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A DFT Study of Diels−Alder Reactions of *o*-Quinone Methides and Various Substituted Ethenes: Selectivity and Reaction Mechanism

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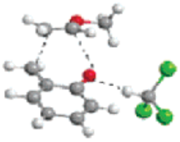

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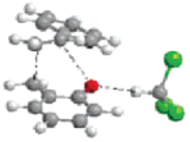

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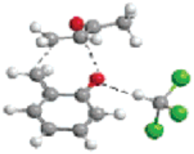

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The Diels−Alder (DA) reactions of various substituted ethenes (methyl vinyl ether (MVE), styrene, and methyl vinyl ketone (MVK)) with *o*-quinone methides (*o*-QM) are studied by means of density functional theory (DFT) at the B3LYP/6-31G(d,p) level. On the basis of analysis for frontier molecular orbital and comparison of the activation energies for different reaction pathways, the ortho attack modes present transition structures more stable than the meta ones. The reactivity, ortho selectivity, and asynchronicity are enhanced with the increase of the electron-releasing character of the substitute on ethene fragment. The discussions for the charge distribution and charge transfer on different transition states indicate that there are different molecular mechanisms for the different substituted ethenes. The calculations show that the effect of solvent decreases the activation energy and increases the asynchronicity. The results also indicate that the hydrogen-bond formation between chloroform and the carbonyl oxygen of the *o*-QM lowers the activation energies and increases the asynchronicity.

Introduction

Quinone methides (QMs) are short-lived reactive species with interesting chemical properties and pronounced biological activity.[1] They can be involved in a large number of chemical and biological process such as biosynthesis of lignin and enzyme inhibition,[2] and in addition, the *o*-QMs have recently been used as covalent β-lactamase, phosphatase, and ribonuclease A inactivators, which indicate that the *o*-QM structures play a key role in the chemistry of several classes of antitumor compounds and antibiotic drugs, including the commercial compounds mitomycin C[3] and anthracycline.[4] These QM antitumor drugs are believed to form covalent linkages with a DNA base through the QM intermediate.[5] DNA cross-linking, which is probably one of the most promising applications of *o*-QMs reactivity, has been obtained as a result of two consecutive alkylating steps, both involving QMs.[6] Such reactivity is mainly due to the

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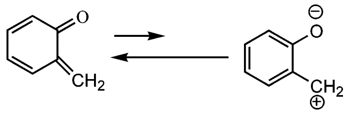

QM electrophilic nature, which is remarkable in the comparison of that of other neutral electrophiles.[7] In fact, QMs are good Michael acceptors, and nucleophiles add readily under mild conditions at the QM exocyclic methylene group to form benzylic adducts. Interactions of the *o*-QMs with simple sulfur-, nitrogen-, and oxygen-centered nucleophiles have been experimentally and computationally investigated.[8] Their reactivity has been also experimentally studied with biologicalnucleophiles such as free amino acid, oligopeptides, and DNA bases.[9]

o-QM (**1**) (Scheme 1) is the prototype of more complex quinone methide-like structures, and they represent simple models which can be used to study the effects of the ortho geometry on the reactivity and selectivity. This structural change makes its reactivity satisfactory, particularly with respect to nucleophiles as the *o*-QM is now quite polarized: simple nucleophilic attack at the methylene carbon returns them to aromatic phenols, gaining an aromatic system in turn. All of these characters are similar to the α,*β*-unsaturated aldehyde/ketone or the other asymmetrical α,*β*-unsaturated compound, in which this kind of heterodiene leads to asymmetry of the charge distribution.[11] Many papers have reported that this kind of compound, as a heterodiene system, reacts with the alkene and found the reaction follows an inverse-electron-demand DA reaction mechanism.[10]

o-QMs act as a similar heterodiene system in inter- and intramolecular DA [2 + 4] cycloadditions with alkenes to give various substituted chromans, a key ring system in some natural products for biosynthesis.[12] There are several elegant syntheses to attain chemical and biological reagents already reported that are based on the DA reactions of *o*-QMs with olefins. Chapman et al.[13] reported a facile, high-yield intramolecular DA reaction of bis-*o*-quinonemethide to synthesize carpanone. Lucidene, an asymmetric reagent, was attained from a double Diels−Alder reaction of a humalene with two molecules of *o*-QM by a biomimetic synthesis. Amouri et al.[14] synthesized the first metal-stabilized *o*-QMs and found that there is good activity in the reaction with alkene. Michihisa et al.[15] found that this kind of compound only reacts with electron-rich olefins, such as phenyl vinyl ether. At the same time, the product is found to be formed in a completely regioselectivity manner; for example, only 2-substituted chroman derivative were produced in the reaction of *o*-QMs with styrene.[16]

