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Conformational Aspects of some Asymmetric Diels-Alder Reactions. A Molecular Mechanics + Polarization Study

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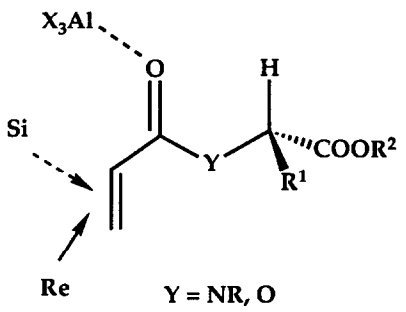
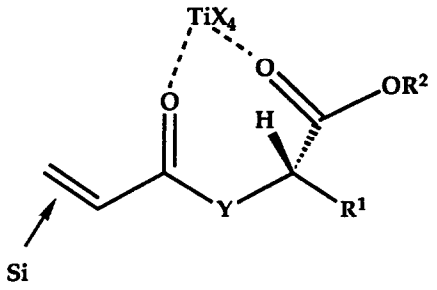
Abstract: The MM2 force field, improved by the inclusion of interacting induced dipole (ID) energies, is used to calculate the conformational preferences of three chiral dienophiles: Acrylate of (S)-ethyl lactate (**1**), N-acryloyl-L-phenylalanine methyl ester (**2**), and N-acryloyl-L-alanine methyl ester (**3**). The results obtained agree with the models previously proposed to account for the asymmetric induction obtained in the reaction of these dienophiles with cyclopentadiene.

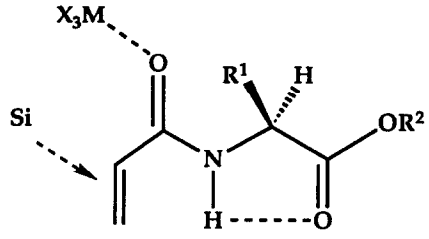
Acrylates of chiral α-hydroxy acid derivatives[1] and N-acryloyl-α-amino acid derivatives[2] have been used as chiral dienophiles in asymmetric Diels-Alder reactions. It has been shown that both the diastereofacial selectivity and the direction of the asymmetric induction, depend on the nature of the dienophile and the Lewis acid used as a catalyst. In order to explain the results obtained, three different models have been proposed for the dienophile-catalyst complexes:



Model 1



Model 2



Model 3

M = Al, Ti

Model 1 is the one proposed for chiral acrylates with only one center capable of coordination[3]. In this model the enoate moiety displays an *s-trans* conformation in which the carbonyl group of the acrylate and the hydrogen of the chiral auxiliary are in a syn-planar disposition. The differentiation between both faces of the double bond is due to the different size of R_1 and $COOR_2$.

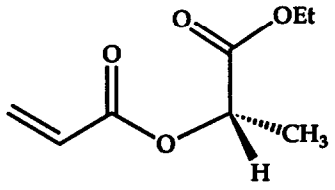
Model 2 has been described by Helmchen *et al.*[4] on the basis of an X-ray study of the acrylate of (S)-ethyl lactate-$TiCl_4$ complex. In this case the dienophile and the catalyst form a chelate complex with the enoate in *s-cis* conformation, the *Re* face of the dienophile is shielded by a chlorine atom of the Lewis acid, and the attack of the diene takes place preferentially on the *Si* face.

Model 3 has been proposed[2c] on the basis of the asymmetric induction observed in the reaction of N-acryloyl-L-phenylalanine and N-acryloyl-L-alanine methyl ester with cyclopentadiene.

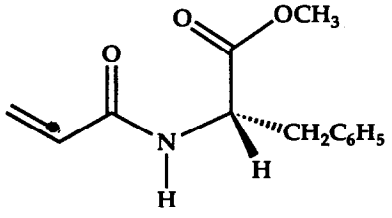
Furthermore, the model is supported by an IR study of the N-acryloyl-L-phenylalanine methyl ester-$TiCl_4$ complex. In this model, the enoate displays an *s-trans* disposition and the conformation of the chiral group is fixed by an intramolecular hydrogen bond. The *Re* face of the dienophile is shielded by R_1 and the diene approaches preferentially on the *Si* face.

