Mo₃S₄(H₂O)]⁴⁺ cation, compound IPF₆ is readily amenable to the ESI-MS technique to yield cation [I]⁺ as the base signal in the ESI mass spectrum; thus ESI-MS monitoring can yield crucial information that may be used as experimental input for computational descriptions of the reaction.

From a computational point of view, the reactivity of [I]PF₆ cluster with alkynes in acetonitrile, and specifically the initial [3 + 2] cycloaddition step, is of great interest due to the reduced number of cases in which one of the atoms of the generated five-membered ring is a metal center. Herein, the process has been thoroughly analyzed by combining DFT methods with the activation strain model (ASM) and frontier molecular orbital (FMO) approaches. The results obtained provide an explanation for the different rates of reaction observed for different alkynes.

Results and Discussion

Kinetic studies on the reaction of [I]⁺ with alkynes

The reaction of [I]⁺ with btd occurs with spectral changes that are slow enough to be monitored with a standard UV/Vis spectrophotometer. The changes show the disappearance of the band at λ = 550 nm for the starting cluster and the appearance of a new band at λ = 880 nm, which disappears in the second step (see Figure 2). The data can be satisfactorily fitted to a model with two kinetic steps to provide values for k₁obs and k₂obs, and the corresponding calculated spectra for different species. The near-IR band is typical for products of the reaction of this kind of cluster and alkynes with the formation of two C=S bonds; thus, kinetic experiments provide information about the process of alkyne activation. Reproducible kinetic data were obtained for both steps, in contrast with previous observations for the reaction of btd with [Mo₃(S)(μ-S)(H₂O)]⁴⁺, for which precipitation hindered kinetic analysis of the second step. Nevertheless, in this case, there are also slower absorbance changes that span over thousands of minutes that could not be analyzed because of irreproducibility. With regard to the rate constants, the k₁obs values show a linear dependence on the alkyne concentration (Figure 3), and fitting to Equation (1) leads to the second-order constant k₂ = (8.1 ± 0.1) × 10⁻¹⁰ M⁻¹ s⁻¹. In contrast, the disappearance of the band at λ = 880 nm is independent of the concentration of alkyne, with k₂ = (1.9 ± 0.4) × 10⁻⁸ s⁻¹.

\[ k_{\text{obs}} = k_1 [\text{alkyne}] \]  

Figure 3. Plot of the dependence of [alkyne] on the rate constants for the reaction of [I]⁺ with btd (triangles) and adc (circles) in acetonitrile. The solid line corresponds to the fit of data with Equation (1). The data for the reaction with btd have been multiplied by 100.

Figure 1. Different structural types reported in the literature for alkyne addition to M₃Q₄ clusters.
The reaction of $[1]^+$ with an excess of adc shows faster spectral changes that make the use of stopped-flow necessary to monitor the appearance of a band at $\lambda = 870$ nm, although the disappearance of this band is much slower and must be monitored with a conventional spectrophotometer. Detailed analysis of the stopped-flow data indicates that a kinetic model with two consecutive steps is required for a satisfactory fit; thus revealing the sequential formation of two compounds with a band in the near-IR. The spectra calculated for different species (Figure 4) indicate that the first step converts the starting compound into an intermediate with a band at $\lambda = 870$ nm, which is converted into a different product in the second step; the latter process is signaled by a shift in the band to $\lambda = 855$ nm. Although such a shift was not observed for the reaction of adc with $[\text{Mo}_3\text{S}_4(\mu_3-S)(\mu_5-S)(\text{H}_2\text{O})]^{4+}$,[7] it has been previously reported for related systems.[6b] On the other hand, a satisfactory fit of the spectral changes recorded for the disappearance of the near-IR band also require a model with two steps (rate constants $k_{\text{obs}}$ and $k_{\text{obs}}$), and the calculated spectra (see the Supporting Information) indicate the formation of an intermediate with a band located at $\lambda \approx 595$ nm. The values of $k_{\text{obs}}$ show a linear dependence on the alkyne concentration, and fitting with Equation (1) leads to $k_1 = 7.8 \pm 0.2 \text{ M}^{-1} \text{s}^{-1}$ (Figure 3). On the other hand, the values of $k_{\text{obs}}$ and $k_{\text{obs}}$ can be fitted to Equation (2) with $a_1 = (4.7 \pm 0.6) \times 10^{-3} \text{ s}^{-1}$ and $b_1 = (0.19 \pm 0.02) \text{ M}^{-1} \text{s}^{-1}$ for the second step, and $a_2 = (2.4 \pm 0.2) \times 10^{-4} \text{ s}^{-1}$ and $b_2 = (3.4 \pm 0.2) \times 10^{-3} \text{ M}^{-1} \text{s}^{-1}$ for the third step (see plots in the Supporting Information). Finally, the values for the fourth kinetic step are independent of the concentration of the alkyne with $k_4 = (1.7 \pm 0.3) \times 10^{-4} \text{ s}^{-1}$.

