The Role of Menthyl Group in Catalyzed Asymmetric Diels−Alder Reactions. A Combined Quantum Mechanics/Molecular Mechanics Study

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The asymmetric Diels−Alder reactions of cyclopentadiene with the complex dienophiles $AlCl_3$−menthyl acrylate and menthoxyaluminum dichloride−acrolein have been studied by means of combined Quantum Mechanics/Molecular Mechanics calculations. The part of the system involved in the reaction has been described using the AM1 method, whereas the MM3 force field has been used in order to account for interactions with the menthyl substituent. We focus our attention on the screening effect produced by the menthyl group, which may be placed in the dienophile or the catalyst. A reaction model has been proposed for the cycloaddition between cyclopentadiene and acrolein catalyzed by menthoxyaluminum dichloride, presenting different geometrical features from those proposed for an analogous reaction. Results indicate that the menthyl group adopts a stacked conformation preferentially, in contrast with previous Molecular Mechanics studies of similar systems. The weak steric hindrance of this conformation allows us to explain the rather low screening effect of the menthyl group. Finally, our results show that the use of the combined AM1/MM3 methodology avoids the artifactual stabilizations of nonbonded hydrogen atom pairs found in full AM1 calculations.

Introduction

The asymmetric Diels−Alder (ADA) reaction is one of the most useful tools to obtain chiral compounds,[1,2] this fact being explained by the one-step formation of two carbon−carbon bonds with several types of stereochemical control.[3] For instance, ADA cycloadditions have been successfully used in the generation of asymmetry in carbon atoms during the total syntheses of many natural compounds, such as prostaglandins, sarkomycin, or shikimic acid.[2]

The asymmetric induction in Diels−Alder reactions can be carried out by linking chiral auxiliaries to at least one of the compounds participating in the cycloaddition: diene,[2] dienophile,[2] and catalyst.[4] Menthol is one of the most common chiral auxiliaries in asymmetric synthesis because of the commercial availability and low cost of both enantiomers.[5] Compounds derived from this and other related alcohols have been used in ADA reactions as dienophiles or catalysts.[5] Obviously, a good knowledge of the features of the menthyl group may help in the design of more efficient chiral auxiliaries. In particular, the influence of the conformation of the isopropyl group on the screening effect of the menthyl substituent is not well-known. Besides, the orientation of the menthyl group in a menthoxyaluminum dichloride−dienophile complex is controversial, and various ADA reaction models[6−8] have been based on the assumption of different conformational features.

Theoretical investigation may throw some light on the exact role that the menthyl group plays in ADA reactions. Unfortunately, the use of quantum mechanical calculations is seriously limited in the field of asymmetric synthesis due to the large size of the systems of experimental interest. Thus, high-level calculations (such as MP3/6-31G* [9] or BLYP/6-31G*)[10] can only be envisaged at present for relatively simple systems. Semiempirical calculations are an alternative,[10,11] though it must be pointed out that these methods present some limitations due to their poor performance for medium-range nonbonding interactions.[12,13] Some effort has also been devoted to the development of Molecular Mechanics (MM) models,[14] but the applicability of such an approach is far from being general since MM potentials cannot be easily

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Chart 1

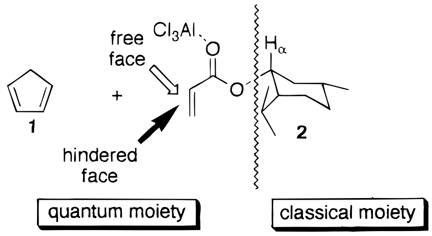
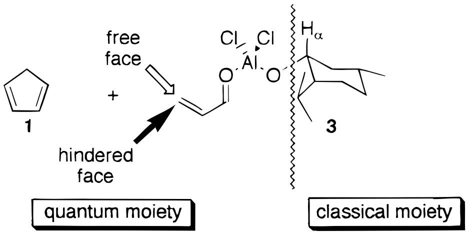


Chart 2



defined to account for formation and breaking of bonds. Hence, new and more general models are clearly needed in order to predict the selectivities of asymmetric reactions.

