Conformational Preferences of Methacrolein in Diels−Alder and 1,3-Dipolar Cycloaddition Reactions

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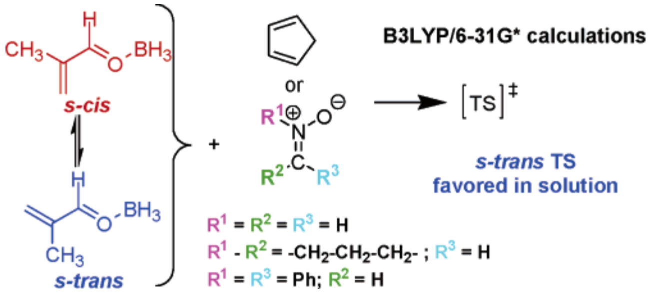
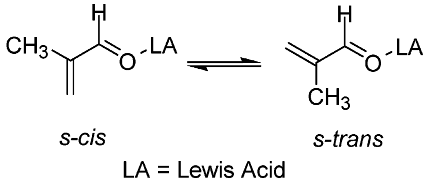


A B3LYP/6-31G* study has been carried out for the reactions of methacrolein with cyclopentadiene, parent nitrone, 1-pyrroline-1-oxide, and (*Z*)-*C*,*N*-diphenylnitrone, in which the coordination of a Lewis acid (borane) and the solvent polarity (dichloromethane) have been taken into account. Calculated activation parameters, regioselectivities (for 1,3-dipolar cycloaddition reactions), and *endo*/*exo* stereoselectivities show good agreement with available experimental data. Gas-phase calculations show a varied behavior of the *s-cis*/*s-trans* TS stability for noncatalyzed reactions (from the systematic *s-cis* preference for the cyclopentadiene reaction to the systematic *s-trans* predilection encountered in the diphenylnitrone cycloaddition). BH_3 coordination leads to a preferential stabilization of *s-trans* TSs in the reactions of cyclopentadiene (*exo* approach) and diphenylnitrone but a larger stabilization of *s-cis* structures in the processes involving the parent nitrone or 1-pyrroline-1-oxide. Additionally, a rather systematic preferential stabilization of *s-trans* structures is induced by solvent polarity in most reactions. As a consequence, an *s-trans* preference is predicted in solution for both thermal and catalyzed types of reactions in most approaches. Such a conclusion is consistent with some experimental results suggesting a preference for a particular conformation of the methacrolein−Lewis acid complexes.

Introduction

One of the most useful methods in Enantioselective Synthesis is based on the use of chiral catalysts. In particular, a great interest has been paid to reactions of methacrolein (2-methylprop-2-enal) as a substrate in Diels−Alder[1] and 1,3-dipolar cycloaddition[2,3] reactions because of its low cost and mechanistic simplicity, as well as the configurational stability of the generated cycloadducts. However, the rational choice of catalysts leading to high yields and stereoselectivities requires some insight into the reaction mechanisms, including the interactions determining the stereoselectivity of the process.

SCHEME 1. ***s-cis*/*s-trans* Equilibrium of the Methacrolein−Lewis Acid Complex**



A factor of complexity is introduced by the existence of an equilibrium between two conformers of the methacrolein

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(namely, *s-cis* and *s-trans*, Scheme 1). Thus, two different enantiomeric adducts are obtained (in reactions with achiral reactants) when the less-hindered face of a chiral methacrolein−catalyst complex is alternatively attacked through *s-cis* or *s-trans* conformations. Since high enantioselectivities have been achieved in a variety of catalyzed asymmetric reactions involving methacrolein under kinetic control, a clear preference for a conformation must be present in the corresponding TS and, hence, the determination of the most stable conformation of methacrolein in the corresponding TSs of Diels−Alder and 1,3-dipolar cycloaddition reactions has become an interesting matter of study.

Literature data on the conformational stability of methacrolein show a noticeable preference for the *s-trans* conformation in different conditions (gas phase,[4−6] solution,[7] and Lewis acid complexes).[7−10] Accordingly, a preference for the *s-trans* conformation has been assumed in a number of reaction models for methacrolein in the Diels−Alder reaction with cyclopentadiene by using chiral catalysts.[8,11] However, it is well-known that the most reactive conformer of a reactant does not necessarily have the most stable conformation. Thus, recent theoretical calculations on the noncatalyzed reaction between cyclopentadiene and methacrolein have shown that this dienophile reacts preferentially through the *s-cis* conformation in gas-phase conditions.[5]

Unfortunately, the currently available information on the conformational preference of methacrolein in catalyzed Diels−Alder reactions is insufficient to obtain a neat conclusion. Thus, two theoretical papers dealing with the catalyzed reaction with cyclopentadiene have recently been published, though we consider that the problem has not been fully solved. Thus, we think that the two-step mechanism inferred for the reactions catalyzed by a cationic oxazaborolidine and BF$_3$[5] may not be representative for a number of typical catalysts. On the other hand, the *s-cis* conformation of methacrolein has been disregarded in a study on the reaction with cyclopentadiene catalyzed by a boron heterocycle.[12]

The methacrolein conformation in a reaction model is so tightly related with the mode of anchoring to the asymmetric Lewis acid that a change in any of them can lead to the configuration reversal of the major product. Thus, theoretical calculations on the anchoring modes of two types of asymmetric Lewis acids (menthoxyaluminum dichloride,[13] substituted oxazaborolidinones)[14] with aldehydes can only explain experimental results on Diels−Alder reactions of methacrolein if the *s-cis* conformation is assumed. However, such an assumption has been called into question by a theoretical study on a catalyzed reaction between cyclopentadiene and α-bromoacrolein[15] (for which the same reaction model as that of methacrolein has been proposed).[7a]

The controversy over the reactivity of *s-cis*/*s-trans* conformations also applies to 1,3-dipolar cycloaddition reactions between α,*β*-unsaturated aldehydes and nitrones. Thus, the *s-trans* conformation of methacrolein has usually been assumed in reaction models derived from experimental studies on 1,3-dipolar cycloaddition reactions with a variety of nitrones catalyzed by chiral complexes of different metals,[10,11,16] though the *s-cis* conformation has been claimed in a study.[17]

Currently, theoretical information on the *s-cis*/*s-trans* preference of α,*β*-unsaturated aldehydes in 1,3-dipolar cycloaddition reactions is scarce. Thus, some conformations have systemati-