The hetero-Diels−Alder (HDA) reaction is a kind of important reaction for carbon−carbon bond formation and widely used to synthesize heterocyclic compounds.[17] It is well-known that the heteroatoms commonly involved in these reactions are N, O, and S, and they can be either in a diene or in a dienophile.[18] Many theoretical[19] and experimental[20] studies have been carried out to rationalize the DA reactions of the great variety of heterodienes and olefins. For example, the reactions of formaldehyde with butadiene proceed by diene HOMO−dienophile LUMO interactions, whereas the reaction of ethylene with acrolein proceeded by diene LUMO−dienophile HOMO (inverse-electron-demand) interaction. It has been believed that the latter inverse-electron-demand is caused by the low energy of LUMO of the hererodiene.[21] The heterodiene and DA reaction mechanism has been the subject of controversy and stimulated debate since its discovery,[22] the general question of whether [4 + 2] cycloadditions are synchronous or asynchronous concerted processes is of considerable current interest.[23,24]

In this paper, the high experimental reactivity of *o*-QM and its unexpected high selectivity in the DA reaction of *o*-QM and substituted ethenes prompted us to further

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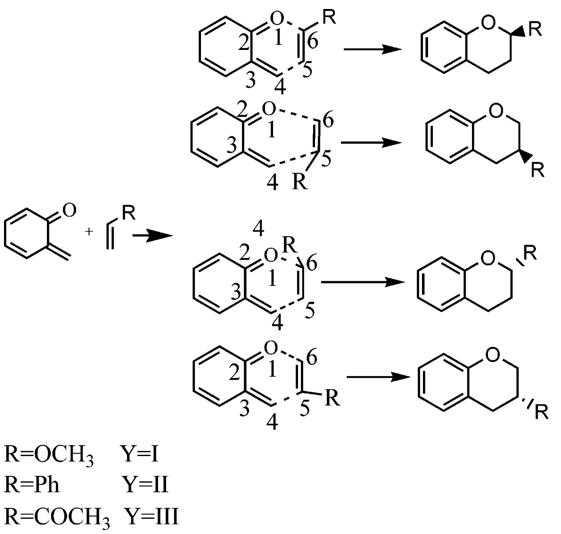
SCHEME 2



investigate ortho/meta selectivity and the role of different reaction pathways (Scheme 2). Thus, we reported a thorough computational DFT investigation on the DA reactions between *o*-QM and various substituted ethenes, i.e., methyl vinyl ether (MVE), styrene, and methyl vinyl ketone (MVK). Our study is aimed at explaining the selectivity and comparing the behaviors of transition structures for different substituted groups on the ethene (electron-releasing and electron-withdraw groups). At the same time, the solvent effect was investigated as well.

Computational Methods

Geometrical optimization, including transition-structure searches, was carried out with the standard 6-31G(d,p) basis set by using the three-parameter hybrid functional developed by Becke in the formulation implemented in the Gaussian 98[25] program (B3LYP), which is slightly different from the original proposed by Becke.[26] The transition states are ascertained by vibrational analysis with only one imaginary frequency mode. In the case of TS, the vibration associated with the imaginary frequency was checked to correspond with a movement in the direction of the reaction coordinate.[27] The values of the relative energies, ΔE, have been calculated on the basis of the total energies of the stationary points. Relative enthalpies, ΔH, and free energies, ΔG, were calculated with the standard statistical thermodynamics at 298.15 K.

The vast majority of chemical reactions are performed in solution, and solvent effects can yield valuable information about the reaction mechanism. The solvent effects have been considered by B3LYP/6-31G(d,p) optimizations of stationary points using a relatively simple self-consistent reaction field (SCRF) method, based on the polarizable continuum model (PCM).[28] The solvents used in the experimental work were toluene and chloroform. Therefore, we have used the dielectric constants 2.4 and 5.5 at 298.15 K for toluene and chloroform, respectively. In order to investigate the effect for different solvents, the other four solvents, cyclohexane, ether, THF, and methanol, were also studied. In this continuum model, the values of ΔE have been calculated.

Result and Discussion

Geometries of the Transition Structures. Four possible reaction channels were investigated for the DA reaction between *o*-QM and various substituted ethenes in the gas phase, depending on the approach of the *o*-QM with respect to the substitutent present on ethylene: exo,ortho; exo,meta; endo,ortho; and endo,meta. Following the convention previously established, we denote the TSs as XR-Y, XM-Y, NR-Y, and NM-Y, respectively. We also note that the corresponding Y = I, II, and III are related to the different groups on the substituted ethene: methyl vinyl ether (MVE), styrene, and ethyl vinyl ketone (MVK), respectively. Selected geometrical parameters of the calculated TSs are shown in Figure 1 and Table 1S (Supporting Information).