A possible way to investigate the reactivity of large systems, which assumes the additivity of electron correlation, basis set, and system effects, has been regarded for some nonasymmetric Diels−Alder reactions.[15] However, the most promising approach to this kind of studies is the coupling of Quantum Mechanics (QM) and MM methods.[16] In these combined QM/MM calculations, the atoms participating in the reaction and those close to them are described by means of QM calculations, whereas the rest of the system is treated through the use of MM force fields. The Hamiltonian of the QM subsystem accounts for the QM/MM interactions including electrostatic and van der Waals terms. The combined QM/MM approach has already been used to study some thermal intramolecular Diels−Alder cycloadditions.[17]

A common problem to all combined methods is the treatment of the QM/MM frontier atoms. Some authors have proposed to replace the MM system by hydrogen or other atoms when computing the wave function of the QM system,[16] whereas others have developed the local self-consistent field (LSCF) method.[18] In the later case, the bond between frontier atoms is described by a frozen-localized molecular orbital.

In this paper, we present theoretical results for the reaction of cyclopentadiene with menthyl acrylate catalyzed by $AlCl_3$ and the reaction of the same diene with acrolein catalyzed by menthoxyaluminum dichloride. The representation of the reactants is shown in Charts1 and 2.

Our aim is 2-fold. First, we analyze the difference between the screening properties of the menthyl group when it is placed in the catalyst or the dienophile. Obviously, this requires a prior investigation of the possible conformations of the dienophile−catalyst complex, which is of primary importance in order to interpret the observed diastereoselectivities. Second, we examine the role of the isopropyl group conformation. The conclusions obtained allow one to predict the influence of other substituents, such a *tert*-butyl group, on the diastereoselectivity.

We have used a combined AM1/MM3 approach. This choice has been done for two reasons. First of all, the use of a molecular mechanics potential to describe the menthyl group avoids the artifactual stabilizing interactions exhibited by AM1 in the study of this type of reactions (see below). Besides, the combined AM1/MM3 approach can be suitable to study other reactions with larger substituents, and the present computations can serve as a test case of the method. Although the combined AM1/MM3 method cannot be expected to yield quantitative selectivities, it is well adapted to investigate qualitatively the role of the chiral auxiliary, which is the scope of the present work. For comparison, full AM1 calculations have also been carried out for all the structures considered.

For the sake of simplicity, the faces of the vinyl group in the dienophiles considered will be named throughout this paper as “hindered” or “free”, depending on the relative position of the isopropyl group.

Methods

The combined QM/MM method used has been described in previous papers.[18] Combined QM/MM calculations of dienophiles and TSs were carried out with the GEOMOP program.[19] This is a modification of the GEOMOS program,[20] which accounts for interactions between QM and MM subsystems within the LSCF approximation. The Hamiltonian of the QM subsystem includes the interactions with the MM one.

QM calculations were carried out by means of the semiempirical AM1 method,[21] which leads to transition-structure (TS) geometries of Diels−Alder reactions in qualitative agreement with those obtained by means of HF/6-31G*[22] and BLYP/6-31G* calculations.[23] For the force field, the MM3 method was chosen due to its good performance in van der Waals interactions[13] and conformational equilibria.[24] Standard MM3 van der Waals parameters,[25] as well as those recently proposed for inorganic chlorine,[26] were included in the GEOMOP program.