$$k_{\text{obs}} = a + b[1^+]$$

(2)

Notably, the amplitudes of the spectral changes obtained for the reaction with both alkynes are independent of the concentration of added alkyne, which indicates that the reactions occur under conditions of irreversibility. The values of $k_1$ for the first step differ by three orders of magnitude for both alkynes; the reaction with adc is much faster. This difference between alkynes is more pronounced than that previously found for an aqueous solution of $[\text{Mo}_3\text{S}_4(\text{H}_2\text{O})]^{4+}$, for which the ratio of rate constants was in the range of 20–60, depending on the pH and supporting electrolyte (Hpts (p-toluenesulfonic acid) or HCl). The initial step always leads to the formation of a species with a band in the near-IR region, which is typical of clusters containing two C=S bonds (type I in Figure 1), compatible with the previously proposed mechanism in which the reaction occurs in a single step with a transition state in which both C=S bonds are formed as the C–C triple bond is weakened.[7] However, the current results for the reaction of $[1]^+$ with adc reveal a more complex situation because now there is the formation of two compounds with a near-IR band, and the first-order dependence with respect to adc for the two first steps suggests that both compounds correspond to the sequential addition of two alkyne molecules. Nevertheless, the third step also shows first-order dependence on the alkyne concentration and it does not lead to the formation of any band between $\lambda = 800$ and 900 nm. Therefore, kinetic data indicate that the entire process requires the participation of three alkyne molecules. However, because the effect is only observed for acidic adc and not for btd, and the formation of adducts with three alkynes has not been reported for this kind of cluster, a tentative explanation is that one of the steps in the reaction with adc actually corresponds to a process in which the alkyne participates as an acid by providing a proton that leads to the formation of type II or III species. The occurrence of this kind of attack has been previously reported by Shibahara et al.,[5, 8] although for reactions in aqueous solution, in which the proton is provided by the solvent. In the present case, the solvent is aprotic and, although the available pK_a data for different acids in acetonitrile indicate that adc should behave as a weak acid,[10] the only source of the protons required for the formation of type II or III adducts is the alkyne. In agreement with this interpretation, the kinetics of the reaction with btd are simpler because the protons necessary for the formation of type II or III adducts cannot be provided and so the initial formation of a type I adduct continues with a process similar to that observed in the fourth step of the reaction with adc. Because the formation of a type III adduct requires two $\mu_2$-S bridges, and the product formed in the first step only has one, the adc molecule acting as acid should be the one participating in the second kinetic step, which should lead to an intermediate with a type II structure that would convert into a type III structure in the third step. However, against this interpretation is the fact that in that case the spectrum of the intermediate formed in the second step should lack the band experimentally observed in the near-infrared region. It is shown below that ESI-MS and additional kinetic experiments favor an alternative explanation that involves substitution of the ancillary py ligand.

NMR spectroscopy and ESI-MS studies on the reaction of $[1]^+$ with alkynes

To obtain additional information on the products formed, ESI-MS and NMR spectra were used to monitor the reactions. Both...
techniques have previously been shown to provide very useful information on other reactions of these clusters.\textsuperscript{19} The ESI mass spectrum of green solutions of \([1]^+\) in CH\(_3\)CN shows a prominent signal centered at \(m/z\) 950 that can be attributed to the \([1]^+\) cation on the basis of the \(m/z\) value and its characteristic isotope pattern (see Figure S6 in the Supporting Information). A weaker signal appears at \(m/z\) 873 and it can be assigned to the product of the dissociation of one py ligand \([1–py]^–\). Upon reaction of \([1]^+\) with btd, a weak signal at \(m/z\) 1036, which can be assigned to the \([1+\text{C}_2\text{O}_4\text{H}_6]^+\) adduct, is observed in the ESI mass spectrum; this formally results from the addition of a single alkyne molecule. The weakness of the signal can be rationalized by invoking the kinetic results because the existence of biphasic kinetics with close values of rate constants for both steps hinders the accumulation of the intermediate formed in the first step. Unfortunately, attempts to increase the intensity of this signal by adding larger amounts of alkyne lead to overall reduced ion abundances for all Mo,\(\text{S}_2\)-based species due to strong ion suppression effects. The absence of other signals assignable to the cluster suggests that the second kinetic step corresponds to decomposition of the addition product containing one alkyne.