In view of these models, the direction of the asymmetric induction depends on two main factors: the conformation of the enoate moiety and the conformation of the chiral auxiliary.

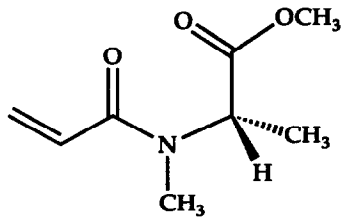
In order to understand the behaviour of this kind of dienophile we have carried out a molecular mechanics conformational analysis of the following compounds: acrylate of (S)-ethyl lactate (1), N-acryloyl-L-phenylalanine methyl ester (2), and N-methyl-N-acryloyl-L-alanine methyl ester (3):



1



2



3

There are many force field programs available today, the most frequently used being the Molecular Mechanics packages developed by Allinger's group (MM2[5], MM3[6]). Standard MM2 force fields describe molecular steric energy as a sum of stretching, bending, stretching-bending, Van der Waals, torsional and electrostatic interaction energy components, but no polarization energy term is, in general, included. The appropriate treatment of many-body inductive forces has been a long-standing problem because of the non-additivity of this kind of interaction.[7-11] However, in order to predict with accuracy the molecular conformation in molecules with intramolecular hydrogen bonds, the polarization energy term may be essential. So we have considered the inclusion of this term in this study important.

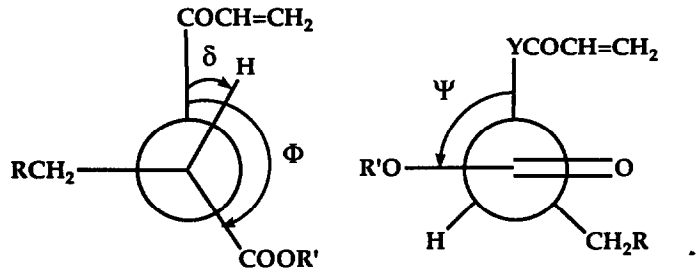
METHODS AND COMPUTATIONS

A model of interacting induced dipoles (ID) was first proposed by Gray[12] and Siberstein,[13] and applied quantitatively for diatomic molecules and qualitatively for polyatomic molecules. A quantitative extension of the model of Silberstein for polyatomics was developed by Applequist.[14] In this model, one assumes that each atom of the molecule responds to an electric field by the induction of a dipole moment located at the nucleus and defined as a linear function of the local field. The total electric field at atom i consists of the external field plus the field arising from all the other induced dipoles in the molecule. One obtains a set of coupled linear equations for the induced dipole moments that can conveniently be expressed in compact

matrix equation form if one introduces the atom-atom dipole field tensors. The many-body polarizability matrix can be obtained by matrix inversion. This matrix describes a non-local polarizability response of the system.

The ID method of Applequist has been implemented[15] in a version of the MM2 program. We have, in addition, improved the MM2 program for properly describing the hydrogen bonding interactions following the method of Allinger et. al.[16] and we have used a new MM2(87) force field which includes parameters for peptides.[17,18]

The potential energy surface as a function of the dihedral angles Φ and Ψ (Figure 1) has been inspected for the three molecules studied.



1: R=H; R'=Et; Y=O

2: R=Ph; R'=Me; Y=NH

3: R=H; R'=Me; Y=NMe

Figure 1

Conformational energy minimizations have been carried out for these dienophiles in the two possible conformations of the enoate moiety, *s-cis* and *s-trans*. As expected, several minima are obtained for each molecule, but only the most stable ones will be discussed here for simplicity. The conformations that have been retained are labelled with the letters **r**, **s**, and **t** in order of decreasing stabilities.

In the case of molecule **3**, the *s-trans* conformation is not included here because owing to the desestabilizing interaction between the N-methyl group and the N-acryloyl terminal CH_2 group, its energy is substantially greater (about 23 kJ· mol^{-1}) than that of the *s-cis* conformation.