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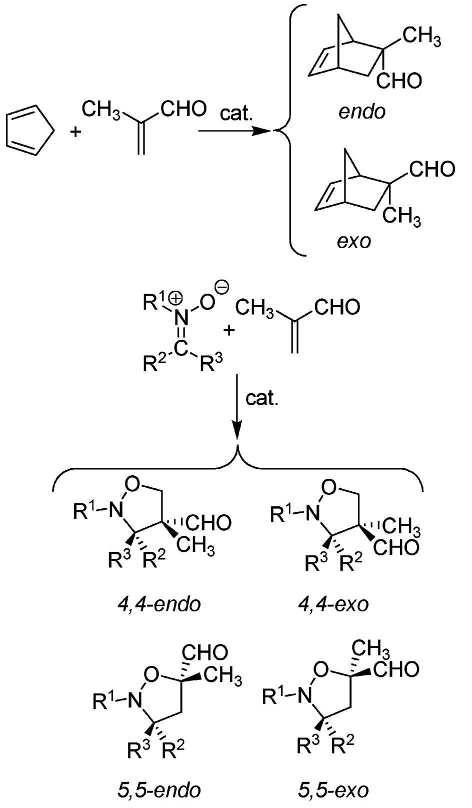
SCHEME 2. Reactions of Methacrolein with Cyclopentadiene and Several Nitrones (Absolute Configuration not Specified)



parent nitrone: $R^1 = R^2 = R^3 = H$

1-pyrroline-1-oxide: R^1 - R^2 = $-CH_2-CH_2-CH_2-$; $R^3 = H$

diphenylnitrone: $R^1 = R^3 = Ph$; $R^2 = H$

cally been disregarded in two theoretical studies (*s-trans* forms for the parent nitrone + methacrolein reaction,[18] *s-cis* structures for the catalyzed parent nitrone + acrolein process).[19] Fortunately, the *s-cis*/*s-trans* preference has been regarded in other two studies on the parent nitrone + acrolein reaction in gas-phase conditions, and a predilection for the *s-cis* conformation in the TS has been encountered.[18,20]

In this work we present a theoretical study (by means of BL3YP/6-31G* calculations) to establish the relative reactivity of *s-cis* and *s-trans* conformations of methacrolein in both Diels–Alder and 1,3-dipolar cycloaddition reactions. Since a major aim of this study was to obtain conclusions for relevant asymmetric-catalyzed reactions, special interest was paid to the methacrolein reactions involving counterparts often used in experimental studies: cyclopentadiene for the Diels–Alder reaction as well as 1-pyrroline-1-oxide and (*Z*)-*C*,*N*-diphenylnitrone (hereafter, diphenylnitrone) for the 1,3-dipolar cycloaddition (Scheme 2). Furthermore, the reaction of methacrolein with the parent nitrone has also been drawn in comparison with other theoretical studies (Scheme 2). Both *endo* and *exo* approaches have been considered in all cases, whereas approaches leading to 4,4- as well as 5,5-disubstituted isoxazolidines have been considered for the 1,3-dipolar cycloaddition reactions. Solvent modeling (through a continuum model representing dichloromethane) as well as coordination of a Lewis acid (BH_3) to methacrolein has also been included.

Methods

Geometries of energy minima and TSs were localized at the B3LYP/6-31G* level by using the Gaussian 03 package[21] because of the good performance of such a methodology in recent theoretical studies for pericyclic reactions of medium-size systems.[22] BH_3 was regarded as a catalyst model because of the poor performance of other Lewis acids (BF_3, AlH_3, $AlCl_3$) in a preliminary study, due to their tendency to form strong electrostatic interactions with aliphatic hydrogen atoms in the calculated TSs.[23]

Stationary points were characterized according to the correct number of negative eigenvalues of the exact Hessian (zero for energy minima and one for TSs) at the corresponding theoretical level for each solvent model (gas phase or dichloromethane). Thermodynamical properties (Gibbs free energies, enthalpies, and entropies) have been calculated at 25 °C by using nonscaled frequencies, though some activation entropies calculated at other temperatures have also been included in the text. The activation parameters reported in the paper refer to the *s-trans* conformation of methacrolein as a reactant.

The energies of structures in solution were calculated by using the Polarizable Continuum Models (PCM), representing dichloromethane as the solvent. As a general rule, solvation calculations were obtained by total optimization of the structures in the presence of the PCM reaction field. However, despite exhaustive searches most TSs corresponding to the BH_3-catalyzed reactions between methacrolein and all three nitrones could not be optimized by using the solvent model, in agreement with the poor geometric performance of the PCM method for large and flexible systems.[24] As a consequence, activation parameters for BH_3-catalyzed 1,3-dipolar cycloaddition reactions in solution have been obtained by means of the PCM by using structure geometries optimized in the gas phase (vibrational corrections corresponding to gas-phase calculations).

Results and Discussion

Theoretical calculations on isolated methacrolein show a clear preference for the *s-trans* conformation, in qualitative agreement with experimental results. Thus, the calculated energy differences (2.6 kcal mol^{-1} in gas phase, 2.7 kcal mol^{-1} in dichloromethane) are close to the experimental value obtained by Durig et al. (2.2 kcal mol^{-1}),[4] though significantly greater than the experimental result reported by Geise and co-workers (1.2 kcal mol^{-1}).[6]

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TABLE 1. Activation Parameters (Gibbs Free Energies, Enthalpies, and Entropies) for the Diels−Alder Reaction (in Both Thermal and BH_3-Catalyzed Conditions) between Cyclopentadiene and Methacrolein in Both Gas-Phase and Dichloromethane Solution, According to B3LYP/6-31G* Calculations

	gas phase (thermal)			gas phase (BH_3-catalyzed)			solution (thermal)			solution (BH_3-catalyzed)		
approach	$\Delta G^{\ddagger\,a}$	$\Delta H^{\ddagger\,a}$	$\Delta S^{\ddagger\,b}$	$\Delta G^{\ddagger\,a}$	$\Delta H^{\ddagger\,a}$	$\Delta S^{\ddagger\,b}$	$\Delta G^{\ddagger\,a}$	$\Delta H^{\ddagger\,a}$	$\Delta S^{\ddagger\,b}$	$\Delta G^{\ddagger\,a}$	$\Delta H^{\ddagger\,a}$	$\Delta S^{\ddagger\,b}$
endo s-cis	32.9	19.7	−44.4	25.3	12.0	−34.5	32.4	19.2	−44.1	23.4	10.6	−32.5
endo s-trans	34.4	20.9	−45.2	27.7	14.6	−33.7	33.2	19.8	−44.7	23.2	10.7	−31.4
exo s-cis	31.8	18.1	−45.9	25.1	11.7	−34.8	31.1	17.6	−45.3	22.3	9.4	−32.8
exo s-trans	33.2	19.6	−45.4	26.1	13.2	−33.2	31.6	18.2	−44.9	21.4	9.3	−30.2

[a] Energy given in units of kcal mol^{-1}. [b] Entropy given in units of cal mol K^{-1}.

Interesting results are obtained for calculations on the BH_3−methacrolein complex. Thus, an *E* arrangement of the C−C═O···B sequence is predicted, in agreement with the X-ray diffraction data of different Lewis acid−methacrolein complexes.[9−11] A *syn*-periplanar arrangement of the C═O···B−H sequence is predicted for the complexes, in agreement with a theoretical study on complexes between formyl compounds and boron Lewis acids.[25] The coordination of BH_3 to methacrolein is energetically favored (ca. 7 kcal mol^{-1} in gas phase; ca. 11 kcal mol^{-1} in solution). Calculated energies indicate that the *s-trans* preference is hardly altered by the coordination of BH_3 or solvent modeling.