The kinetic results indicate that the treatment of \([1]^+\) with adc leads to the rapid formation of the addition product containing one alkyne molecule, and this reaction is manifested in the ESI mass spectrum by the appearance of signals assigned to the \([1+\text{C}_2\text{O}_4\text{H}_2]^+\) cation (\(m/z\) 1066) and its corresponding homologue formed by the release of py, namely, \([1–py+\text{C}_2\text{O}_4\text{H}_2]^+\) (\(m/z\) 987; see Figure 5). Simulations of the isotopic distribution of these signals perfectly match with those observed experimentally. In addition, there are signals centered at \(m/z\) 1026 and 1099 that can be assigned to addition products, \([1–py+2\text{C}_2\text{O}_4\text{H}_2]^+\) and \([1–2py+2\text{C}_2\text{O}_4\text{H}_2]^+\), containing two alkyne molecules and two or one py ligands, respectively. It is noteworthy that, whereas the intensity of the signal for \([1–py]^–\) is weaker than that corresponding to the starting \([1]^+\) (\(I_{[1]}\) to \(I_{[1–py]}\) ratio = 14.3, in which \(I\) stands for the ion intensity of each species), the signal for \([1–py+\text{C}_2\text{O}_4\text{H}_2]^+\) is stronger than that of \([1+\text{C}_2\text{O}_4\text{H}_2]^+\) (\(I_{[1+\text{C}_2\text{O}_4\text{H}_2]}\) to \(I_{[1–py+\text{C}_2\text{O}_4\text{H}_2]}\) ratio = 0.4). This is even more pronounced for the adduct with the two alkyne molecules in which the \([1–2py+2\text{C}_2\text{O}_4\text{H}_2]^+\) (\(m/z\) 1026) species is dominant and the putative \([1+2\text{C}_2\text{O}_4\text{H}_2]^+\) compound is not observed by ESI-MS. This suggests that the py ligands are more prone to dissociation in the gas phase (under identical ESI-MS conditions) as the number of alkyne molecules increases. This experimental evidence is attributed to the more congested chemical environment imparted by the newly formed dithiolene functional group. Remarkably, this gas-phase observation parallels the solution behavior for these systems, as evidenced by the appearance of new signals corresponding to py substitution by MeCN after allowing the reaction mixtures to stand for 30 min.

\(^{1}H\) NMR spectroscopy experiments were carried out on the reaction of \([1]^+\) with btd. No information could be derived for the reaction with adc because a carbon spectrum of suitable quality could not be recorded at the cluster concentrations achievable, and the only alkyne signal in the proton spectrum was that for the acidic groups, which always appeared as broad signals. However, the proton signals of the methylene groups of btd provide valuable information and confirm the formation of the addition product. Thus, the \(^{1}H\) NMR spectrum of a mixture of \([1]^+\) and btd (\([1]^+\) = \(9\times10^{-3}\) \text{m}, [btd] = \(9\times10^{-3}\) \text{m}, solvent = CD\(_3\)CN, 25.0 °C) aged for 90 min shows, in addition to the py and acac protons in the cluster,\textsuperscript{25} two pairs of doublet signals at \(\delta = 3.88\) and 4.24 ppm (\(\delta_{(H,H)} = 13.5\) Hz), and \(\delta = 3.99\) and 4.35 ppm (\(\delta_{(H,H)} = 13.2\) Hz; see Figure 6).

![Figure 5. ESI-MS spectrum of \([1]^+\) at \(U_s = 5\) V in acetonitrile in the presence of adc.](image)

This pattern corresponds to inequivalent diastereotopic methylene groups and the coupling constants match well with geminal coupling. These split signals contrast with the singlet observed at \(\delta = 4.17\) ppm for the methylene groups in the free alkyne. Because of the coexistence of several species in solution, the NMR spectra were very complex, but a DOSY spectrum confirmed that these protons corresponded to an adduct with the cluster (see the Supporting Information). The calibrated diffusion coefficients (\(D\)) obtained were \(25\times10^{-10}\) \text{m}^2\text{s}^{-1} for

![Figure 6. g-COSY NMR spectrum of \([1]^+\) with btd after 90 min in CD\(_3\)CN.](image)
the free alkyne, $11 \times 10^{-10} \text{m}^2\text{s}^{-1}$ for $[1]^+$, and $8.3 \times 10^{-10} \text{m}^2\text{s}^{-1}$ for the addition product.