In all combined AM1/MM3 calculations, the classical part described by the MM3 force field is limited to the menthyl group. Because of the possibility of rotation for the isopropyl substituent in this group, three conformations of the classical subsystem were considered for all the structures studied. The nomenclature used in this work for these conformers is based

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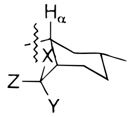
Chart 3



axial X=H, Y=Z=CH_3
equatorial Y=H, X=Z=CH_3
stacked Z=H, X=Y=CH_3

on that proposed by Maddaluno et al.,[27] though the original name for the “trans” conformation has been substituted by “equatorial” in order to avoid confusion with the s-trans conformer of α,*β*-unsaturated carbonyl compounds. Thus, menthyl conformers will be named throughout this work as axial, equatorial, and stacked (see Chart 3). It can be expected that the corresponding conformational equilibrium is closely related to the discriminating ability of the chiral auxiliary, so that all three conformers were systematically considered throughout this work.

Since the classical part of our system contains only $C_{sp^3}-H$ and $C_{sp^3}-C_{sp^3}$ bonds, the AM1/MM3 interactions are limited to van der Waals terms; i.e., there are no electrostatic interactions. The following parameters are necessary for QM/MM LSCF calculations: length of the border bonds as well as electronic population and hybridization coefficient of the localized orbital on the frontier quantum atoms. These values were calculated for stacked conformers of **2** and **3** by using the Ruedenberg's method of molecular orbital localization[28] by means of a full AM1 calculation of these structures and using the GEOMOP program.

The geometries of all three conformers of the menthyl group have been obtained from MM3 calculations of **2** with the TINKER program.[29] MM3 parameters corresponding to esters[30] and conjugated ketones[31] had been incorporated in the TINKER parameters file. In addition, a new torsion parameter set for the connection of atom types $H-C_{alkene}-C_{ester}-O_{C-O-C}$ had also been included. It was based on that used by Corey and Ponder[32] for MM2 calculations and corrected in order to describe the relative energies of methyl acrylate conformers at the MP3/6-311++G**//RHF/6-311++G** level.[33] The corresponding values were the following: $V_1 = 1.168$, $V_2 = 10.516$, and $V_3 = 0.000$.

For combined AM1/MM3 calculations, all internal coordinates corresponding to the quantum moiety were optimized, except for the position of the atom bonded to the frontier quantum atom. The coordinates of this atom, which defines the relative orientation between quantum and classical moieties, were obtained from MM3 (AM1) calculations for all three conformers of *s-trans*-**2** (*s-cis*-**3**) for the study of the corresponding reactivity.

Interactions between atoms belonging to the “classical moiety” were obtained by means of MM3 calculations and using TINKER program. Results indicated that interactions within the menthyl group favor the axial conformer relative to equatorial and stacked conformations by 0.4 kcal/mol, both later forms presenting the same energy.

In addition to these QM/MM computations, some full QM calculations were carried out for comparative purposes, both at semiempirical and density functional levels. Full AM1 calculations were achieved by means of the GEOMOP program. In the case the BF_3-catalyzed reaction between cyclopentadiene and methacrolein, exo s-cis and exo s-trans TSs were located by means of Schlegel's algorithm[34] by using the B3LYP functional[35] and the 3-21G basis set as implemented in the Gaussian94 package.[36]

Table 1. AM1 Relative Energies (kcal/mol) of Different Conformations of 2 Depending on the H$_\alpha$−C−O−C Dihedral Angle (Isopropyl Group in Stacked Position)

dihedral angle (deg)	energy	dihedral angle (deg)	energy
−150	3.6		
−120	8.2	60	0.9
−90	13.9	90	3.9
−60	6.7	120	8.2
−30	1.5	150	3.6
0	0.5	180	1.2
30	0.1	global minimum (38)	0.0

All TSs were characterized by the presence of only one negative eigenvalue of the corresponding exact Hessian matrices.

Results and Discussion

Let us first make some comments concerning the conformation of **2**. In general, the coordination of acrylic esters with Lewis acids induces a shift on the s-cis/s-trans conformational equilibrium toward the s-trans form.[37] Furthermore, experimental[2] and theoretical[38,39] studies have shown that catalyzed Diels−Alder reactions of these dienophiles proceed mainly through s-trans TSs. For this reason, only this conformation has been considered for **2** in this study.