Furthermore, the activation barriers for the interconversion between *s-cis* and *s-trans* conformers of methacrolein have been calculated by means of the corresponding TSs. The calculated activation energy for isolated methacrolein shows a low value (9.5 kcal mol^{-1} in both gas phase and solution), indicating a very fast interconversion even at low temperature. The interconversion barrier is slightly increased by means of BH_3 coordination in the gas phase (10.9 kcal mol^{-1}) as well as in solution (11.9 kcal mol^{-1}). Therefore, the conformational interconversion of methacrolein (in isolated and in coordinated forms) is expected to be very fast in standard reaction conditions, in agreement with the rapid *s-cis*/*s-trans* equilibrium observed for $SnCl_4$-complexed (*E*)-4-ethylhex-2-enal at −50 °C.[26]

Activation parameters (Gibbs free energies, enthalpies, and entropies) for the Diels−Alder reaction between cyclopentadiene and methacrolein are shown in Table 1, whereas the corresponding TS geometries have recently been reported.[5] In both thermal and catalyzed versions, activation barriers for the Diels−Alder reaction are significantly higher than those for the conformational inverconversion of methacrolein (by at least 9.5 kcal mol^{-1}), indicating that the Curtin−Hammett principle is met and, hence, the product ratio is independent from the conformational energies of methacrolein in ground state.

The calculated activation enthalpy for the most-favored (*exo s-cis*) approach for the reaction of cyclopentadiene with methacrolein in gas phase (18.1 kcal mol^{-1}) is essentially identical to the experimental value for crotonaldehyde in solution (17.6−18.7 kcal mol^{-1}) and somewhat higher than the experimental result for acrolein (12.0−12.5 kcal mol^{-1}).[27]

The calculated activation entropy of the cyclopentadiene + methacrolein reaction (−45.9 cal mol^{-1} K^{-1} at 25 °C, −44.4 cal mol^{-1} K^{-1} at 100 °C) presents a greater magnitude than experimental values (at 100 °C) for the reactions of cyclopentadiene with crotonaldehyde (−29 ± 2 cal mol^{-1} K^{-1}) or acrolein (−36.5 ± 0.5 cal mol^{-1} K^{-1}).[27] A similar overestimation of the magnitude of activation entropies has been found in other B3LYP/6-31G* calculations on the Diels−Alder cycloaddition, such as those corresponding to the reactions of butadiene with ethylene (calculated, −42.8 cal mol^{-1} K^{-1} at −273.15 °C[28] and −40.6 cal mol^{-1} K^{-1} at 25 °C;[29] experimental, −30 cal mol^{-1} K^{-1} at 400−600 °C)[30] or acrolein (calculated, −45.6 cal mol^{-1} K^{-1} at 25 °C;[31] experimental, −35.4 cal mol^{-1} K^{-1} at 155−332 °C).[32]

Calculated activation enthalpies for the cyclopentadiene + methacrolein reaction show a preference for the *exo* approach (by 1.5 kcal mol^{-1} in gas phase and 1.6 kcal mol^{-1} in dichloromethane), in excellent agreement with the experimental value for a solvent-free reaction mixture (1.5 kcal mol^{-1}).[33] Such an *exo* preference can be attributed to steric repulsion between the cyclopentadiene methylene group and the methacrolein methyl substituent in the *endo* TSs.[34] On the other hand, calculations show a greater entropy for the *endo* approach in comparison with that for the *exo* approximation (by 1.4 cal mol^{-1} K^{-1} in gas phase and 1.1 cal mol^{-1} K^{-1} in dichloromethane), in excellent agreement with the corresponding experimental value (by 0.9 ± 0.1 cal mol^{-1} K^{-1} in the solvent-free reaction mixture at 25 °C),[33] though the close similarity between the compared figures may be due, in some measure, to a lucky cancellation of errors.

TSs energies for the reaction between gas-phase cyclopentadiene + methacrolein reaction show a clear preference for the *s-cis* conformation (by 1.5 kcal mol^{-1} for the *endo* approach and 1.4 kcal mol^{-1} for the *exo* approximation), in qualitative agreement with a previous theoretical study.[5] Hence, a noticeable larger reactivity of the *s-cis* (vs that of *s-trans*) conformer (by 4.2 kcal mol^{-1}) is found if the corresponding energy gap for isolated methacrolein is taken into account. The larger reactivity of the *s-cis* conformer of methacrolein is consistent with Houk's results on the butadiene + acrolein reaction.[35] Thus, our results are consistent with the lower energy of LUMO for the *s-cis*

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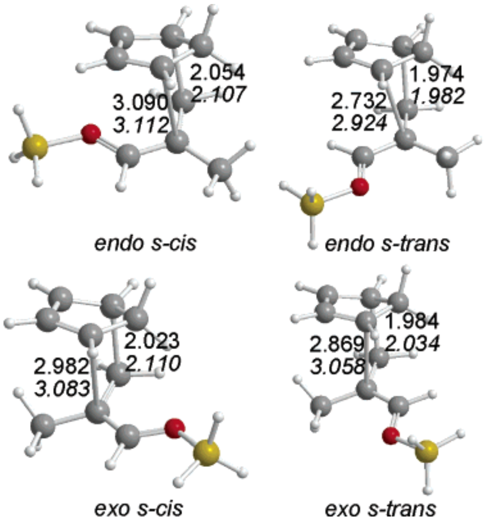

endo s-cis *endo s-trans*

exo s-cis *exo s-trans*

FIGURE 1. Geometries of TSs for the BH_3-catalyzed cyclopentadiene + methacrolein reaction, according to B3LYP/6-31G* calculations. Lengths of incipient σ-bonds (in Å), as derived from gas phase (plain text) and solution (italics) calculations, are also shown.

conformation (−0.061 hartrees) in comparison with that of the *s-trans* form (−0.058 hartrees), though other effects might also be involved.

The calculations of the TSs corresponding to the BH_3-catalyzed cyclopentadiene + methacrolein reaction (shown in Figure 1) in gas phase have provided interesting results. Thus, BH_3 coordination leads to a significant decrease of the activation barrier (by 6.7−8.0 kcal mol^{-1}), in agreement with the experimental reduction of the reaction time observed for some cyclopentadiene + methacrolein reactions catalyzed by Lewis acids.[36]

The high *exo* preference predicted for thermal reactions is significantly lowered by Lewis acid coordination in gas-phase calculations. A preferential stabilization of the *s-trans* TSs is induced by Lewis acid coordination in the most stable approach (*exo*), though a larger stabilization of the *s-cis* structure is found for the *endo* approximation. Nevertheless, a preference for the *s-cis* conformation of methacrolein in the TS is kept for both *endo* (by 2.4 kcal mol^{-1}) and *exo* (1.0 kcal mol^{-1}) approaches, in agreement with previous theoretical results on the butadiene + acrolein reaction.[31,37]