**Kinetic studies in the presence of additional py**

Motivated primarily by ESI-MS experiments revealing that py dissociation may take place both in $[1]^+$ and, to a larger extent, in the alkyne addition products, some kinetic measurements on alkyne addition were carried out in the presence of excess py. Unfortunately, the reaction of $[1]^+$ with adc could not be studied under these conditions because precipitation of a white solid, presumably a pyridinium salt, made all attempts to measure the kinetics unsuccessful. However, satisfactory kinetic results could be obtained for the reaction with btd. In these experiments, the alkyne concentration was kept constant (0.05 m) and the py concentration changed in the range 0.01–0.10 m. Under those conditions, the reaction shows characteristic spectral changes for the addition reaction. Thus, the spectrum of $[1]^+$ in acetonitrile is initially unaffected by the addition of excess py (up to 0.10 m), but there are spectral changes with time that lead to the disappearance of the band at $\lambda = 550$ nm and the appearance of the type I adduct band at $\lambda = 880$ nm. As occurs in the absence of py, kinetic traces at $\lambda = 880$ nm clearly indicated biphasic kinetics (Figure 7) and so the spectral changes were fitted with two exponentials. The observed rate constant for the first step was independent of the py concentration with a value of $k_{1obs} = (4.3 \pm 1.1) \times 10^{-4} \text{s}^{-1}$, which led to a second-order constant of $k_1 = (8.6 \pm 0.5) \times 10^{-3} \text{M}^{-1}\text{s}^{-1}$ when the alkyne concentration used (0.05 m) was considered. This value is in good agreement with that obtained in the absence of excess py, $k_1 = (8.1 \pm 0.1) \times 10^{-3} \text{M}^{-1}\text{s}^{-1}$; thus showing that the addition of py does not cause any changes in the kinetics of formation of the addition product. In contrast, the disappearance of the band occurs with slower kinetics in the presence of additional py and the values of $k_{2obs}$ show an inverse dependence on the py concentration (Figure 8). The fit of the experimental data to Equation (3) leads to $a = (4.9 \pm 0.2) \times 10^{-7} \text{M}^{-1}\text{s}^{-1}$. This finding is in agreement with a process involving the initial dissociation of py [Eq. (4)] followed by rate-determining decomposition of the intermediate formed in the previous step [Eq. (5)]. The rate law for this mechanism is shown in Equation (6), which can be simplified to give Equation (3) with $a = K_2aK_{2b}$ if $[py] \gg K_2a$. This kind of process would also provide an explanation for the first-order dependence on the alkyne observed for the second step in the reaction with adc, in which Equation (5) could consist of attack by a second molecule of alkyne to the intermediate formed in Equation (4); thus causing substitution of py by an $\eta^2$-alkyne and formation of a type I adduct that is different from the one initially formed, with the consequent shift of the near-IR band (Figure 4).

$$k_{2obs} = \frac{a}{[py]}$$

$$[\text{Mo}_3\text{S}_4(\text{acac})_3(\text{py})_3 + \text{btd}]^+ \rightarrow [\text{Mo}_3\text{S}_4(\text{acac})_3(\text{py})_2 + \text{btd}]^+ + \text{py}; K_{2a}$$

$$[\text{Mo}_3\text{S}_4(\text{acac})_3(\text{py})_2 + \text{btd}]^+ \rightarrow [\text{Mo}_3\text{S}_4(\text{acac})_3(\text{L})(\text{py})_2 + \text{btd}]^+; k_{2b}$$

$$k_{2obs} = \frac{K_{2a}K_{2b}}{K_{2a} + [py]}$$

**DFT studies on the formation of type I products**

The experimental results shown above indicate that the reaction between $[1]^+$ and the alkynes adc and btd lead to the formation of type I cycloaddition products in the first common kinetic step. In contrast, the subsequent reactivity of the species thus formed remains less clear and involves dissociation of the ancillary py ligand and the eventual degradation of the cluster cores. Given the importance of cycloaddition reactions in chemistry,[15] in this section we present the results of a thorough computational study on the $[3 + 2]$ cycloaddition reaction that leads to the formation of type I products, followed by a detailed analysis of the factors that control the differences in reactivity between both alkynes. This has been carried out by using the ASM[22] and FMO approaches, which have already...
been employed successfully for the study of cycloaddition reactions between organic substrates.\[16\]