RESULTS AND DISCUSSION

The results of the computations are summarized in Table 1. The optimized geometries are represented in Figure 2

Three minima of acrylate of (S)-ethyl lactate (**1**) are reported in Table 1 for each conformation *s-cis* and *s-trans*. The most stable geometries correspond to a nearly syn-periplanar position of the hydrogen atom in the chiral carbon with respect to the enoate carbonyl group. This what is usually expected for these compounds[19]. However, because of the different steric hindrance of the two substituents on the chiral carbon, the CH and the CO carbonyl bonds are not exactly coplanar. This should require the dihedral angle δ=0 (note that the acrylate skeleton is planar).

The computations predict δ=-37.1 degrees instead. for the two other conformations, the twist is even larger, with δ=63.2 degrees (s) and δ=68.7 degrees (t), but these values are still comparable with chrystallographic data for esters of secondary alcohols where the corresponding torsion lies in the interval ±60 degrees.[19]

Table 1. Molecular Mechanics Results for Dienophile Conformations. Dihedral Angles (in degrees) and Total Energy Differences (in kJ· mol^{-1}).

		MM2					MM2+ID				
Conformation		**Φ**	**δ**	**Ψ**	**E**	**ΔE**	**Φ**	**δ**	**Ψ**	**E**	**ΔE**
Molecule 1											
s-cis	r	-153.3	-37.1	65.9	72.8	0.0	-153.9	-38.0	59.8	64.0	0.0
	s	-57.7	63.2	144.5	74.3	1.5	-56.5	64.7	139.6	65.6	1.6
	t	-50.7	68.7	-41.3	74.8	2.0	-50.3	69.4	-41.8	66.3	2.3
s-trans	r	-154.1	-38.0	64.7	76.8	0.0	-155.4	-39.4	59.3	68.0	0.0
	s	-58.1	62.8	145.1	78.6	1.8	-57.9	63.3	141.9	69.9	1.9
	t	-51.1	68.2	-45.0	78.9	2.1	-52.7	67.0	-45.3	70.4	2.4
Molecule 2											
s-cis	r	-153.1	-36.4	149.6	-0.4	0.0	-139.4	-22.3	148.2	-9.6	0.0
	s	-83.9	36.7	132.9	5.3	5.7	-73.8	46.8	133.5	-3.7	5.9
s-trans	r	-152.5	-35.7	149.2	2.5	0.0	-142.6	-25.6	146.4	-7.8	0.0
	s	-83.3	37.4	132.9	8.5	6.0	-77.4	43.4	133.7	-2.0	5.8
Molecule 3											
s-cis	r	-120.0	-5.2	45.8	38.6	0.0	-125.7	-10.9	45.3	29.2	0.0
	s	55.0	167.3	38.9	41.4	2.8	62.5	175.2	34.9	33.7	4.5
s-trans	r	-99.3	17.8	42.9	61.9	0.0	-107.8	9.5	44.3	55.2	0.0
	s	51.7	163.7	37.9	64.5	2.6	50.9	163.2	36.7	56.4	1.2
	t	-139.7	-26.3	52.2	64.6	2.7	-140.6	-26.9	54.1	55.2	0.0

A detailed analysis of our results shows that the Van der Waals interaction between the hydrogen attached to the chiral carbon and the enoate carbonyl oxygen atom substantially stabilizes the complexes, so that syn-periplanar conformations are favoured.

For each minimum r, s or t, the *s-cis* conformation is always lower in energy by about 4 kJ· mol^{-1}, which is in agreement with experimental data for the simple methyl acrylate.[20] It should be noted that different topological properties are exhibited by this compound following the sense of the rotation around the OC bond, *i.e.*, depending on the sign of δ. The destabilizing steric interactions between the ester group on the chiral carbon and the enoate moiety are minimized for negative values of this angle (conformation r). In addition, our results show that for positive values of δ there are, in general, two conformations of close energy which are approximately deduced one from other, by a rotation of 180 degrees in Ψ (conformations s and t illustrated this property). Conversely, the corresponding conformations obtained for negative δ values have quite different stabilities.