On the other hand, possible rotation around the border bond in **2** has to be considered. A rotational analysis has been carried out using AM1 relative energies of different conformations derived from rotation of the H$_\alpha$−C−O−C dihedral angle of **2** in the stacked form, and results are shown in Table 1. The data exhibit a significant energy variation depending on the dihedral angle, the most stable conformation corresponding to 38°. This value is exactly that found in MM3 calculations and agrees with experimental data on the most stable conformation (nearly syn-periplanar) of esters derived from secondary alcohols.[40]

For the study of the effect of the isopropyl group rotation, combined AM1/MM3 as well as full AM1 calculations were achieved, relative energies of all three conformers (axial, equatorial, and stacked) of **2** being shown in Table 2. Irrespective of the method considered, results indicate a preference for the stacked conformation, in contrast with molecular mechanics studies for *s-trans*-menthyl crotonate[27] and $TiCl_4$−(menthyl acry-

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Table 2. Relative Energies (kcal/mol) of Conformers of 2 after Combined AM1/MM3 and Full AM1 Calculations

conformation	combined AM1/MM3 energy	full AM1 energy
axial	1.1	1.3
equatorial	0.3	0.9
stacked	0.0	0.0

Table 3. Relative Energies (kcal/mol) of Transition Structures for the Reaction between 1 and 2 after Combined AM1/MM3 and Full AM1 Calculations

approximation	conformation	attacked face	combined AM1/MM3 energy	full AM1 energy
endo	axial	hindered	4.6	2.5
endo	axial	free	2.1	2.0
endo	equatorial	hindered	3.2	2.2
endo	equatorial	free	1.4	1.5
endo	stacked	hindered	1.0	0.5
endo	stacked	free	0.9	0.6
exo	axial	hindered	4.2	3.0
exo	axial	free	1.0	1.4
exo	equatorial	hindered	6.5	2.7
exo	equatorial	free	0.4	1.0
exo	stacked	hindered	0.7	0.2
exo	stacked	free	0.0	0.0

late)$_2$ complex,[41] where equatorial and axial conformers, respectively, are preferred. The results obtained in the present work can be explained by larger steric repulsions when the methyl group is placed in position Z in both axial and equatorial conformations. These results agree with experimental data indicating that most menthyl esters adopt the stacked conformation in the solid state,[42] though some exceptions are known.[43]

For the reaction between **1** and **2**, there are 12 possible transition structures resulting from endo/exo attack on the free/hindered face of the dienophile and all three conformations of the menthyl group (axial, equatorial, and stacked). The combined AM1/MM3 and full AM1 relative energies corresponding to these TSs are gathered in Table 3. The structure of stacked conformations that are energetically clearly are displayed in Figure 1. The combined AM1/MM3 TSs considered present the typical geometrical features described for AM1 calculations on Diels–Alder reactions,[44] with bond-forming lengths ranging between 1.97 and 2.32 Å.

Note that for a given attacked face and conformation of the menthyl group, combined AM1/MM3 results indicate a preference for the exo approximation, which is a general trend in AM1 calculations for carbonyl dienophiles. Experimentally, the endo/exo selectivity in solution has been determined[45] and shows that the endo structure is preferred.