The cycloaddition reaction between [1] and the alkynes adc and btd was initially studied by using the methodology previously employed for a similar reaction between [Mo3S4(H2O)9]4+ and btd.\[7\] In agreement with the kinetic results, the calculations indicate that the formation of type I products from [1] occurs in a single step via concerted transition states similar to that found for the reaction between the aqua cluster and btd, and in which the formation of two C–S bonds take place simultaneously. Nevertheless, an important difference arose from changes to the Mo3S4 cluster core ligands, whereas the aqua cluster formed stable hydrogen-bonded adducts with btd prior to cycloaddition, no outer-sphere adducts were found with [1]+. Thus, Figure 9 includes the structures of the concerted transition states and corresponding type I cycloaddition products with both alkynes; their energies relative to the separated reactants are included in Table 1. Importantly, intermediate structures with one C–S bond, which would be indicative of an alternative stepwise mechanism, were only located in the triplet potential energy surface (PES) and showed relative energies much higher (> 40 kcal mol\(^{-1}\)) than those on the singlet PES. A comparison of the selected bond lengths and angles of TS1_adc and TS1_btd in Figure 9 reveals only small differences associated with the nature of the alkyn. In both cases the structures are close to the C\(^{3v}\) symmetry point group (d(S1–C2)\(≈\)d(S2–C2) and d(Mo1–S1)\(≈\)d(Mo1–S2)) and show the C=C bond of the alkyn approaching the cluster through the plane formed by the S1–Mo1–S2 moiety. The preferential interaction between these moieties is also characterized by shortening of Mo1–S1 and Mo1–S2 distances in the transition states (2.31 Å in both cases, cf. 2.33 Å in [Mo3S4(acac)3(py)3]4+) and lengthening of the Mo2–S2 and

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<th>Reaction</th>
<th>(\Delta G^\ddagger)</th>
<th>(\Delta G)</th>
<th>(\Delta E)</th>
<th>(\Delta E_{\text{strain alkyne}})</th>
<th>(\Delta E_{\text{strain cluster}})</th>
<th>(\Delta E_{\text{strain total}})</th>
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<tr>
<td>([1]^+ + \text{btd})</td>
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<td>6.0</td>
<td>25.0</td>
<td>9.6</td>
<td>23.0</td>
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Figure 9. Computed structures for the transition states and type I products of the reaction between [1] and the alkynes adc and btd. See the Supporting Information for a color version of this figure.
Mo3–S1 distances by about 0.05 Å. Similar trends are observed when comparing metal–metal interactions; the Mo1–Mo2 and Mo1–Mo3 distances are about 0.06 Å longer than that of Mo2–Mo3. It is noteworthy that, although this cluster features three symmetry-equivalent Mo(μ-S)2 moieties capable of undergoing a [3+2] cycloaddition, none remain in the type I products, and therefore, no subsequent [3+2] cycloaddition reactions are possible.

From an energetic point of view, a comparison of the activation free energies for the reaction with adc and btd, 13.3 and 21.9 kcal mol⁻¹, respectively (see Table 1), qualitatively agrees with the much faster reaction observed for the former in the kinetic experiments. In addition, the results also indicate that the reaction with adc is thermodynamically more favored than that with btd. The former is exergonic by 0.7 kcal mol⁻¹, whereas surprisingly the latter is computed to be endergonic by 6.0 kcal mol⁻¹. Despite the fact that these ΔG values do not necessarily disagree with the observation of the cycloaddition products, which could be explained by taking into account that both the excess of alkyne used in the experiments and the existence of subsequent exergonic transformations will drive the processes towards product formation, it clearly poses some doubts on the accuracy of the employed computational method. Recent studies aiming to compute accurate thermodynamic data for cycloaddition reactions between organic substrates have shown that, although the B3LYP functional usually gives good results, in some cases, it can generate large errors. These reasons prompted us to carry out a number of functional test calculations, the results of which are included in the Supporting Information. In brief, these tests showed that, although the absolute activation and reaction free energies were largely dependent on the selected functional, the relative differences for the reaction with the two alkynes were virtually constant, with ΔG°(btd) – ΔG°(adc) ≈ 8 kcal mol⁻¹ and ΔG°(btd) – ΔG°(adc) ≈ 6 kcal mol⁻¹.

Activation strain analysis and FMO results

Despite agreement between experimental and computational results for the formation of prod1_adc and prod1_btd, these also show that the factors that control such differences cannot be clearly ascribed to geometrical differences in the corresponding transition-state structures. Thus, to gain more insight into the origins of such differences, they have been further analyzed by using the ASM. In brief, here the total electronic energy (ΔE(x)) along a selected reaction coordinate, x, that connects reactants and products is dissected into strain energy (ΔEstrain(x)), which represent the energy required to deform the reactants from their ground-state structures into those at each point along the reaction coordinate, and the interaction energy (ΔEint(x)) between those deformed fragments.