Some interesting trends can be observed by comparing gas-phase and solution calculations for the reaction between cyclopentadiene and methacrolein. Thus, a slight decrease of the activation barrier is noted (by 0.5−1.6 kcal mol^{-1}), in agreement with the regression analysis between the kinetic data[27] for the reaction in nine solvents (excluding acetic acid) and the E_T^N solvent parameter[38] ($\log k$ at 80 °C = (0.855 ± 0.057) + (1.203 ± 0.124)E_T^N, $r = 0.96$). Furthermore, a slight increase of the *exo* preference is also found in solution, in agreement with the experimental relationship occurring between the *endo*/*exo* selectivity and the E_T^N parameter for a set of 10 solvents[27] (log *endo*/*exo* at 30 °C = −(0.66 ± 0.02) −(0.24 ± 0.04)E_T^N, $r = 0.89$, aqueous mixtures being excluded). Interestingly, such a decrease of the *endo*/*exo* ratio by the solvent polarity is opposite to results corresponding to other typical dienophiles.[39] On the other hand, calculations indicate that *s-trans* TSs are preferentially stabilized in solution in comparison with their *s-cis* counterparts, analogous to theoretical results on the cyclopentadiene + methyl acrylate reaction.[40]

Solvent modeling leads to some noticeable effects on the BH_3-catalyzed cyclopentadiene + methacrolein reaction in calculations. Thus, BH_3 coordination leads to a significant decrease of the activation barrier (by 2.1−4.7 kcal mol^{-1}). No significant changes on the *exo* preference are found for both *s-cis* and *s-trans* conformations. Finally, a strong preferential stabilization of *s-trans* conformations can be observed. In fact, a larger stability of *s-trans* conformations is predicted for the BH_3-catalyzed reaction in dichloromethane in both *endo* and *exo* approaches, in contrast with results corresponding to the gas-phase reaction.

Some care should be taken for the extrapolation of the *s-trans* preference in the Diels−Alder reaction of methacrolein to experimental studies because of the roughness of the models corresponding to the solvent (dielectric continuum) and the Lewis acid (BH_3). The relative stability of *s-trans* conformations in the *exo* approach (which is the most favored approximation, according to theoretical and experimental results) can be increased by raising the solvent polarity and/or the Lewis acidity of the catalyst. As a consequence, the interpretation of experimental results on catalyzed cyclopentadiene + methacrolein reactions by using a theoretical model requires a careful analysis of the reaction conditions (such as catalyst or solvent).

Activation barriers for the 1,3-dipolar cycloaddition reaction between the parent nitrone and methacrolein are shown in Table 2. Results obtained for the thermal parent nitrone + methacrolein reaction show a very strong preference for 5,5- (rather than 4,4-) cycloadducts (by 1.8−5.2 kcal mol^{-1}), in qualitative agreement with a previous theoretical study (though *s-trans* TSs were not included in that work).[18] Such a preference for the 5,5-regioisomers is consistent with previous theoretical results for the reactions of the parent nitrone with acrolein[18] and acrylonitrile.[41]

The source of the preference for the 5-regioisomers in 1,3-dipolar cycloaddition reactions between nitrones and moderately electron-deficient dipolarophiles has been a matter of debate. Thus, a possible explanation has been attributed to the control of the regioselectivity by $\mathrm{HOMO_{dipolarophile}}$−$\mathrm{LUMO_{dipole}}$ interactions.[42] However, our calculations on efficient π-frontier molecular orbitals show a significantly lower energy gap for the $\mathrm{HOMO_{dipole}}$−$\mathrm{LUMO_{dipolarophile}}$ interaction (*s-cis*, 0.167 hartrees; *s-trans*, 0.170 hartrees) in comparison with that for the ($\mathrm{HOMO_{dipolarophile}}$-1)−$\mathrm{LUMO_{dipole}}$ interaction (*s-cis*, 0.247 hartrees; *s-trans*, 0.254 hartrees). Such results would predict the favored formation of the 4,4-cycloadduct, in sound contradiction to the results indicated by our TSs energies.

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TABLE 2. **Activation Energies (Gibbs Free Energies, Enthalpies, and Entropies) for the 1,3-Dipolar Cycloaddition Reaction (Gas-Phase, Solution, and BH_3-Catalyzed Versions) between the Parent Nitrone and Methacrolein, According to B3LYP/6-31G* Calculations**

	gas phase (thermal)			gas phase (BH_3-catalyzed)			solution (thermal)			solution (BH_3-catalyzed)	
approach	$\Delta G^{\ddagger\,b}$	$\Delta H^{\ddagger\,b}$	$\Delta S^{\ddagger\,c}$	$\Delta G^{\ddagger\,b}$	$\Delta H^{\ddagger\,b}$	$\Delta S^{\ddagger\,c}$	$\Delta G^{\ddagger\,b}$	$\Delta H^{\ddagger\,b}$	$\Delta S^{\ddagger\,c}$	$\Delta G^{\ddagger\,a,b}$	$\Delta H^{\ddagger\,a,b}$
4,4-*endo s-cis*	24.1	10.8	−44.6	17.2	2.3	−49.8	27.5	14.3	−44.3	23.1	8.2
4,4-*endo s-trans*	25.6	12.4	−44.3	19.4	6.7	−42.4	27.3	14.2	−44.0	19.5	6.9
4,4-*exo s-cis*	26.7	13.5	−44.3	21.1	8.3	−43.1	28.8	15.6	−44.3	20.6	7.7
4,4-*exo s-trans*	26.1	13.0	−44.1	22.7	9.3	−44.9	28.3	15.1	−44.1	21.1	7.7
5,5-*endo s-cis*	18.9	5.5	−44.8	13.7	−1.5	−51.1	22.2	9.2	−43.7	20.4	5.2
5,5-*endo s-trans*	22.4	9.7	−42.7	18.5	5.9	−42.3	22.9	10.3	−42.3	17.3	4.7
5,5-*exo s-cis*	23.8	10.7	−43.8	21.6	7.9	−45.8	25.6	12.7	−43.3	22.4	8.8
5,5-*exo s-trans*	24.4	11.4	−43.7	22.4	8.7	−45.8	25.6	12.6	−43.5	21.6	7.9

[a] Calculated at gas-phase optimized geometries. [b] Energy given in units of kcal mol^{-1}. [c] Entropy given in units of cal mol K^{-1}.

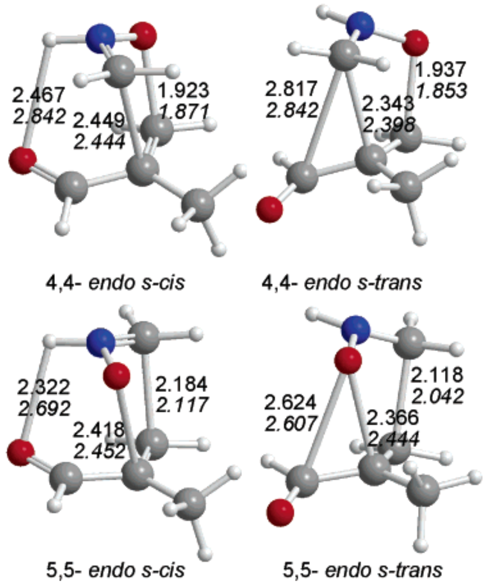

FIGURE 2. Geometries of the *endo* TSs for the parent nitrone + methacrolein reaction, according to B3LYP/6-31G* calculations. Some selected distances (in Å), as derived from gas phase (plain text) and solution (italics) calculations, are also shown.