An analysis of the geometrical parameters indicates that the XR-I, NR-I, XR-II, and NR-II cycloadditions take place along a highly asynchronous transition structure in which the shorter of the forming bonds is the one between C4 and C5 atoms. The extent of the synchronicity can be measured by means of the difference between the distances of the bonds that are being formed in the reactions, i.e., Δd = (O1−C6)−(C4−C5) for all of the transition states (TS) (see Table 1). For the reaction of *o*-QM with MVE and styrene, the Δd values of *o*-TSs are all larger than 0.48 Å in the TSs, which indicates that the *o*-TSs are calculated to proceed through highly asynchronous pathways. However, the Δd values of *m*-TSs are less than 0.06 Å, which indicates that these TSs proceeded through little asynchronous process. The Δd values of *o*-TSs for the reaction of *o*-QM with MVE are larger than those of the reaction of *o*-QM with the styrene, which correspond to the electron-releasing ability of the electron-releasing group substituted on the ethene. Thus, we can conclude that the stronger electron-releasing ability of the substituting group on ethene, the Δd values of *o*-TSs are larger, and the TSs are more asynchronous.

Activation Energy and Selectivity. The calculated activation energies for different TSs of the DA reaction of MVE, styrene, and MVK with *o*-QM are gathered in Table 1, together with the activation enthalpies and free energies calculated from the thermodynamic properties at 298.15 K.

The regioselectivity in a polar DA reaction has been explained using the local electrophility index in a recent report.[29] For the reaction of the *o*-QM with styrene, the

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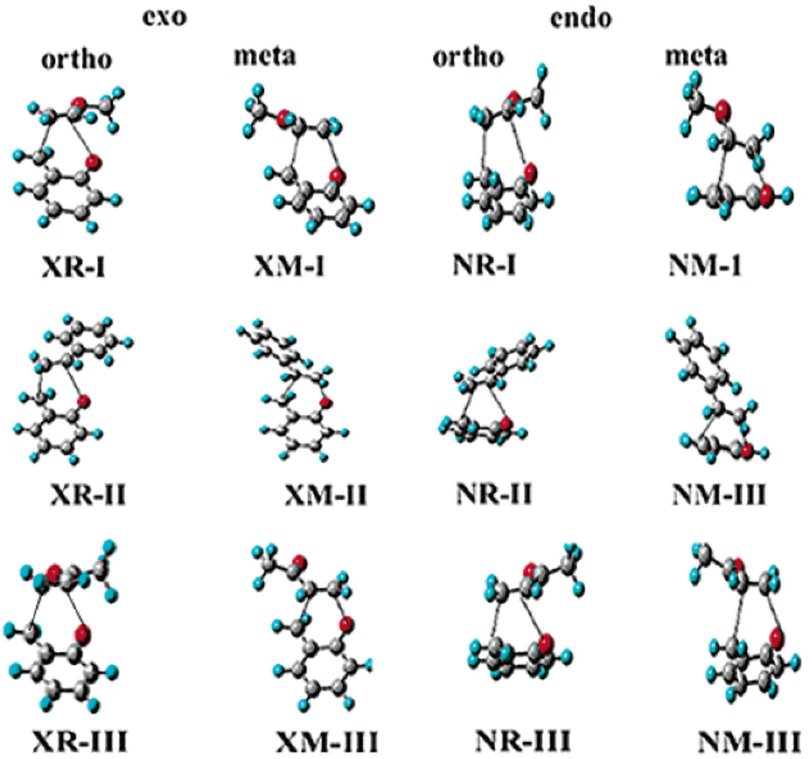

FIGURE 1. Transition structures corresponding to the gas reactions between *o*-QM and methyl vinyl ether R1, styrene R2, methyl vinyl ketone R3 substituted ethenes.

TABLE 1. Activation Energies, Enthalpies, and Free Energies (in kcal mol^{-1}) of the Reaction between *o*-QM and Various Substituted Ethenes (MVE, Styrene, and MVK)

TS	Δd (Å)	$\Delta E^{\ddagger}_{0}$	$\Delta E^{\ddagger}_{298}$	$\Delta H^{\ddagger}_{298}$
XR-I	0.49	6.53	6.36	5.77
XM-I	0.04	20.64	20.32	19.72
NR-I	0.59	6.84	6.61	6.00
NM-I	0.00	19.30	18.92	18.31
XR-II	0.48	10.53	10.61	10.04
XM-II	0.06	16.00	15.9	15.30
NR-II	0.51	10.37	10.41	9.82
NM-II	0.06	15.40	15.28	14.68
XR-III	0.31	8.89	8.78	8.22
XM-III	0.17	12.73	12.63	12.07
NR-III	0.07	8.48	8.39	7.83
NM-III	0.23	12.39	12.26	11.69