The activation strain diagrams obtained for the reaction between [Mo3S4(acac)3(py)]⁺ and the alkynes adc and btd by using the two carbon–sulfur distances as the reaction coordinate (x = d(S1–C1) = d(S2–C2)) are included in Figure 10, whereas the values of the strain (ΔEstrain) and interaction (ΔEint) energies computed at the transition states are included in Table 1. This reaction coordinate undergoes a well-defined change in the course of the reaction, and it was computed from 4.0 (close to noninteracting reactants) to 1.9 Å (near the cycloaddition products). In all cases, in the early stages of the reaction (between 4.0 and ca. 2.8 Å), the total energy (ΔE(x)) increases monotonically as the reactants approach each other, indicating the absence of cluster–alkyne adducts. This gradual destabilization results from the addition of two unfavorable terms: the energy required to deform the reactants and the unfavorable interaction between those deformed species. As expected from the already-bent geometry of the Mo(μ-S)2 fragment of [Mo3S4(acac)3(py)]⁺ (S-Mo-S angle of 97.1°), the energy required to deform the cluster fragment, ΔEstrain(cluster), throughout the whole process is much smaller than that for the alkyne, ΔEstrain(alkyne), and a comparison of the plots for ΔEstrain(cluster) in its reaction with both alkynes indicates that this term is practically independent. This is evidenced by the similarity of the ΔEstrain(cluster) values at the transition-state geometries (ca. 3 kcal mol⁻¹, see Table 1). The majority of the
strain energy arises from deformation of the alkynes, which have to undergo significant R–C≡C angle changes (R = COOH or CH₃OH) to reach product-like structures. The ΔE°strain(alkyne) values at the transition states are 20.9 and 23.0 kcal mol⁻¹ for adc and btd, respectively. Despite this difference being in agreement with the lower reaction barrier for adc, to fully understand the pronounced changes in the computed barriers, it is also necessary to pay attention to the evolution of the interaction energies, ΔE°int, along the reaction coordinate, x. In both cases, this term is negligible at the beginning of the reaction and progressively increases as the reactants get closer due to steric (Pauli) repulsion. At distances between 2.5 and 2.8 Å ΔE°int reaches its maximum, and at this point significant differences are already observed between the plots for adc and btd; ΔE°int(max(btd)) is about 5 kcal mol⁻¹ larger than ΔE°int(max(adc)). Such a difference remains approximately constant at shorter distances; the ΔE°int values for both reaction decreases in an almost linear manner until the cycloaddition products are reached. Interestingly, for the reaction with adc, the interaction energy, ΔE°int, becomes negative at a distance about 0.1 Å shorter than that for btd (values of 2.5 and 2.4 Å, respectively), and this seems to be the main factor that contributes to the difference in the average C–S bond lengths found between TS$_1$-adc and TS$_1$-btd. Similar behavior was previously reported for ethylene addition to osmium tetroxide.\[^{[11b]}\] The computed ΔE°int values at the transition-state geometries are −6.6 and −1.1 kcal mol⁻¹, respectively (Table 1); thus indicating that the cluster–alkyne interaction in TS$_1$-adc is 5.5 kcal mol⁻¹ more stabilizing than that for TS$_1$-btd.

Overall, analysis of the transition-state structures shows that, despite the geometrical similarities between TS$_1$-btd and TS$_1$-adc, both strain and (mostly) interaction factors contribute to the lower activation barrier computed for the reaction with adc, that is, the energetic cost to deform the cycloaddition partners is 2.3 kcal mol⁻¹ smaller with adc, and at the same time they interact 5.5 kcal mol⁻¹ more strongly. Interestingly, these results differ, for instance, from those of Fernández et al. on the [3 + 2] cycloaddition reactions between Group 14 heteroallenones and acetylene.\[^{[11a]}\] They found that the energy to deform the reactants to the transition-state geometry represented the major factor in controlling the barrier heights; a difference probably associated with the already-bent geometry of the fragment of [1]⁺ that interacted with the alkyne in the present case.