A different source for the preferential formation of 5,5-substituted cycloadducts in 1,3-dipolar cycloaddition reactions has been proposed in a theoretical study on the reactions of fulminic acid with crotonaldehyde and acrolein.[43] According to that work, the preference for the 5,5-approach can be attributed to the occurrence of a stabilizing (possibly electrostatic) interaction between the dipole oxygen and the carbonylic carbon from the dipolarophile. The relatively short distances in the calculated TSs geometries corresponding to the gas-phase parent nitrone + methacrolein reaction are consistent with the existence of attractive interactions between the nitrone oxygen and the carbonylic carbon of methacrolein in the 5,5-TSs (e.g., $O_{nitrone}\cdots C_{aldehyde} = 2.624$ Å for the 5,5-*endo s-trans* TS, Figure 2). Instead, larger interatomic distances are found for the interactions involving the nitrone carbon and the carbonylic carbon in the 4,4-TSs (e.g., $C_{nitrone}\cdots C_{aldehyde} = 2.817$ Å for the 4,4-*endo s-trans* TS, Figure 2). These behavior differences can be attributed to the greater asynchronicity of 4,4-TSs (in comparison with 5,5-structures) that leads to increased separation between the atoms involved in electrostatic interactions and, hence, a lesser stabilization. The interpretation of the regioselectivity of the nitrone + methacrolein reaction in terms of C···O stabilizing interactions allows the explanation of experimental data on reactions of substituted nitrones showing a 5-preference with carbonyl- or cyano-substituted alkenes[44] but a 4-predilection with dipolarophiles bearing other electron-withdrawing substituents (such as nitroethylene,[45] vinyl sulfoxides,[46] phenyl vinyl sulfone,[44] or ethenesulfonic acid derivatives).[47]

A net preference for the *endo* (vs *exo*) approach can be observed for calculations on the gas-phase reaction involving the parent nitrone (by 0.5−4.9 kcal mol^{-1}). The high *endo* preference in 1,3-dipolar cycloaddition reactions of nitrones with some dipolarophiles has been attributed in some cases to the existence of attractive *Secondary Orbital Interactions* (SOI) between the nitrone nitrogen atom and the dipolarophile substituent in the *endo* TS,[3,18,45,48] though such an explanation has been questioned.[41,49] Thus, a noticeable repulsion (rather than an attraction) should be expected in our case from the atomic coefficients and energies of the efficient π-frontier molecular orbitals for the $HOMO_{dipole}-LUMO_{dipolarophile}$ interaction as well as a very low stabilization corresponding to the $(HOMO\text{-}1_{dipolarophile})-LUMO_{dipole}$ interaction (*s-cis* approach is illustrated in Scheme 3; *s-trans* approximation shows very similar results). The lack of attractive SOI in this cycloaddition reaction is consistent with our previous results on Diels−Alder reactions pointing to the negligible role of such interactions.[34,50]

An interesting analogy between our results for the parent nitrone + methacrolein reaction and a theoretical study for the reactions of the parent nitrone with several vinylborane derivatives can be found.[51] Thus, the preferences for 5,5- (or 5-) regiochemistry and *endo* stereoselectivity, predicted in both studies, can be attributed to the existence of attractive interac-

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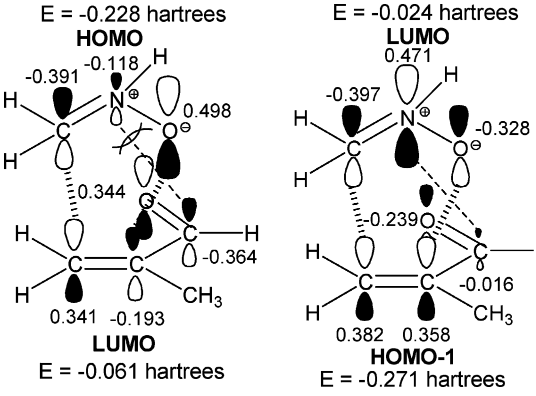
SCHEME 3. Interactions between π-Efficient Frontier Molecular Orbitals Corresponding to the Parent Nitrone + Methacrolein Reaction (*endo s-cis* Approach)[a]



[a] Energies and $2p_z$ Atomic Coefficients (Calculated at B3LYP/6-31G* Level) are Shown

tions involving an electron-deficient atom ($C_{nitrone}\cdots C_{aldehyde}$ and $O_{nitrone}\cdots C_{aldehyde}$ interactions in this paper; $C_{nitrone}\cdots B_{dipolarophile}$ and $O_{nitrone}\cdots B_{dipolarophile}$ in the aforementioned work). Such a similarity of interactions had been previously proposed by us for the Diels−Alder reactions of butadiene with vinylborane and BF_3-coordinated acrolein.[31]

A major point of interest is the *s-cis*/*s-trans* preference in the gas-phase parent nitrone + methacrolein reaction. Thus, a very high preference can be found for the *endo s-cis* approach for both 4,4- and 5,5-approaches that can be attributed to the occurrence of an $N^+{-}H\cdots O{=}C$ electrostatic attraction, as indicated by the corresponding H···O distances in both 4,4-*endo s-cis* (2.467 Å) and 5,5-*endo s-cis* (2.322 Å) structures (Figure 2), in addition to the lower LUMO energy of methacrolein noted for the Diels−Alder reaction. Because of the existence of $N^+{-}H\cdots O{=}C$ electrostatic interactions in both *endo s-cis* TSs, it must be concluded that the parent nitrone should not be considered a good model for *N*-substituted nitrones. A dichotomic behavior on the *s-cis*/*s-trans* selectivity can be found for the *exo* approaches. Thus, whereas an *s-trans* preference is found for the 4,4-*exo* approaches, an *s-cis* predilection is observed for the 5,5-*exo* approximations (both by 0.6 kcal mol^{-1}). This dichotomic behavior agrees with that reported for the fulminic acid + acrolein cycloaddition reaction, which was attributed to the larger stabilization of *s-cis* (rather than *s-trans*) TSs by means of electrostatic interactions, such an effect being larger for $O\cdots C{=}O$ interactions (5,5-TSs) rather than $C\cdots C{=}O$ interactions (4,4-TSs).

Several effects can be observed for the BH_3 coordination to the parent nitrone + methacrolein reaction in gas-phase conditions. Thus, a significant decrease of the activation barriers (by 2.0−6.9 kcal mol^{-1}) can be found, in agreement with the decrease of the $HOMO_{dipole}{-}LUMO_{dipolarophile}$ energy gap, as usually found in normal electron demand cycloaddition reactions. Interestingly, the coordination of the Lewis acid leads to a decrease of the 5,5-preference (a 4,4-preference is found for the *exo s-cis* approaches). Such a result may be attributed to the rise in asynchronicity induced by the Lewis acid coordination that simultaneously weakens the stabilizing interaction of the 5,5-TSs.