activation energy for the XR-II and NR-II TSs are lower than the other two TSs (XM-II and NM-II TSs), which indicates that the XR-II and NR-II are the main channels for this reaction. For the reaction of *o*-QM and MVE, though the XR-I TS is more stable than the NR-I TS, the activation energy of the XR-I TS is only 0.31 kcal/mol lower than that of the NR-I ones. In addition, the activation energies of the two TSs are much lower than the values of the XM-I and NM-I. Therefore, there is a pronounced ortho regioselectivity for this DA reaction, and analysis of the activation energies of TSs for the reaction of *o*-QM with MVK reveals that the ortho approaches are favored over the meta ones and the XR-III and NR-III are more stable than XM-III and NM-III in the range of 3.72−4.24 kcal/mol. There is also a lower activation energy for NR-III than for XR-III is because coefficients of the HOMO of o-QM and the LUMO of dienophile allow for a number of positive overlaps, or stabilizing interactions, which indicates NR-III TSs are more stable than XR-III TSs.[21b] Thus, we conclude that there is an ortho regioselectivity for these types of DA reactions, which is in agreement with experiments.[16]

There have been several attempts to explain the origin of the activation energies of the TSs of the DA reactions. It has been described that, for unsymmetrical substituted dienophiles, the more asynchronous the TS, the lower the barriers.[30] Although it is difficult to find a rigorous theoretical justification for this result, it has become an empirical rule that holds for a variety of DA reactions. Therefore, we can use our results to test if the above-mentioned empirical rule is also of general validity in the present system. As can be seen from Figure 1 and Table 1, the XM-II TS is always more synchronous than their corresponding XR-II TSs, and so it would be expected that XM-II TS has also higher activation energy (Table 2). At the same time, for the reactions of *o*-QM with MVE/MVK, it is similar to the above result, in which the more synchronous XM TSs have higher energies than those of XR TSs.

Comparison of the Mechanism for the Different Transition States. On the basis of the above discussion, the XR and NR channels are the main reaction channels. Thus, we only discuss the ortho channels in the next section.

To study the different behaviors of the TSs, the net charges and the charge transfer on the main atoms at the stationary point are provided in Tables 3 and 4. For the reactions of *o*-QM with the styrene and MVK, the

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TABLE 2. Relative Energies and Thermodynamic (at 298.15 K) Properties (in kcal mol^{-1}) of the Transition Structure of the Reaction between *o*-QM and Various Substituted Ethenes (MVE, Styrene, and MVK)

TS	$\Delta\Delta E_0$	$\Delta\Delta E_{298}$	$\Delta\Delta H_{298}$
XR-I	0.00	0.00	0.00
XM-I	14.11	13.31	13.59
NR-I	0.31	2.16	0.23
NM-I	6.20	12.56	12.45
XR-II	0.00	0.00	0.00
XM-II	5.47	5.29	5.26
NR-II	−0.16	−0.20	−0.22
NM-II	4.87	4.67	4.64
XR-III	0.00	0.00	0.00
XM-III	4.25	4.24	4.24
NR-III	−0.41	−0.39	−0.39
NM-III	3.91	3.72	3.86

TABLE 3. Net Charge (e) of the Transition Structure of Some Atoms[a]

TS	O1	C4	C5	C6
XR-I	−0.558	−0.279	−0.558	0.291
XM-I	−0.468	−0.218	−0.160	−0.162
NR-I	−0.574	−0.441	−0.592	0.306
NM-I	−0.497	−0.533	−0.018	−0.258
XR-II	−0.562	−0.256	−0.298	−0.016
XM-II	−0.552	−0.249	−0.179	−0.119
NR-II	−0.562	−0.254	−0.296	−0.038
NM-II	−0.555	−0.252	−0.186	−0.114
XR-III	−0.559	−0.270	−0.264	−0.025
XM-III	−0.546	−0.273	−0.272	−0.032
NR-III	−0.559	−0.270	−0.264	−0.025
NM-III	−0.551	−0.257	−0.182	−0.097

[a] The number of the atom can see from the Scheme 2.

TABLE 4. Dipole Moment (Debye) and Charge Transfer (e) to the *o*-QM on the Transition Structures of the Diels−Alder Reaction between *o*-QM and Various Substituted Ethenes (MVE, Styrene, and MVK)

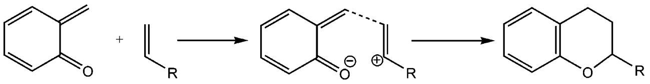
TS	CT[a]	DM[b]	TS	CT	DM	TS	CT	DM
XR-I	0.231	2.3425	XR-II	0.175	2.432	XR-III	0.08	3.475
XM-I	0.173	4.0768	XM-II	0.134	2.109	XM-III	0.069	4.270
NR-I	0.253	2.8503	NR-II	0.154	2.642	NR-III	0.047	2.077
NM-I	0.220	3.8698	NM-II	0.137	2.109	NM-III	0.057	2.769

[a] Charge transfer. [b] Dipole moment.

negative charges on the O1 are −0.559e for XR-III and NR-III TSs and −0.562e for XR-II and NR-II TSs. The values on C6 are −0.016e and −0.038e for the XR-II and NR-II TSs and 0.025e for both XR-III and NR-III TSs. Moreover, the negative charges on the C5 atom are larger than those of the C6 atom for the ortho channels, which makes the C5 atom more nucleophilic than the C6 atom. Consequently, as a type of electrophilic center, the C5 atom is easier to attack than the C4 atom of *o*-QM, which results in a stronger and shorter C4−C5 bond at these transition structures. On the basis of the above analysis, it is shown that the *o*-TSs of the above two reactions take place by asynchronous concerted mechanisms.