To better understand the differences in ΔE°int, the energies of relevant FMOs of the ground-state species of [1]⁺, adc, and btd, as well as the transition states TS$_{adc}$ and TS$_{btd}$, were computed at the B3LYP/BS2/PCM/B3LYP/BS1/PCM level. In Figure 11, the left and right columns of each diagram show the energies of the HOMO and LUMO of [1]⁺ and the alkyne in their ground-state geometries, whereas the central column shows those deformed into the transition-state geometry. Plots of these orbitals are included in Figure S7 in the Supporting Information. As a general feature of cycloaddition reactions, the deformation of the two partners into their transition-state geometries leads to an increase in the energy of their respective HOMOs and a decrease in that of their LUMOs. Thus, the HOMO–LUMO gaps of the two interacting species in the transition states shrink relative to those in the ground-state geometries, and this facilitates the interaction between their molecular orbitals. In agreement with the negligible differences in the strain energy values discussed above for cluster [1]⁺ (ΔE°strain(cluster), Table 1), the results in the central column of both diagrams in Figure 11 indicate that the HOMO and LUMO energies of [1]⁺ at the structures of the transition states TS$_{adc}$ and TS$_{btd}$ are very similar. Conversely, significant differences are observed between the two alkynes studied; the HOMOs and LUMOs of adc are about 1 and 2 eV more stable, respectively, than those of btd in both their ground and corresponding transition-state geometries.

Analysis of these orbitals (Figure S7 in the Supporting Information) shows that the extra stabilization is due to the larger extent of delocalization over the substituents in adc; an effect associated with the greater electron-withdrawing character of the –COOH group versus that of –CH$_3$OH. As a result, the smallest HOMO–LUMO gap between [1]⁺ and alkyne is 2.5 eV for TS$_{adc}$ (on going from the HOMO of [1]⁺ to the LUMO of adc) and 4.1 eV for TS$_{btd}$ (on going from the HOMO of btd to the LUMO of [1]⁺). It is worth noting that the effect is similar to that observed in Diels–Alder reactions, in which the presence of electron-withdrawing groups in the dienophile lowers the energy of its LUMO and is conducive to normal electron demand reactions, whereas electron-donating groups have the opposite effect and favor inverse electron demand conditions. Qualitatively, these results agree with the trend observed for the interaction energies, ΔE°int, in TS$_{adc}$ and TS$_{btd}$, which can then be explained in terms of more favorable FMO interactions in the former due to extra orbital stabilization generated by the –COOH substituents of adc. Importantly, a similar explanation could be used to rationalize analogous behavior observed for the reaction of these alkyne with the cluster [Mo$_5$(µ$_3$-S)(µ$_3$-S)$_3$(H$_2$O)$_9$]$^{11}$ in water.\[^{[11]}\] Nevertheless, it is important to highlight that in such cases the cycloaddition reactions are
preceeded by the formation of hydrogen-bonded adducts between the substituents of the alkynes and water molecules co-ordinated to the cluster, and their different stabilities will also be a factor to consider when comparing their reactivity in water.

Conclusion
We reported further experimental and computational evidence for alkyne activation in the presence of M₃S₄ clusters. Alkynes, such as adc and btd, initially react with [1]⁺ to form cycloaddition products with a type I structure through a concerted mechanism in which the alkyne approaches the cluster at the proximities of two μ-S units in such a way that the carbon=carbon bond is weakened at the same time as both C–S bonds are formed. However, the products initially formed evolve in subsequent steps to form different compounds, resulting from substitution of ancillary ligands (py in the present case) or reorganization to give compounds with type II or III structures. The initial step leading to the formation of two C–S bonds can be considered as a [3 + 2] cycloaddition between the alkyne and a Mo(μ-S)₂ moiety of the cluster, and it occurs with a rate that is strongly dependent on the nature of the alkyne, despite the fact that the structures calculated for the transition states are similar. Application of the ASM[12] to this step reveals that the differences in the interaction energy between the two reacting species at the transition-state geometries represent the major contribution to the change in the activation barrier for the reactions with adc and btd, and further FMO calculations allow the rationalization of such differences based on the effect of the alkyne substituents. The reaction is faster for adc because the FMOs of the two cycloaddition partners at the transition-state geometries are closer in energy, and this allows for a stronger interaction.

Experimental Section
General
The [1]PF₆ cluster was prepared by following a literature procedure.[19] The UV/Vis spectrum of these solutions had bands at λ = 348 and 550 nm with molar absorptivities of ε = 4230 and 572 m⁻¹ cm⁻¹, respectively.