Inspection of TSs geometries for the BH_3-catalyzed parent nitrone + methacrolein reaction reveals the existence of stabilizing dihydrogen bonds[52] between a negatively charged borane hydrogen atom and a positive N−H hydrogen in two structures (Figure 3). Thus, the occurrence of such bonding interactions for both 4,4-*endo s-cis* and 5,5-*endo s-cis* TSs is consistent with the corresponding short H···H distances (2.065 and 1.992 Å, respectively), the low enthalpy activation values (a negative figure is found for the 5,5-*endo s-cis* approach), and the anomalous results of activation entropies (ca. −50 cal mol^{-1} K^{-1}, out of the −42/−46 cal mol^{-1} K^{-1} range of all other TSs).

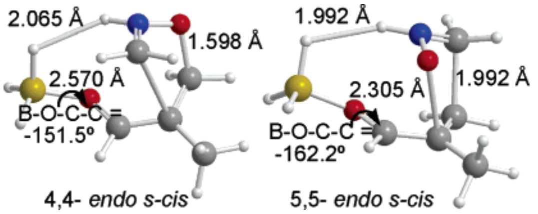


FIGURE 3. Geometries of 4,4-*endo s-cis* (left) and 5,5-*endo s-cis* (right) TSs for the gas-phase BH_3-catalyzed parent nitrone + methacrolein reaction, according to B3LYP/6-31G* calculations. Some selected geometric parameters are also shown.

Some interesting effects can be observed by means of solvent modeling on the parent nitrone + methacrolein reaction. Thus, a rise of the activation barrier of the thermal reaction by solvent polarity is observed, in agreement with other theoretical studies on 1,3-dipolar cycloaddition reactions of the parent nitrone with several dipolarophiles.[53] This result can be attributed to the high solvation energy of the 1,3-dipole in ground state due to its highly polarized structure.[54] The increase of the activation barrier by means of solvent modeling for the parent nitrone + methacrolein reaction is high in both 4,4-*endo s-cis* (3.5 kcal mol^{-1}) and 5,5-*endo s-cis* (3.3 kcal mol^{-1}) approaches, in agreement with the existence of specific electrostatic interactions in both *endo s-cis* TSs (H···O distances do significantly increase, Figure 2), whereas it is only moderate in all other structures (0.5−2.1 kcal mol^{-1}). Solvent polarity induces a raise of the *endo* preference for the *s-trans* conformation but a decrease of such a preference for the *s-cis* form (because of the strong destabilization of both *endo s-cis* TSs) in solution. A strong preferential stabilization of the *s-trans* TSs by solvent polarity can thus be observed (but a negligible variation was observed for the 4,4-*exo* approach), leading to the *s-cis*/*s-trans* stability reversal in the case of the 4,4-*endo* approximation.

Solvent modeling on the BH_3-catalyzed reaction between parent nitrone and methacrolein leads generally to very little variations of the free energy barriers in comparison with the corresponding thermal reactions. Nevertheless, very high values of the activation barriers are found for 4,4-*endo s-cis* and 5,5-*endo s-cis* approaches, presumably due to the weakening of the corresponding dihydrogen bonds (see length changes in Figure 2).

The incorporation of solvent effects in the BH_3-catalyzed parent nitrone + methacrolein reaction shows interesting results. Thus, a preferential stabilization of *exo* (rather than *endo*) and 5,5- (rather than 4,4-) TSs can be observed in most approaches. Interestingly, it can be found that a systematic differential stabilization of the *s-trans* (rather than *s-cis*) TSs leads to a

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TABLE 3. Activation Parameters (Gibbs Free Energies, Enthalpies, and Entropies) for the 1,3-Dipolar Cycloaddition Reaction (Gas-Phase, Solution, and BH_3-Catalyzed Versions) between 1-Pyrroline-1-oxide and Methacrolein, According to B3LYP/6-31G* Calculations

	gas phase (thermal)			gas phase (BH_3-catalyzed)			solution (thermal)			solution (BH_3-catalyzed)	
approach	$\Delta G^{\ddagger\,b}$	$\Delta H^{\ddagger\,b}$	$\Delta S^{\ddagger\,c}$	$\Delta G^{\ddagger\,b}$	$\Delta H^{\ddagger\,b}$	$\Delta S^{\ddagger\,c}$	$\Delta G^{\ddagger\,b}$	$\Delta H^{\ddagger\,b}$	$\Delta S^{\ddagger\,c}$	$\Delta G^{\ddagger\,a,b}$	$\Delta H^{\ddagger\,a,b}$
4,4-*endo s-cis*	25.9	12.8	−46.1	16.8	1.5	−45.5	30.0	16.5	−45.6	21.1	5.8
4,4-*endo s-trans*	25.4	12.0	−47.0	17.3	4.0	−46.7	28.7	14.9	−46.5	19.3	6.0
4,4-*exo s-cis*	28.5	15.6	−45.1	21.3	8.4	−45.4	31.5	18.0	−45.3	22.7	9.8
4,4-*exo s-trans*	28.0	15.1	−45.2	21.7	8.7	−46.0	31.2	17.5	−46.0	22.6	9.5
5,5-*endo s-cis*	22.2	9.2	−45.7	15.0	1.6	−46.9	26.2	12.6	−45.8	18.8	5.4
5,5-*endo s-trans*	24.3	11.6	−44.7	18.5	6.4	−42.7	25.8	12.6	−44.4	18.3	6.2
5,5-*exo s-cis*	26.7	13.7	−45.7	22.2	9.6	−44.4	29.8	16.4	−45.0	24.3	11.7
5,5-*exo s-trans*	27.4	14.6	−45.0	23.4	11.0	−43.8	29.3	15.8	−45.3	23.8	11.3

[a] Calculated at gas-phase optimized geometries. [b] Energy given in units of kcal mol^{-1}. [c] Entropy given in units of cal mol K^{-1}.

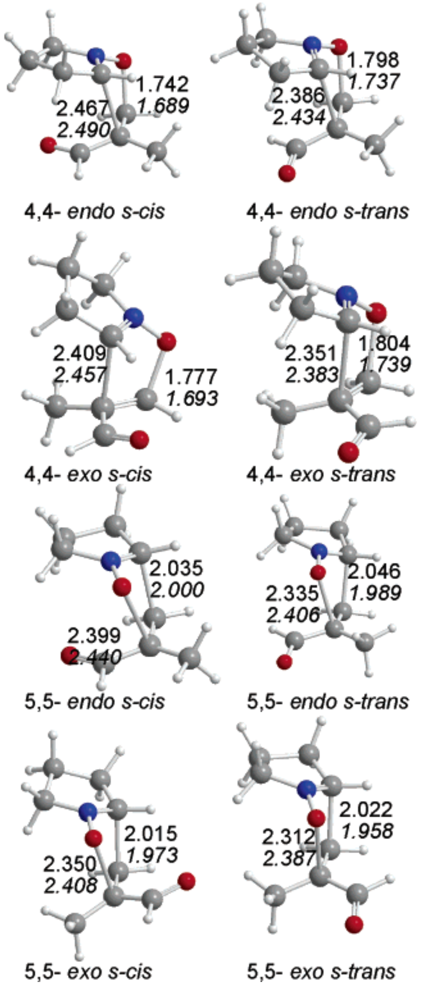

FIGURE 4. Geometries of the TSs corresponding to the thermal 1-pyrroline-1-oxide + methacrolein reaction, according to B3LYP/6-31G* calculations. Lengths of the incipient σ-bonds are shown, as obtained from gas-phase (plain text) and solution (italics) calculations.

preference for the *s-trans* conformation in all approaches (except for the 4,4-*exo* approximation).