For the reaction of *o*-QM with MVE, the charge distributions on O1, C4, and C5 atoms are similar to those of the above two reactions. However, the distributing charge is positive (0.21) on the C6 atom for the XR-I and NR-I TSs, which is opposite to that for the XR-II, NR-II, XR-III, and NR-III TSs. The obvious charge change on the C6 atom at the two TSs (XR-I and NR-I) in the reaction progress makes the mechanism of the DA reaction slightly different from other cycloadditions. These facts allow us to predict the mechanism of the TS as follows (Scheme 3):

SCHEME 3. Mechanism of the Transition State



This kind of TS is described as a zwitterionic transition state that is formed by the interaction between the positive ion of the C6 atom and the negative ion of the O1 atom. With the increase of the interaction of the ion pair, the C6−O1 bond becomes shorter. The two strong centers interact between the electrophile site of *o*-QM and the C4 atom, and the more nucleophile center of MVE, the C5 atom at XR-I, is necessary for the formation of the zwitterionic TS that makes the bond between O1 and C6 atom easier to form and largely decreases the activation energy.[31] At the same time, in this kind of zwitterionic TS, the C5 atom, as an nucleophilic center, attacks the C4 atom, which is similar to the 1,4-addition reaction and results in the short distance between C4 and C5 atom.

The charge transfers from substituted ethenes to the *o*-QM on the transition structures of the DA reactions are given in Table 4. For the cycloaddition reaction of *o*-QM with MVE, the transfer charges are 0.231e for XR-I TS and 0.253e for NR-I TS. The charge-transfer results the change of charge distribution, particularly, the increased negative charge on the O1 atom of the *o*-QM, and the positive charge on the C6 atom of MVE.

From Table 4, we find that the more asynchronous concerted TSs, XR and NR, are easier to transfer the charge, and the difference of electrophility of the two reactants is larger as well. On the contrary, the synchronous concerted XM and NM TSs hold low values of the charge transfer. It is probably that the short C4−C5 bond is advantageous for charge transfer for the asynchronous transition structure and the charge transfers mainly through the bond. But for the synchronous concerted state, the C4−C5 bond length is large, which makes to the charge transfer more difficult via the C4−C5 bond.

The presence of an electron-releasing group on the ethene leads to the enhancement of the C5 atom negative charge and makes it easy to attack the C4 atom and form the short C4−C5 bond as well as the large charge transfer. Thus, we can deduce that the presence of an electron-releasing group (H_3CO-) on the ethene system will promote the charge-transfer process from the substituted ethene to the *o*-QM system. On the contrary, the presence of the electron-withdrawing group (C=O) on the ethene leads to the negative C5 atom decrease, which results in the long bond length of C4−C5 and little charge transfer.

To understand the chemical process associated with each one of the TSs found along the stepwise reaction pathway, the imaginary frequency and transition vector of the TS are presented in Table 5. The components of the transition vector corresponding to the imaginary frequency allowed us to observe the motion of the atoms

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[31] Domingo, L. R.; Aurell, M. J.; Perez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417.

TABLE 5. Imaginary Frequency and the Main Component of the Transition Vector for the Transition States of the Diels−Alder Reaction

TS	bond	I.Fr[a]	T.Ve[b]	TS	bond	I.Fr[a]	T.Ve[b]
XR-I	C4−C5	−317.1	0.676	XR-II	C4−C5	−379.4	0.710
	C6−O1		0.015		C6−O1		0.073
XM-I	C4−C5	−491.7	0.475	XM-II	C4−C5	−445.3	0.556
	C6−O1		0.206		C6−O1		0.271
NR-I	C4−C5	−325.2	0.722	NR-II	C4−C5	−385.3	0.729
	C6−O1		0.070		C6−O1		0.074
NM-I	C4−C5	−468.3	0.444	NM-II	C4−C5	−430.7	0.471
	C6−O1		0.339		C6−O1		0.202
XR-III	C4−C5	−359.8	0.656	NR-III	C4−C5	−407.7	0.419
	C6−O1		0.094		C6−O1		0.273
NR-III	C4−C5	−380.08	0.704	NM-III	C4−C5	−413.05	0.405
	C6−O1		0.085		C6−O1		0.322