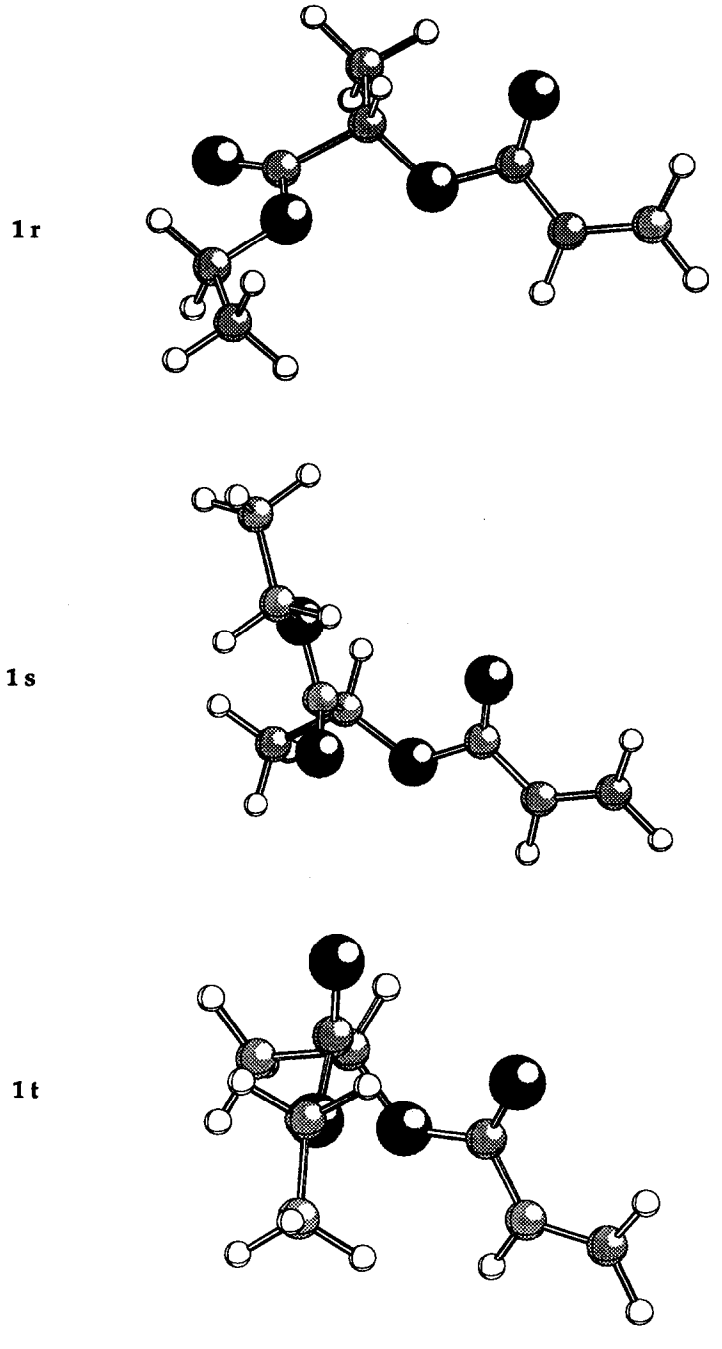
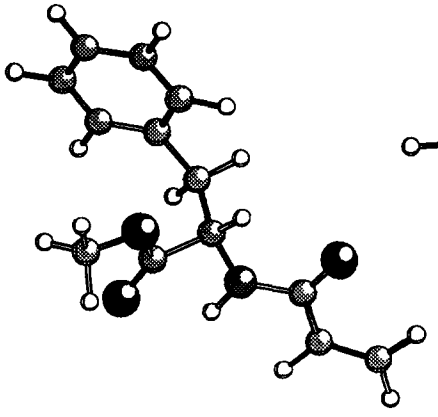
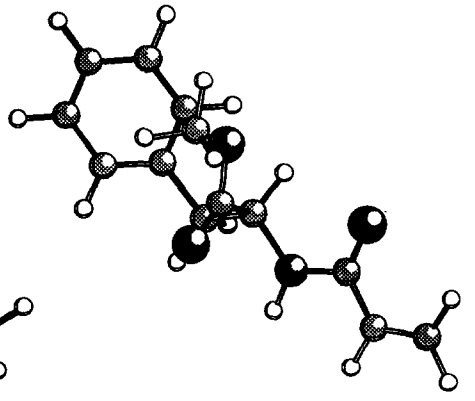