Results on activation energies for the reaction between 1-pyrroline-1-oxide and methacrolein are presented in Table 3, whereas the corresponding TS geometries for thermal conditions are presented in Figure 4. The calculated activation barriers are generally somewhat higher than those corresponding to the parent nitrone (but a slight decrease was found for the 4,4-*endo s-trans* structure). Nevertheless, such activation energies are significantly greater than those corresponding to the *s-cis*/*s-trans* interconversion of methacrolein, in agreement with the Curtin−Hammett principle.

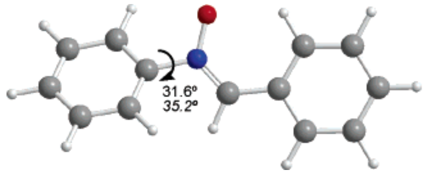

FIGURE 5. Geometry of diphenylnitrone, according to B3LYP/6-31G* calculations. The torsion angle of the $C_{Ph}-C_{Ph}-N-O$ arrangement, as derived from gas-phase (plain text) and solution (italics) calculations, is also shown.

Theoretical results for the thermal 1-pyrroline-1-oxide + methacrolein reaction in gas phase show a preference for 5,5- (vs 4,4-) and *endo* (vs *exo*) approaches, as observed for the reaction of the parent nitrone. Furthermore, a significant *s-cis* predilection for 5,5-approximations (0.7−2.1 kcal mol^{-1}) is found, whereas a slight *s-trans* preference (0.5 kcal mol^{-1}) is observed in 4,4-approaches, analogous to results corresponding to the reaction of the parent nitrone in *exo* approaches (*endo* results being seriously affected by electrostatic interactions).

Some interesting results are found for the BH_3-catalyzed 1-pyrroline-1-oxide + methacrolein reaction, in comparison with the corresponding thermal process. Thus, a significant decrease of the activation barriers can be observed (1.6−2.7 kcal mol^{-1}), in agreement with experimental data showing a yield rise when Lewis acids are used as catalysts under the same conditions.[16,55] An increase of the *endo*/*exo* selectivity can be also observed (by 0.5−1.4 kcal mol^{-1}), leading to very high ratios, in agreement with experimental results on catalyzed reactions showing total stereoselectivity.[10b,16,55] Furthermore, a significant differential stabilization of the *s-cis* TSs (by 0.2−2.2 kcal mol^{-1}) can be found.

Calculations on the thermal 1-pyrroline-1-oxide + methacrolein reaction including solvent modeling show a preference for 5,5- (rather than 4,4-) and *endo* (rather than *exo*) TSs, in agreement with experimental data showing the exclusive formation of the 5,5-*endo* stereoisomer.[16] Solvent modeling induces the preferential stabilization of the *s-trans* (excepting a negligible variation corresponding to the 4,4-*exo* approach). As a result, a preference for *s-trans* TSs is found for all approaches in solution.

Some trends can be observed for the incorporation of solvent modeling on the BH_3-catalyzed 1-pyrroline-1-oxide + methacrolein reaction. Thus, a rise of the activation barrier, as well as a decrease of the 4,4- and *endo*-preferences is generally found. Interestingly, a significant relative stabilization of the *s-trans*

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TABLE 4. Activation Parameters (Gibbs Free Energies, Enthalpies, and Entropies) for the 1,3-Dipolar Cycloaddition Reaction (Gas-Phase, Solution, and BH$_3$-Catalyzed Versions) between Diphenylnitrone and Methacrolein, According to B3LYP/6-31G* Calculations

	gas phase (thermal)			gas phase (BH$_3$-catalyzed)			solution (thermal)			solution (BH$_3$-catalyzed)	
approach	$\Delta G^{\ddagger\ b}$	$\Delta H^{\ddagger\ b}$	$\Delta S^{\ddagger\ c}$	$\Delta G^{\ddagger\ b}$	$\Delta H^{\ddagger\ b}$	$\Delta S^{\ddagger\ c}$	$\Delta G^{\ddagger\ b}$	$\Delta H^{\ddagger\ b}$	$\Delta S^{\ddagger\ c}$	$\Delta G^{\ddagger\ a,b}$	$\Delta H^{\ddagger\ a,b}$
4,4-*endo s-cis*	32.3	18.3	−46.8	23.9	8.7	−51.0	33.9	20.2	−46.1	21.1	5.8
4,4-*endo s-trans*	31.0	17.2	−46.3	21.8	7.5	−48.0	32.3	18.5	−46.1	19.3	6.0
4,4-*exo s-cis*	33.9	20.2	−46.0	26.7	12.4	−47.9	35.6	21.8	−46.0	22.7	9.8
4,4-*exo s-trans*	32.0	18.4	−45.6	25.2	11.8	−45.0	33.5	20.1	−45.2	22.6	9.5
5,5-*endo s-cis*	29.4	16.0	−44.9	24.5	10.9	−45.7	32.0	18.4	−45.5	18.8	5.4
5,5-*endo s-trans*	28.7	14.9	−46.1	23.2	9.8	−45.1	29.9	16.3	−45.4	18.3	6.2
5,5-*exo s-cis*	32.9	19.4	−45.5	28.9	15.4	−45.1	36.0	20.8	−51.0	24.3	11.7
5,5-*exo s-trans*	31.5	23.9	−51.0	27.3	13.9	−44.9	33.2	19.5	−45.9	23.8	11.3

[a] Calculated at gas-phase optimized geometries. [b] Energy given in units of kcal mol^{-1}. [c] Entropy given in units of cal mol K^{-1}.

TSs can be encountered, leading to a systematic *s-trans* preference for all approaches.

The calculated geometry for diphenylnitrone shows a coplanar arrangement of the *C*-phenyl substituent relative to the nitrone functional group, whereas a skew disposition is found for the *N*-phenyl group (Figure 5), in agreement with experimental data.[56] Such features indicate the full conjugation of the *C*-phenyl group, but only partial conjugation of the *N*-phenyl substituent, both effects being kept in all TSs.

Results on activation parameters for the reaction between diphenylnitrone and methacrolein are presented in Table 4. The calculated activation enthalpy for the most favored approach (14.9 kcal mol^{-1}) is close to the experimental value for the *N*-methyl-*C*-phenylnitrone + methyl methacrylate reaction in toluene (15.7 kcal mol^{-1}). Conversely, a significant discrepancy can be found for activation entropies (calculated, −46.1 cal mol^{-1} K^{-1} at 25 °C, −45.9 cal mol^{-1} K^{-1} at 85 °C; experimental value of the aforementioned reaction at the 85−120 °C range, −32.4 cal mol^{-1} K^{-1}),[57] analogous to the results for the cyclopentadiene + methacrolein Diels−Alder reaction.