[a] Imaginary frequency. [b] Transition vector.

in the transition structure. For the XR channels of the reaction between the *o*-QM and MVE/styrene, the main component of the transition vector of the C4−C5 atom pair (0.71 for XR-II and 0.676 for XR-I) that is associated with the C4−C5 forming bond is greater than that corresponding to the C6−O1 (0.073 for XR-II and 0.015 for XR-I) atom pair in the XR TS, which is the same as the NR channels. These movements are related to the very small activation energy and asymmetric transition structure. These favorable interactions allow an increase of the charge-transfer process for these TSs. For the meta channels, the components of the transition vector for the C4−C5 atom pair are 0.556, 0.475, 0.471, and 0.444 for the XM-II, XM-I, NM-II, and NM-I TSs, respectively, which are associated with the C4−C5 forming bond. While the main components of the transition vector for O1−C6 atom pair are 0.271, 0.206, 0.339, and 0.202 for XM-II, XM-I, NM-II, and NM-I TSs, respectively, which are associated with the O1−C6 forming bond. So we can find that the form of the C4−C5 and C6−O1 bond is almost concerted.

The imaginary frequency values for the ortho TSs are in the range of 317−385 cm^{-1}, while those for the meta TSs are in the range of 430−491 cm^{-1}. For the ortho TSs, there is a decrease of the imaginary frequency value, which is parallel to the increase of the asynchronicity of these processes, and these values are lower for the exo TSs than for the endo ones. The asynchronicity in the bond formation process is also shown by the fact that the imaginary frequency of the ortho TS has a larger participation in the motion of the C4−C5 bond formation than that for the O1−C6 bond.

Frontier Molecular Orbital Analysis. These reactions appear to be under frontier orbital (FMO) control, as the FMO model is capable of explaining the effects of substituted group for these inverse-electron-demand cycloadditions, which require an electron-poor diene and an electron-rich dienophile. Very recently, an analysis[32] based on the reactivity indexes defined within the DFT has been used to explain the reactivity of electron-deficient dienes and electron-deficient ethylenes in DA reactions. In Figure 2, this main effect for the present cycloadditions is rationalized by using an FMO analysis. The HOMO_{QM} of the *o*-QM is quite low in energy (−6.2 ev), less than that of the MVK and MVE (−6.04 and −5.93 ev). Moreover, the value of the HOMO for *o*-QM (−2.61ev) is less than that of the MVK and MVE as well (−0.84 ev and 1 ev). It is obvious that the energy difference between HOMO_{QM} and $\text{LUMO}_{\text{ethene}}$ is greater than the difference of $\text{HOMO}_{\text{ethene}}$ and LUMO_{QM}. Thus, the main HOMO−LUMO interaction occurs between LUMO_{QM} and $\text{HOMO}_{\text{ethene}}$. From Figure 2, it is easy to find that the DA cycloadditions of *o*-QM with MVE have a better reactivity and lower activation energy than that of the reaction between *o*-QM with styrene. On the basis of the FMO theory, for an inverse-electron-demand DA reaction, the presence of an electron-releasing group on the dienophile leads to a contraction of the more relevant ($\text{HOMO}_{\text{ethene}} - \text{LUMO}_{\text{QM}}$) energy separation, and the reactivity increases consequently. On the contrary, the electron-withdrawing group on the ethene, such as MVK, would lead to the enhancement of the difference between $\text{HOMO}_{\text{ethene}}$ and LUMO_{QM}.

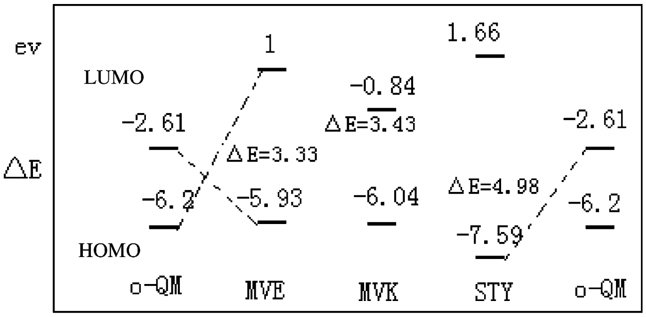

FIGURE 2. Frontier molecular orbitals on the cycloaddition reaction between *o*-QM and the methyl vinyl ether (MVE), styrene (STY), and methyl vinyl ketone (MVK). The Δ*E* value is the difference between $\text{HOMO}_{\text{ethene}}$ and LUMO_{QM}.