Combined AM1/MM3 calculations predict in all cases that the attack through the free face is preferred over the corresponding attack through the hindered one, in agreement with experimental results.[45] This result is due to the steric repulsion between isopropyl group and cyclopentadiene. Stacked conformations lead to lower diastereofacial selectivities (compare free and hindered face energies) than those corresponding to axial and equatorial forms. This is explained by the different steric screening of the group present in the Z position (see Chart 3), being a hydrogen atom in the case of the stacked conformation and a methyl group in the other cases. In fact, the small size of hydrogen atom leads to a very low diastereofacial selectivity for the endo approximation on the stacked conformer. Since calculations indicate that the stacked TSs are also the most stable ones, our results are consistent with the rather low experimental screening effect of menthyl group.[5] It may be expected from the results shown in Table 3 that the presence of a methyl group in position Z should lead to a noticeable increase of the diastereofacial selectivity. Further AM1/MM3 calculations carried out for model transition structures derived from the previous ones through the replacement of the isopropyl group in the menthyl moiety by a *tert*-butyl substituent support this conclusion. Thus, the free-face attack is favored over the hindered-face one by 1.4 kcal/mol for endo approach and by 3.1 kcal/mol for the exo one. These results compare well with experimental data on Paternò–Büchi reactions that show a noticeable increase of diastereofacial selectivity when the aforementioned replacement is considered.[46]

Irrespective of the menthyl group conformation, the exo approximation leads to larger diastereofacial selectivities than the endo approximation, in agreement with experimental results found for various ADA reactions.[45,47]

The experimental diastereofacial selectivity through the endo approximation for the reaction between **1** and **2** at 25 °C (adducts ratio = 2.50)[45] corresponds to an energy difference of 0.5 kcal/mol, slightly larger than the values predicted by our combined AM1/MM3 calculations (0.1 kcal/mol). In contrast, a MM study carried out for this reaction by Houk and co-workers showed a significantly larger value (1.8 kcal/mol).[38] However, from Figure 2 of that paper one can note that the conformation of the menthyl group assumed by the authors is stacked (equatorial) for the attack through the free (hindered) face. If we assume the same conformations, using the values in Table 2, one deduces a diastereofacial selectivity equal to 2.3 kcal/mol, which is close to that reported by Houk.

Therefore, the order of magnitude of the diastereofacial selectivity predicted by the combined AM1/MM3 computations is reasonable considering the approximate nature of the approach. The computations predict a stacked conformation for the isopropyl group, and it can be noted that the diastereofacial selectivities that could be obtained using other isopropyl structures would lead to substantially larger values than the experimental quantity.

Full AM1 results show, in general, the same trends that combined AM1/MM3 calculations for the reaction

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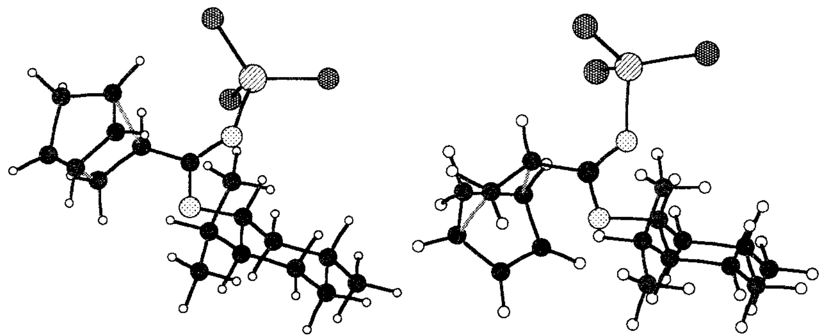
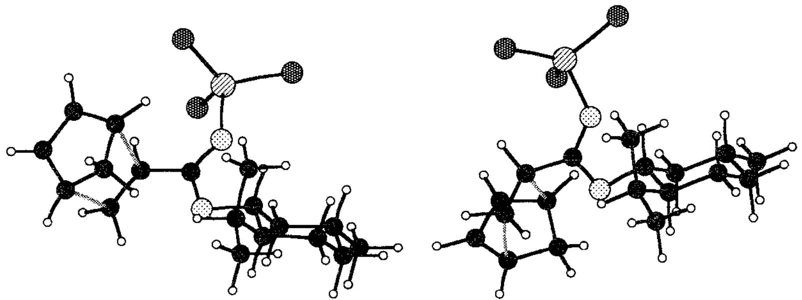


(endo approximation, hindered face) (endo approximation, free face)



(exo approximation, hindered face) (exo approximation, free face)

Figure 1. Stacked TSs for the reaction **1** + **2** after combined AM1/MM3 calculations.