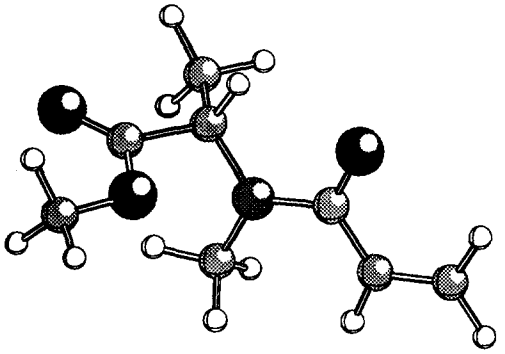
Figure 2



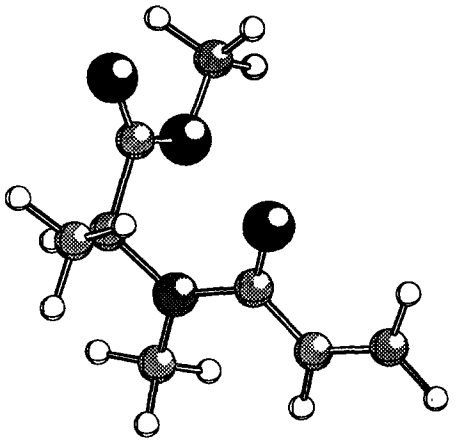
2r



2s



3r



3s

Figure 2

Considering now the relative orientation of the carbonyl groups, it appears from Fig. 2 that conformation **s** has a "pro-chelate" structure, *i.e.*, the carbonyls are oriented in such a way that bonding to $TiCl_4$ as a chelate is favoured. For instance, the distance between the oxygen atoms is 3.2 Å, which may be compared with the crystal structure of the chelate **1**-$TiCl_4$ of 2.8Å.[4] Although this structure does not correspond to the most stable one at the MM2 level, its energy is not much higher, so that one may expect chelate formation to be relatively easy for this compound.

The minima **r** and **s** for N-acryloyl-L-phenylalanine methyl ester (**2**) present a similar arrangement (see Fig. 2d-e). In contrast with molecule **1**, for which several local minima have been found at relative low energies, for molecule **2** the computations predict all other local minima to be at least 7 $kJ \cdot mol^{-1}$ (in the MM2+ID model) above the most stable conformation **r**. Again, the *s-cis* conformations are more stable than the corresponding *s-trans* structures.

The most striking feature for this molecule is that some particular conformations are stabilized by the intramolecular hydrogen bond which takes place between the hydrogen atom attached to the amide nitrogen atom and the carbonyl oxygen atom of the chiral auxiliary. It leads to the formation of a five-membered ring comparable to that found for N-acetyl-N'-methylglycynamide.[21] Besides, as for molecule **1**, there is a stabilizing van der Waals interaction which takes place between the hydrogen atom attached to the chiral carbon atom and the carbonyl oxygen atom in the N-acryloyl moiety. Both interactions determine the main geometrical parameters for this molecule. Although the Van der Waals interaction is expected to be similar for positive and negative values of δ, the hydrogen bond strongly favours negative δ values (as in conformation **r**), which correspond to lower O··H distances. Some parameters describing these hydrogen bonds are given in Table 2.

The contributions to the total energy from the dipole-dipole electrostatic interaction of the NH··CO bonds and the Van der Waals interaction of the H··O pair show that the force of this hydrogen bond decreases when passing from minimum **r** to **s**, corresponding to an enlargement of the H··O distance and a net increase in of the HNCC dihedral angle. The difference in NH··CO electrostatic energy between these conformations roughly corresponds to the difference in the total electrostatic energy, which reflects the fact that on going from conformation **r** to **s** only the hydrogen bond part of the total electrostatic interaction is substantially modified. The same applies to for the Van der Waals interaction. Notice also that the induction energy also favours conformation **r**, which is also related to the formation of a more efficient hydrogen bond, although in this case the absolute value of the variation is smaller.

The presence of an intramolecular hydrogen bond in both conformers moves the carbonyl oxygen atoms apart so that the CO bonds are in anti-periplanar arrangement. Stable "pro-chelate" structures are then not found for this molecule. Chelation should require the breaking of the intramolecular hydrogen bond and, although the formation of such complexes cannot be excluded from only these calculations, the computed hydrogen bond energies indicate that it is much less likely than for molecule **1**.