We have found that the HOMO of the MVK is a nonbonding orbital in which the lone-pair electrons of the O atom are involved. Therefore, this orbital is not suitable to be involved in the [4 + 2]-cycloaddition reaction. The nearest occupied orbital to the latter (HOMO_{-1}) is 0.871 ev lower in energy than that of HOMO, and it has the right symmetry to the react as a HOMO, having a nodal plane coincident with the plane of the *o*-QM symmetry. Thus, the HOMO_{-1} will be considered as the reacting HOMO of MVK. For the reactions of *o*-QM with MVK, an analysis of the difference in the energy for the FMOs of the reactants, $\text{HOMO}_{\text{ethene}} - \text{LUMO}_{\text{QM}}$ and $\text{LUMO}_{\text{ethene}} - \text{HOMO}_{\text{QM}}$ allows us to conclude that none of them can be neglected albeit the first interaction is slightly lower. However, from Table 4, the charge transfer values from the MVK to *o*-QM at the TS for this reaction are 0.08e, 0.069e, 0.047e, and 0.057e for the XR-III, XM-III, NR-III, and NM-III TSs, respectively. Thus, it can be shown that the latter interaction, namely, $\text{HOMO}_{\text{ethene}} - \text{LUMO}_{\text{QM}}$, is the main interaction for this reaction. All of these results can indicate that this kind of reaction belong to an inverse-electron-demand DA reaction. Comparing the difference between LUMO_{QM} and $\text{HOMO}_{\text{ethane}}$, we show that the order of the reactivity for the three reactions is MVE > MVK > STY, which is in agreement with the conclusion from the activation energy.

Solvent Effect Calculation. Solvent effects on DA reactions are well-known and have received considerable attention,[33] especially in the past few years, because these studies can clarify the role of the solvent on related

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[32] Domingo, L. R. *Eur. J. Org. Chem.* **2004**, 4788.

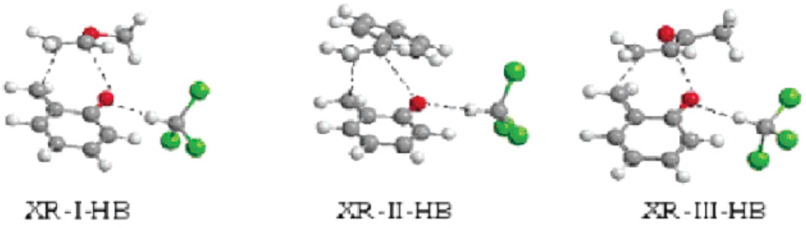

FIGURE 3. Transition structure to the discrete-contiunuum models for the cycloaddition between the *o*-QM and various substituted ethenes, in the presence of one chloroform molecule.

TABLE 6. Solvent Effect of the Toluene and Chloroform ($\Delta E^{\ddagger}_0$: kcal/mol^{-1})

TS	Δd (Å)	$\Delta E^{\ddagger}_0$	CT (e)
XR-I-tS[a]	0.51	5.60	0.236
XR-II-tS	0.50	9.76	0.181
XR-III-tS	0.36	6.40	0.079
XR-I-cS[b]	0.67	3.95	0.261
XR-II-cS	0.62	5.06	0.213
XR-III-cS	0.38	4.75	0.082
XR-I-HB[c]	0.69	3.42	0.254
XR-II-HB	0.58	4.12	0.211
XR-III-HB	0.44	3.89	0.082

[a] tS: solvent effect of toluene. [b] cS: solvent effect of chloroform. [c] Present of one chloroform molecule.

TABLE 7. Solvent Effect of Different Solvent for XR-I Reaction Channel ($\Delta E^{\ddagger}_0$, kcal/mol^{-1})

solvent	cyclohexane	toluene	ether	chloroform	THF	methanol
DC[a]	2.01	2.4	4.33	5.5	7.58	33.7
$\Delta E^{\ddagger}_0$	7.82	5.6	5.32	3.948	3.76	3.82
Δd (Å)	0.510	0.512	0.570	0.67	0.600	0.646

[a] Dielectric constants.

cycloaddition reactions.[34] Solvent effect of chloroform and toluene has been modeled using the PCM method by means of geometrical optimizations of the stationary points.[35] Table 6 presents the relative energies(ΔE), Δd, and CT.

A comparison of the geometrical parameters of TS in the gas phase and in solvent shows that with the inclusion of the solvent effect there is an increase of the asynchronicity in the bond-formation process that can be related with the dielectric constant of the solvent (see Tables 6 and 7). For the reaction channel of XR-II, the Δd is 0.48 Å in the gas phase and 0.62 Å in the chloroform. For the XR-I and XR-III channels, the corresponding values are 0.49 and 0.31 Å in the gas phase and 0.67 and 0.38 Å in chloroform, respectively.

Solvent effects also show that the activation energies decrease and the asynchronicity increases for all TSs (see Tables 6 and 7). The activation energy of XR-II in the gas phase is only larger 0.77 kcal/mol than that of XR-II-tS in toluene. However, for the reaction between *o*-QM and methyl vinyl ketone, the difference between XR-III and XR-III-tS is 4.76 kcal/mol. This decrease of the activation energy is due to a larger solvation of the zwitterionic TS than reagents. As expected, because of the large dielectric constant for chloroform, the activation energies for all of the modes in chloroform is lower than that in toluene (see Table 6).