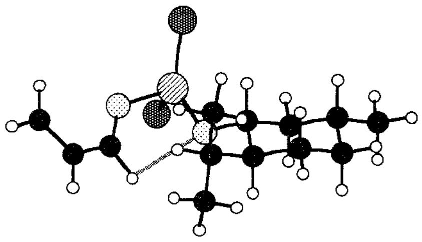


Figure 2. AM1 structure for **3**.

between **1** and **2**. However, a preference for the cyclopentadiene attack to the hindered face of stacked **2** can be observed for the endo approximation, leading to a wrong prediction of the major adduct of the reaction. Inspection of the AM1 geometries shows a pair of nonbonded hydrogen atoms situated at 2.38 Å in the hindered-face TS. As shown before, hydrogen atom pairs at distances near 2.3 Å lead to artifactual stabilizations of ca. 0.3 kcal/mol,[13] which allow us to explain the wrong selectivity predicted by AM1 method.

For the cycloaddition between **1** and **3**, the combined AM1/MM3 methodology was also used. A similar reaction has been investigated experimentally but using methacrolein instead of acrolein.[6−8,48] Our choice for acrolein is based on the results of a preliminary AM1 study for the BF_3- and $AlCl_3$-catalyzed reactions between cyclopentadiene and methacrolein. Indeed, such a study indicated a two-step mechanism. Experimentally, results indicate that Diels−Alder reactions of cyclopentadiene with acrolein and methacrolein catalyzed by chiral Lewis acids lead to similar enantiomeric excesses,[50] suggesting a concerted mechanism for both reactions and a minor role for the methyl group in methacrolein. Furthermore, density functional calculations (at the B3LYP/6-31G* level) on the BF_3-catalyzed reaction between cyclopentadiene and methacrolein agree with a concerted mechanism. These computations have also predicted a larger stability of the s-cis TS (by 0.9 kcal/mol) relative to the s-trans one for the exo approach, in agreement with B3LYP/6-31G* results[49] obtained for the BF_3-catalyzed cycloaddition between butadiene and acrolein. For this reason, only s-cis conformers have been considered for the study of the reactivity of **3**.

An exhaustive examination of the potential energy hypersurface of the s-cis conformation of **3** was achieved by means of full AM1 calculations and allowed the localization of a plethora of energy minima. The ensemble of these energy minima may be separated into two groups depending on the existence or not of a hydrogen bond between the aldehydic hydrogen and the oxygen atom of the menthoxy group. Such an interaction is substantially stabilizing and is present in the global minimum, as represented in Figure 2. The existence of this hydrogen-bonded structure agrees with that recently proposed by Corey et al.,[8] though other previous reaction models did not exhibit hydrogen bonds.[6,7] The main differences between the geometry found here and the model proposed by Corey (for the corresponding reaction with methacrolein)[8] lie on the dienophile conformation and the relative orientation of the menthyl group. These features are represented in Chart 4 for the reaction between **1** and **3** (A, model proposed here; B, Corey's model).[8]

It is important to note that the attack of the diene through the free (or hindered) faces of A and B models would lead to the same adducts. The choice of the s-trans conformation for the dienophile in model B[8] was not clearly justified, and in fact, the s-cis conformation was proposed in later studies by Corey et al.[51] of the same reaction when other catalysts were considered. The

