Intramolecular π-Stacking and Asymmetric Induction: A Semiempirical Theoretical Study

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The conformations of several substituted cyclohexyl esters involved in highly diastereoselective organic reactions that have been rationalized by intramolecular π-stacking were investigated by resorting to the semiempirical SIBFA procedure. Different cases, for which experimental results featuring a large set of chiral auxiliaries are available, were studied. For the cyclohexyl-based asymmetric crotonates and glyoxylates, the stabilization of the sterically demanding face-to-face "stacked" conformers increases, as expected, with the absolute value of the dispersion energy contribution. We report a good correlation between the experimental de and the stability of the stacked conformer over the other possible ones. In addition, the analysis of the energy contributions for these two series of esters also indicates that the electrostatic forces are of prime importance for the conformational preferences observed. For both sets of compounds, this last result suggests substitution patterns that could be used to improve the auxiliaries' efficiency. Proton NMR shieldings calculated for the most stable conformations are in good agreement with available experimental data and therefore support our energetics results. For butadienyl *O*-methylmandelate, the phenyl ring is found to be roughly perpendicular to the conjugated diene moiety, a feature in qualitative agreement with that of another recently published semiempirical study on the same compound. The quality of the correlation between the stacked conformers population and the reported diastereoselectivities shows the importance of the conformations of the chiral substrate for the stereochemical outcome of the reactions considered in this study.

Introduction

After years of attention and many major advances, attaining absolute control of asymmetry remains a challenging goal in organic synthesis. The search for parameters well suited to the evaluation of potential asymmetric inductors actively continues. The origin of diastereoselection has in a rapidly increasing number of cases being attributed to a through-space intramolecular interaction between π electronic systems, that leads to compact structures that present only one sterically available face to their reaction partners. This phenomenon, present for at least 20 years[1] in the literature, is often referred to as the π-stacking effect. Among the very early applications of this concept, several examples deserve special mention.

First prepared under its (+) form in 1975 by Corey,[2] 8-phenylmenthol has turned out to be a versatile tool in asymmetric synthesis,[3] and has been successfully employed in a variety of different types of reactions such as Diels-Alder cycloadditions,[2,4] ene,[5] or addition[6] reactions, as well as Michael-type additions.[7] Experimental studies on its esters have led to the hypothesis of π-stacking between the ester moiety and the aromatic ring[4a] (Scheme 1) which has been supported in one case by a study of photophysical intramolecular quenching[8] and by several NMR studies on model compounds.[5c,6b,7b,9] For phenylmenthol esters, the three conformers represented on Scheme 1 have been considered.[5c,9] Fine tuning of these structures led Whitesell[5c,10] to propose *trans*-2-phenylcyclohexanol as a powerful chiral auxiliary[11] that affords high levels of asymmetric induction in the ene reaction.

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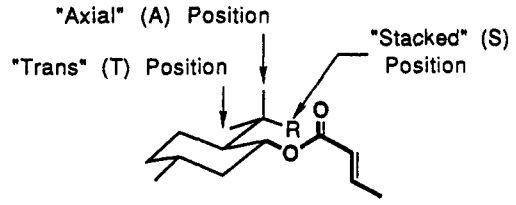
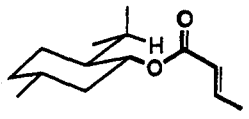
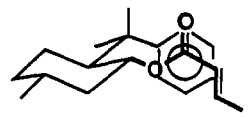
Scheme 1



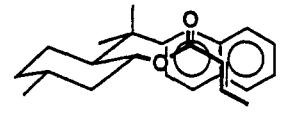
R = H	HM
R = Ph	PM
R = β-Naphthyl	NM
R = p-Ph-O-Ph	PPP
R = p-MeO-Ph	POP
R = m-MeO-Ph	MOP
R = o-MeO-Ph	OOP