The different values for the charge-transfer process of these TSs are given in Table 6. An analysis of these results indicates that the most remarkable effect is the increase of the charge transfer for XR-II-tS relative to XR-II (0.006e) and the relative values for XR-I-tS is 0.004e. These facts are in agreement with the strong decrease of the activation energy and the larger increase of dissymmetry in the bond formation found for XR-II-tS and XR-I-tS. A comparison of the geometrical parameters and the activation energies of TSs in toluene and chloroform indicate that the activation energies and the asynchronicity decrease with the enhancement of the dielectric constants of solvent.

To investigate the effect for different solvents, cyclohexane, toluene, ether, chloroform, THF, and methanol were included in these studies as well. As presented in Table 7, it is obvious that the activation energies decreased with an increase of the dielectric constants, which are in agreement with the experiment that indicates the cycloaddition is very fast in the polar solvent.[36] Moreover, Δd was also enhanced with the increase of the dielectric constants.

Huang and Rawal[36] found that the chloroform produced a more significant rate acceleration than other polar organic solvents. The authors believe that the hydroge bond between chloroform and the carbonyl oxygen promoted this kind of reaction. To explain the reduction of the activation energy in chloroform, we suppose that the decrease of the activation energy could arise from a C−H···O bond between the chloroform and the carbonyl oxygen of the *o*-QM, which would render the *o*-QM a strong electrophile. The transition structures are given in Figure 3 and Table 6.

Domingo and Andres[35] reported that the hydrogen bond between chloroform and the carbonyl oxygen can enhance the reactivity of DA cycloaddition and also largely decrease the activation energy. From Table 6, because of the activation of the hydrogen bond (HB), activation energies were decreased in the XR-II mode from 5.06 to 4.12 kcal/mol^{-1} and in the XR-I mode from 3.98 to 3.42 kcal/mol^{-1}, and also it decreased from 4.75 to 3.89 kcal/mol^{-1} in the XR-III TS. All these results indicate that the HB formation between chloroform and the carbonyl oxygen of the *o*-QM lowers the activation energies. At the same time, the hydrogen bond also leads to the increases of the Δd value in the three reaction

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(33) (a) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (b) Li, J. C. *Chem. Rev.* **1993**, *93*, 2023. (c) Blokzijl, W. J.; Engberts, B. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545. (d) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 7430.

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(36) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662.

modes, which suggests that the asynchronicity will increase by the activation of HB. The analysis of charge-transfer in the reaction process also shows that the HB results in the slight increase of the charge transfer.

Therefore, it is suggested that the strong HB formation between the acidic hydrogen and the carbonyl oxygen of the *o*-QM can be responsible for the large rate acceleration. Thus, we anticipate that polar solvents, such as chloroform, methanol, and the other alcohols that hold large dielectric constants and strong capability for the HB formation, are appropriate for this kind of reaction.

Conclusions

DFT calculations at the B3LYP/6-31g(d,p) level have been used to study the DA reactions between the *o*-QM and various substituted ethenes (MVE, styrene, and MVK). Several conclusions can be drawn from the results described for the theoretical investigations.

For the reactions of the *o*-QM with MVE, styrene, and MVK, the energy ordering of four TSs is XR = NR > XM > NM. This energy ordering shows that the ortho channels are more favorable than the meta ones. At the same time, there is a relationship between the nature of the molecular mechanism and the polar character of the substituted ethene, increasing the electron-releasing character of the substituent enhances the asynchronicity and the charge-transfer process as well as a significant decrease of the activation energy. These results agree with those expected from frontier molecular orbital theory.

The molecular mechanism of the reaction of *o*-QM with styrene and methyl vinyl ketone corresponds with an asynchronicity concert cycloaddition mechanism. While for the reaction of *o*-QM with methyl vinyl ether, the molecular mechanism is described as a zwitterionic transition state mechanism that is formed by the strong two centers interaction between the more electrophile site of *o*-QM, the methylene carbon atom, and the more nucleophile site of MVE, the nonsubstituted ethylene carbon atom.

The calculations also indicate that the solvent effects decrease the activation energy and increase the asynchronicity of these processes as well as the charge transfer from the substituted ethene to *o*-QM. For different solvents, the activation energy and the asynchronicity will decrease with the enhancement of the dielectric constants of solvent. We expect that polar solvents, such as chloroform, methanol, and other alcohols, are appropriate for this kind of reaction.

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Supporting Information Available: Table with the bond length (Å) of the transition state of the DA reaction between *o*-QM and various substituted ethenes (styrene, MVE, and MVK) and Cartesian coordinates of all reported structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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