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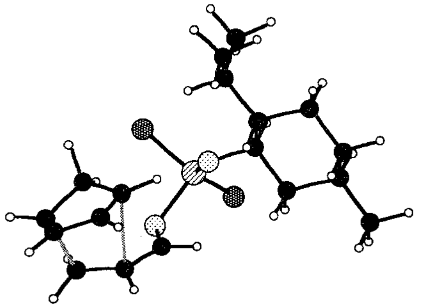
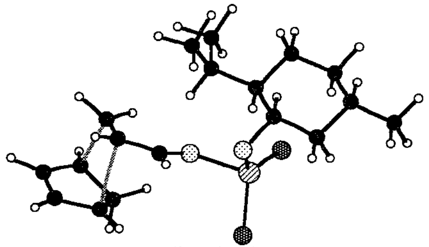


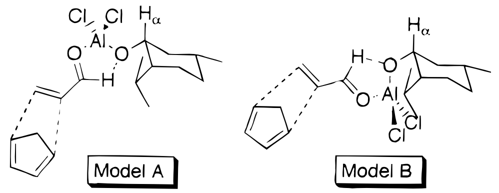
(hindered face)



(free face)

Figure 3. Stacked TSs for the reaction **1** + **3** after combined AM1/MM3 calculations.

Chart 4



choice of the s-cis conformation in our model is supported by the clear preference for s-cis TSs shown in B3LYP/3-21G calculations for the BF_3-catalyzed reaction between cyclopentadiene and methacrolein. Obviously, the choice of the s-trans or s-cis conformation is quite important and cannot be dissociated from the relative position of the aluminum atom with respect to the menthyl α hydrogen atom. Thus, the structure in Figure 3 displays a dihedral angle H_α–C–O–Al of 39° (i.e., nearly syn-periplanar), in contrast with the anti-periplanar conformation shown in Corey's model. The nearly syn-periplanar arrangement of our model agrees with experimental data for several aluminum isopropoxides (absolute values being lesser than 60° if bridged alkoxy groups are disregarded).[52]

As we have shown previously for the reaction between **1** and **2**, the conformation of the menthyl group is an important aspect of the reaction model. Concerning this, our results indicate a preference for the stacked conformation, in agreement with experimental data of various aluminum menthoxides.[53]

Table 4. Relative Energies (kcal/mol) of Conformers of 3 after Combined AM1/MM3 and Full AM1 Calculations

conformation	combined AM1/MM3 energy	full AM1 energy
axial	5.2	1.7
equatorial	4.6	1.7
stacked	0.0	0.0

Table 5. Relative Energies (kcal/mol) of Exo Transition Structures for the Reaction between 1 and 3 Calculated after Combined AM1/MM3 and Full AM1 Calculations

conformation	attacked face	combined AM1/MM3 energy	full AM1 energy
axial	hindered	4.5	1.9
axial	free	3.9	1.9
equatorial	hindered	3.1	1.7
equatorial	free	3.2	1.7
stacked	hindered	0.0	0.2
stacked	free	0.0	0.0

Relative energies of axial, equatorial, and stacked conformers of **3** obtained with combined AM1/MM3 and full AM1 methods are shown in Table 4, both predicting the stacked form to be the most stable form. The analysis of combined QM/MM energy terms allows us to conclude that this result is due to considerable van der Waals repulsion of the oxygen frontier and aluminum atoms with the isopropyl group. According to combined AM1/MM3 results, this effect is larger in axial and equatorial conformations, whereas full AM1 calculations predict a similar stability for both conformers.

In the study of the reaction between **1** and **3**, endo TSs were excluded because of the impossibility to locate the corresponding geometries, analogously to earlier ab initio RHF calculations for the BF_3-catalyzed reaction between butadiene and acrolein.[49] Disregarding the endo TSs does not affect the analysis of the results, since the exo structures lead to the major adducts of the reaction.[48] Relative energies are shown in Table 5. Because of the greater stability of stacked TSs, only these structures are shown in Figure 3. The TSs studied present features analogous to other Diels–Alder TS geometries at the AM1 level,[33] with bond-forming lengths ranging between 1.95 and 2.43 Å.