Table 2. Molecular Mechanics Results for Dienophile **2**. Hydrogen Bond Distances (in Å) and HNCC Dihedral Angles (in degrees). Dipole-dipole (DD), van der Waals (VW) and Polarization (P) Contributions to the Total Energy (in $kJ \cdot mol^{-1}$).

Method	Conformation		distance	dihedral	DD		VW		P
			H···O	HNCC	NH·CO	Total	H·O	Total	Total
MM2	*s-cis*	r	2.399	28.1	-11.4	-24.5	-9.0	32.0	-
		s	3.092	88.8	-7.6	-20.8	-2.2	39.1	-
	s-trans	r	2.386	28.7	-11.5	-24.7	-9.2	32.2	-
		s	3.096	89.6	-7.6	-21.0	-2.2	39.5	-
MM2+ID	*s-cis*	r	2.414	37.7	-11.4	-23.9	-8.7	34.3	-11.7
		s	3.176	96.4	-7.2	-20.6	-1.9	40.7	-10.1
	s-trans	r	2.381	35.6	-11.6	-24.4	-9.3	35.1	-12.8
		s	3.103	92.1	-7.5	-20.8	-2.2	41.6	-11.4

In the N-methyl-N-acryloyl-L-alanine methyl ester (**3**), which will be considered only in the *s-cis* conformation, as we have already mentioned, the presence of a methyl group in the amide nitrogen atom inhibits the formation of hydrogen bonds. Besides, the methyl group may, in principle, favour a pyramidalization of the N atom, although the results show that this pyramidalization is only small (out-of-plane angle of the NH bond equal to 5 degrees). Again, the most stable conformation **r** presents the CH bond at the chiral carbon atom in a syn-periplanar position to the amide CO bond in the N-acryloyl moiety (see Fig. 2f). However, the conformation **s**, for which carbonyls appear in a "pro-chelate" structure (the O··O distance is 3.4 Å) corresponds to anti-periplanar CH/CO bonds. The relative stabilization of this structure for this molecule is not surprising because the anti-periplanar position minimizes the steric interaction of the amidic methyl group with the substituents on the chiral carbon.

In order to relate this computational calculations to the experimental results, Table 3 summarizes the most relevant results obtained in the reactions of dienophiles **1-3** with cyclopentadiene.

Table 3. Experimental results of the reaction between dienophiles **1-3** and cyclopentadiene, along with the models explaining the stereochemical results.

Dienophile	Catalyst	Model	Attack Face	%de	Ref.
1	$AlCl_3$	1	*Re*	28	1a
	$TiCl_4$	2	*Si*	74-86	1a
2	$AlCl_3$	3	*Si*	20-52	2c
	$TiCl_4$	3	*Si*	24-64	2c
3	$AlCl_3$[a]	1	*Re*	52	2c
	$TiCl_4$	2	*Si*	46	2c

[a] The reaction is very slow, and a great excess of diene is needed.

As can be seen, model 1 accounts for the results obtained in the $AlCl_3$-catalysed reactions of **1** and **3**. This model is represented by the *s-trans* **r** conformations. In the case of dienophile **1**, the interaction of the $AlCl_3$ with the methylene group of the double bond may overcome the 4 $kJ \cdot mol^{-1}$ preference of the *s-cis* conformation, as shown by semi-empirical calculations.[22] In the case of dienophile **3**, the greater preference for the *s-cis* conformations makes the $AlCl_3$-catalysed reaction difficult.

Model 2 accounts for the results obtained in the $TiCl_4$-catalysed reactions of **1** and **3**. The *s-cis* conformations, with the carbonyl oxygens in a "pro-chelate" disposition, are not far from the absolute minima, represented by conformations **r**.

Model 3 accounts for the results obtained with both Lewis-acids catalysed in the reactions of dienophile **2**. Molecular mechanics calculations show that the presence of a hydrogen bond hinders the formation of "pro-chelate" conformations. As stated for model 1, the co-ordination of the catalyst may change the *s-cis*/*s-trans* conformational equilibrium.

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