Kinetic experiments
The kinetic experiments were carried out with an Applied Photophysics SX-17MV stopped-flow spectrometer provided with a PDA1 photodiode array detector, and with a Cary 50 Bio UV/Vis spectrophotometer. All experiments were carried out at (25.0 ± 0.1) °C by mixing a solution of [1]PF₆ with another solution containing an excess of the alkyne (btd or adc) under a nitrogen atmosphere. The alkyne concentration range was 0.01–0.05 mM in the stopped-flow experiments and 0.02–0.15 mM in the conventional spectrophotometer experiments; this was enough to ensure pseudo-first-order conditions in all experiments. The solutions of the complexes were prepared at concentrations of about 1.5–3 x 10⁻⁶ M in acetonitrile and preliminary experiments at two different complex concentrations were carried out to confirm the first-order dependence of the observed rate constants on the complex concentration. In all cases, the spectral changes were measured over a wide wavelength range and analyzed with the program SpectroFit.[19] Satisfactory fits required the use of kinetic models with more than one consecutive kinetic steps, as indicated for each reaction in the Results and Discussion section.

Physical measurements
ESI mass spectra were recorded with a Q-TOF I (quadrupole-hexapole-time-of-flight) mass spectrometer with an orthogonal Z-spray electrospray interface (Micromass, Manchester, UK) operating at a resolution of approximately 3000 (full-width at half-maximum (FWHM)). The instrument was calibrated by using a solution of NaI in isopropanol/water from m/z 100 to 1900. Sample solutions (1 x 10⁻⁵ M) in acetonitrile were introduced through a fused-silica capillary to the ESI source by means of a syringe pump at a flow rate of 10 μL.min⁻¹. The cone voltage was set at 5 V, unless otherwise stated, to control the extent of fragmentation. Nitrogen was employed as the drying and nebulizing gas. Isotope experimental patterns were compared with theoretical patterns obtained by using the MassLynx 4.0 program. NMR spectra of a mixture of [1]⁺ and btd aged for 90 min were recorded on Agilent 500 MHz or 600 MHz instruments at 25.0 °C. All samples were prepared by using CD₃CN as the solvent and were referenced to the residual solvent signal (referenced to tetramethyilsilane (TMS)). A stoichiometric amount of alkyne was added to the cluster solution ([1]⁺ = 9 x 10⁻⁵ M). To characterize the adduction product (type I), a combination of standard high-resolution NMR spectroscopy experiments, such as 1D ¹H NMR, 2D g-COSY, and high-resolution 2D-DOSY were recorded.

DFT calculations
The DFT calculations were performed by using Gaussian 09.[18] Geometry optimizations were carried out at the B3LYP/BS1 level of theory[16] without any symmetry constraints (C₁ point group), and included the effects of the solvent (CH₃CN, ε = 35.688) self-consistently through the polarizable continuum model (PCM) method.[20] The basis set system BS1 employed the SDO relativistic ECP and associated basis set for Mo and S atoms,[21] with added polarization functions for the latter (ζ = 0.503),[22] and the 6-31G** basis set for C, O, and H atoms.[23] The computed geometry of [Mo₃S₄(acac)₆(py)₃]⁺ was in good agreement with its X-ray structure at this level of theory (see Table S1 in the Supporting Information). All stationary points were characterized by analytical frequency calculations as either minima (all positive eigenvalues) or transition states (one negative eigenvalue), and intrinsic reaction coordinate (IRC) calculations and subsequent geometry optimizations were used to confirm the minima linked by each transition state. To obtain improved energetic values, all energies were recomputed by single-point calculations with a larger basis set system, BS2, which also included solvent effects (PCM).[20] BS2 differed from BS1 in the employment of 6-311 + G(2d,2p) for C, O, and H atoms. Thus, unless stated otherwise, energies shown herein refer to Gibbs free energies in solution, and were obtained by adding zero-point and thermal effects at 298.15 K, as well as D3(BJ) dispersion effects,[24] to the electronic energies computed by single-point calculations on the previously optimized structures with the basis set system BS2 and also by including solvent effects (PCM).[20] The ASM[12] was employed to obtain more insight into the different contributions to the PES associated with the formation of different type I reaction products. This model constituted a systematic extension of the fragment approach from equilibrium structures to
transition states and nonstationary points along a reaction coordinate. At each computed point along a selected reaction coordinate, \( x \), the energy of each fragment was compared with that of its original structure (reactant), and this allowed its disposition into two main components \([\text{Eq. } (7)]\): the strain energy \( \Delta E_{\text{strain}} \), which involved the geometric and electronic changes to deform reactants into their current structures, and the interaction energy \( \Delta E_{\text{int}} \) between those deformed fragments. Importantly, it was the interplay between these two terms that determined the energy of each point along the reaction coordinate, \( x \).

\[
\Delta E(x) = \Delta E_{\text{strain}}(x) + \Delta E_{\text{int}}(x)
\]

\( (7) \)

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