The experimental selectivity for this reaction (using methacrolein instead of acrolein) may be estimated to be 0.5 kcal/mol (calculated from 57% enantiomeric excess for the reaction achieved at −78 °C).[6] This value is close to that found for the reaction between **1** and **2** described above. It confirms that the menthyl group induces a small selectivity and that this property is similar independent of the use of a chiral catalyst or a chiral dienophile. Both combined AM1/MM3 and full AM1 computations predict a preferential attack to the stacked conformation of the menthyl group. The former method predicts a negligible selectivity, whereas the latter predicts a very low preference for the free-face attack. It could be concluded that AM1 results are better than combined AM1/MM3, but the relatively good agreement between experiment and AM1 is fortuitous. Indeed, as in the case of the reaction **1** + **2** above, inspection of the geometries of the TSs shows that AM1 calculations predict the occurrence of nonbonding interactions between hydrogen atom pairs for the cyclopentadiene

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attack, but in this case, such interactions are present for the attack through the free face of the stacked conformation.

Before ending the discussion, the role of the solvent on ADA reactions must be commented on since effects of the medium can modify significantly the selectivities of Diels–Alder reactions.[54] In the case of diastereofacial selectivity, noticeable medium effects are expected for the reactions of α,β-unsaturated carbonyl compounds when the energy difference between s-cis and s-trans transition states is low.[55] In the reactions studied here this is not the case, the diastereofacial selectivity being essentially determined by the differential interactions in the attack through the free and hindered faces. The corresponding transition structures exhibit similar charge distribution and polarity, and therefore, the solvent effect is expected to be very slight. It could modify the diastereofacial selectivity a little bit, but it would not change appreciably the conclusions on the role of the menthyl group, which is the main subject of the present work. We must note, however, that due to the small selectivities predicted by our calculations, the role of solvent on the diastereofacial selectivity cannot be completely disregarded.

Conclusions

The Diels–Alder reactions of cyclopentadiene with $AlCl_3$–menthyl acrylate and menthoxyaluminum dichloride–acrolein complexes were studied by means of combined AM1/MM3 calculations and compared to full AM1 results.

In most cases, AM1 results are qualitatively similar to those obtained with the combined AM1/MM3 approach. However, the artifactual stabilization of hydrogen atom pairs placed at ca. 2.3 Å can lead to anomalous results, such as the wrong prediction of the major adduct of the **1** + **2** reaction.

In general, the attack of the diene through the free face of the dienophile-catalyst complex is predicted to be more favorable. However, in some cases, the energy difference of the corresponding TSs is very low or even zero. The experimental values of diastereofacial selectivities for the corresponding reactions are also low (0.5 kcal/mol).

The weak steric hindrance of the most stable stacked conformations allows us to explain the low screening effect of the menthyl group. Though this screening effect obtained for the two reactions studied is always small, combined AM1/MM3 results predict that the discriminating power of the menthyl group is a little larger when it is carried out by the dienophile. Our results can be also used to predict the screening effect of other substituents since we have computed the energies of all the possible transition sturctures resulting from the three possible conformations of the isopropyl group. These results contrast with previous MM calculations, which predicted the axial[41] and the equatorial[27] conformations to be the most stable in related compounds.

A reaction model has been proposed for the menthoxyaluminum dichloride-catalyzed cycloaddition between cyclopentadiene and acrolein, which presents substantial differences relative to other models described in the literature for an analogous reaction. The model proposed in this work assumes an s-cis TS, which presents a formyl–menthoxy hydrogen bond as well as a nearly synperiplanar conformation for the atom sequence H_α–C–O–Al. These geometrical characteristics are supported by theoretical and experimental results.

Quantitative prediction would require carrying out more sophisticated computations. This could be done by using the combined QM/MM approach with high-level methods to describe the QM part and more ellaborated force fields in the classical part. Nevertheless, the main interest of combined AM1/MM3 results is that they allow to make a qualitative analysis of the main factors that permit to increase the efficiency of chiral auxiliaries.

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