Gas-phase activation barriers for the diphenylnitrone + methacrolein reaction are relatively high (28.7−33.9 kcal mol^{-1}), indicating that the Curtin−Hammett principle is met. These activation barriers are significantly larger than those corresponding to 1-pyrroline-1-oxide (by 4.0−7.2 kcal mol^{-1}), in agreement with kinetic data for the reactions with ethyl crotonate in solution (showing a greater reactivity of 1-pyrroline-1-oxide by 2.2 kcal mol^{-1}).[57]

The lower reactivity of diphenylnitrone in comparison with the parent nitrone cannot be understood in terms of the Perturbation Theory (unrelated to the reaction thermodynamics) since the substitution of nitrone by phenyl groups leads to a rise of the HOMO energy and, hence, to a decrease of the HOMO$_{\text{nitrone}}$−LUMO$_{\text{dipolarophile}}$ gap.[58] However, the high activation barriers of the diphenylnitrone reaction can instead be attributed to the gradual loss of conjugation between the nitrone group and the *C*-phenyl substituent (as revealed by ^{17}O NMR)[59] throughout the process.

Theoretical results on the gas-phase diphenylnitrone + methacrolein reaction show a preference for the 5,5-cycloadducts (by 0.5−2.9 kcal mol^{-1}), in agreement with experimental data indicating the exclusive formation of 5,5-adducts at room temperature.[10a,55] Such a result can be again attributed to the formation of stabilizing O···C═O interactions (rather than to steric control).[60] A high *endo* over *exo* preference (by 1.0−3.5 kcal mol^{-1}) is also found in all cases, in agreement with the total experimental *endo* selectivity.[10a,55] Furthermore, a preference for the *s-trans* conformation is found for all approaches, in contrast with results corresponding to the parent nitrone, where an *s-cis* preference is generally observed. Such a behavior difference might be attributed to low nitrone···C═O stabilizing interactions (favoring *s-cis* conformations) in the diphenylnitrone + methacrolein reaction because of the charge delocalization through the *C*-phenyl substituent. We can observe that the preference for the *s-trans* conformation in this cycloaddition reaction (by 0.7−1.9 kcal mol^{-1}) is lower than that for isolated methacrolein (2.7 kcal mol^{-1}); in that way the methacrolein *s-cis* conformer is indeed more reactive than the *s-trans* form (by 0.7−1.9 kcal mol^{-1}), as encountered for the Diels−Alder cyclopentadiene + methacrolein reaction.

Some of the trends observed for the BH$_3$ coordination to methacrolein in the reaction with diphenylnitrone are very similar to those corresponding to the parent nitrone. Thus, the preferential stabilization of the 5,5-TSs leads to a regioselectivity reversal, which is consistent with experimental results for the diphenylnitrone + methacrolein reaction involving different Lewis acids.[10a,55,60] Furthermore, a high *endo* preference is predicted for the catalyzed reaction, in agreement with experimental results showing a total *endo*/*exo* selectivity.[10,16,60] However, a relative stabilization of the *s-trans* TSs can be observed for all approaches of the diphenylnitrone reaction (excepting the 4,4-*exo* approximation), in contrast with the preferential stabilization of *s-cis* conformations in reactions involving other nitrones. As a result, an *s-trans* preference is predicted for all approaches.

Whereas theoretical calculations on the parent nitrone + methacrolein cycloaddition show a clear preference for *endo s-cis* TSs in both 4,4- and 5,5-approaches (due to the existence of electrostatic interactions), our computations on the diphenylnitrone + methacrolein reaction indicate a predilection for the *endo s-trans* structure. Thus, it can be inferred that the parent nitrone is not a good model of diphenylnitrone for 1,3-dipolar cycloaddition reactions, in contrast with the assumptions usually made in theoretical studies.[18,53,61]

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Results obtained from the solvent modeling on the diphenylnitrone + methacrolein reaction show the same trends as those from the reaction of the parent nitrone (excepting the lack of anomalous results derived from the $N^+{-}H{\cdots}O{=}C$ electrostatic interactions, due to the *N*-phenyl substitution). Thus, a slight increase of the activation barriers is found (by 1.2−3.1 kcal mol^{-1}), in agreement with experimental data on solvent effects on the *N*-methyl-*C*-phenylnitrone + ethyl acrylate reaction.[57] A slight increase in the relative stabilities of the 5,5-, *endo,* and *s-trans* TSs is also found.

Some interesting results can be found for the solvent modeling on the BH_3-catalyzed diphenylnitrone + methacrolein reaction. Thus, a significant decrease of the activation barriers as well as the relative stabilization of the 5,5- and *endo* TSs can be observed. Interestingly, despite the systematic differential stabilization of the *s-cis* TSs, an *s-trans* preference is observed in all cases.

Conclusions

The *s-cis*/*s-trans* preference of methacrolein in Diels−Alder and 1,3-dipolar cycloaddition reactions derives from a delicate balance between the larger stability of the *s-trans* conformer of ground-state methacrolein and the larger reactivity of the corresponding *s-cis* conformation. As a consequence, varied behavior is found in gas-phase calculations (from the systematic *s-cis* preference of cyclopentadiene to the systematic *s-trans* predilection of diphenylnitrone). Dichotomous behavior is found in BH_3-catalyzed reactions: *s-trans* TSs are preferentially stabilized in processes involving cyclopentadiene (*exo* approach) and diphenylnitrone, but *s-cis* geometries are more stabilized in reactions of parent nitrone and 1-pyrroline-1-oxide. However, solvent modeling induces a rather systematic preferential stabilization of *s-trans* structures for both thermal (all four reactions) and catalyzed (Diels−Alder) reactions. The preferential stabilization of the *s-trans* conformation by solvent polarity[62] and coordination of a Lewis acid[63] has already been reported in experimental studies on the cyclopentadiene + menthyl acrylate reaction.

The *s-trans* preference predicted for methacrolein in catalyzed Diels−Alder and 1,3-dipolar cycloaddition reactions in solution is consistent with experimental data on reactions catalyzed by an Ir(III) catalyst showing a preferential attack of cyclopentadiene,[64] 1-pyrroline-1-oxide,[10b] and diphenylnitrone[10b] through the same side of the chiral catalyst−methacrolein complex.

Nevertheless, some care should be taken in the extrapolation of the theoretical results of our study to experimental systems because of the simplicity of borane as a Lewis acid and the use of a dielectric continuum as a solvent. Thus, a lesser *s-trans* preference (or even an *s-cis* predilection) might be expected for mild Lewis acids and apolar solvents. On the other hand, other effects, such as the steric hindrance of the catalyst or the formation of specific interactions between the methacrolein complex and the counterpart reactant, can also significantly affect the *s-cis*/*s-trans* conformational preference.

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Supporting Information Available: Thermodynamical properties (internal and free energies, enthalpies, entropies) and Cartesian coordinates of all studied structures (for both gas-phase and solution conditions). This material is available free of charge via the Internet at http://pubs.acs.org.

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