HMS

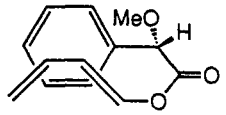


PMS

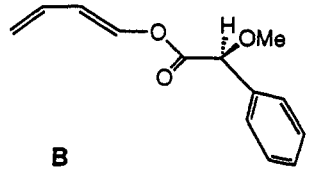


NMS

Scheme 2



A



B

Another example of almost total diastereoselectivity, in the asymmetric Diels–Alder cycloaddition reaction this time, was provided by Trost et al.[12] in their first description of butadienyl *O*-methylmandelate as a chiral diene. This striking result has been first ascribed by these authors to a π-stacking phenomenon between the diene moiety and the ester phenyl ring (Scheme 2A). In a recent paper,[13] Tucker, Houk, and Trost retreated from this statement, based on a molecular mechanics study performed on this same example. Their results clearly indicate that the orientation of the phenyl ring is perpendicular to the diene plane (Scheme 2B), thus excluding any π-stacking contribution to the observed selectivity. This particular trend had been proposed a little ealier based on experimental evidence by Thornton and co-workers.[14]

The increasing number of experimental[15] and theoretical[16] results related to this problem raise questions about the origin(s) and role of stacking phenomenon in asymmetric organic synthesis. In order to investigate the possible correlation between the stability of stacked conformers and diastereoisomeric excess (de) measured in reactions involving the above compounds, we undertook a molecular mechanics study on the reactant carrying the chiral inductor. The analysis of the respective importance of the different contributions to molecular energy may provide insight into the factors responsible for the relative stability of the different conformers and suggest structural trends to promote the stacked arrangements. Underlying this approach is the assumption that the chiral inductor conformation is not thoroughly modified by interaction with the other reactant(s). This will necessarily limit the present investigation to simple cases dealing with formally uncharged species (examples are discussed below).

Because its different energetic contributions were calibrated separately on results of *ab initio* calculations, the SIBFA molecular mechanics[17] appears very appropriate for the type of conformational problem presented above. Albeit applied mainly to the study of biomolecules, this systematic parameterization can be used in the present study since its calibration was not optimized for any particular class of compound. Taking into account the dispersion contribution to the total energy, possibly responsible for the stabilization of stacked structures,[18] it appears to be of prime importance in the menthyl derivative cases. On the other hand, the study of the butadienyl mandelate case should afford the opportunity to check that this energetic component is not overestimated by the method.

In addition, semiempirical computations of proton chemical shifts[19] for the most stable conformations theoretically obtained may also be performed and provide feedback information about their similarities and differences relative to those deduced from experimental (solution) data.

Computational Procedure and Inputs

The SIBFA (sum of interactions between fragments ab initio computed) procedure, which was developed in one of our laboratories,[17] builds up the studied molecule from constitutive molecular fragments, such as cyclohexane,

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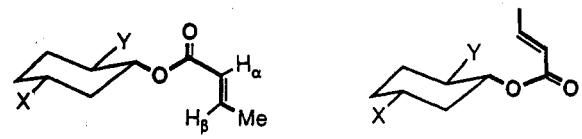
methane, and water in the case of menthol, the main building block of the compounds considered in this work. The cyclohexanol part of the molecule is, for instance, obtained by the superposition of a cyclohexane C–H and a water O–H bond. This "junctional" step also sets the C–O bond with the appropriate length and valence angles. The adapted redistribution of the electronic populations of the two X–H bonds concerned ensures the quality of the overall molecular net charge. The "junctional" bonds retained are those about which the torsion angles vary with the conformational changes considered. This choice, which might appear somewhat arbitrary, has in our opinion an important advantage: the sets of multipoles are totally independent of the conformations considered. The total intramolecular (conformational) energy is computed as the following sum of interfragment interaction energies:

$$E_{intra} = E_{mtp} + E_{rep} + E_{pol} + E_{disp} + E_{tor}$$

In this expression, E_{mtp} denotes the electrostatic (multipolar) interaction energy, computed as a sum of multipole–multipole interactions. These multipoles (charges, dipoles, and quadrupoles) are calculated, once and for all, for each fragment from its *ab initio* SCF molecular wave function and distributed over all atoms and bonds of the entity considered, following the procedure developed by Vigné-Maeder and Claverie.[20] This procedure has been shown to be essential for the fair accounting of the electrostatic contribution to stacking phenomenon.[18,20] E_{rep} is the short-range repulsion/exchange energy. To confer a reasonable orientation behaviour to this term, a sum of bond–bond, bond–lone pair, and lone pair–lone pair terms (instead of the classical atom–atom $1/R^{12}$ summation) is adhered to. E_{pol} is a polarization energy component. Consistent with the development used for E_{mtp}, the polarizing field is calculated from the *ab initio* multipolar expansion; all bond polarizabilities, derived from a set of experimental values,[21] are distributed on the chemical bonds and the heteroatoms bearing lone pairs. The dispersion energy term E_{disp} expresses the interaction between transition dipoles. For a given pair of interacting atoms P and Q belonging to two distinct fragments, it is taken proportional to the inverse of the 6th power of their distance and scaled at the numerator by a factor taking into account the atomic numbers of P and Q and their effective Van der Waals radii (see ref 17 for additional details). Finally, E_{tor} is a torsional energy contribution for the rotation about the junctional bonds. It was calibrated originally on results of conformational *ab initio* SCF computations on a restricted set of molecules, as was done by Houk et al.[13] SIBFA is an extension of a procedure initially devoted to the computation of intermolecular interaction energies.[22] The formulation of the different contributions follows from second-order perturbation terms. This scheme enables computation of both inter and/or intramolecular interaction energies and has been shown to reproduce accurately *ab initio* SCF computations in a series of test cases. Resorting to *ab initio* multipoles on bonds as well as on atoms in the expression of the electrostatic energy, rather than atom-centered charges as in many molecular mechanics force-fields, is a key asset in evaluating the relative stabilities of stacked vs non-stacked arrangements. Thus, the predominant role of the higher-than-monopole terms in stacked complexes of aromatic nucleic acid bases was underlined by Langlet et al.[18] The explicit taking into account of a dispersion term, which would require post-SCF treatments (CI, MP2, MP4) in quantum mechanical computations, can be an additional crucial feature in many intramolecular problems. Finally, the expression of the total energy under the form of physically-defined separated terms can provide an additional advantage if one is to rationalize the energetic factor(s) leading to the prevalence of a given conformation.

Scheme 3



A B

X = Me, Y = CH_2-Ph BC
X = H, Y = Ph PC

The torsion angles about the interfragment junctional bonds are the only geometrical parameters considered in the molecular energy optimization. We are aware that conformations obtained with this limitation cannot correspond to the exact overall global minimum of the potential energy surface. Were we investigating the reaction mechanism itself, the calculation procedure of Houk et al.[13,23] would undoubtedly be more appropriate. However, our approach should be fully relevant to the current problem since (i) the stacked/unstacked energy difference should, hopefully, not be strongly dependent on precise geometrical parameters of the different fragments; (ii) the optimization process has been repeated starting from all different conformers (S, T, and A of Scheme 1 plus the two orientations of the ester carbonyl, shown in Scheme 3, parts A and B, in the cases of the substituted menthyl crotonates for instance). This procedure should overcome the problem of the barriers between the different energy minima; (iii) conformational refinements on the absolute energy minimum should be of little consequence in the context of an approach neglecting the substrate–reactant interaction.

The energy minimizations have been carried out without taking into account the polarization contribution. For each of the molecules studied, this term was calculated in a second step for the conformations corresponding to the two lowest energy minima only. This procedure, which saves computer-time, appeared reasonable since (i) for most compounds studied here (14 out of 16) polarization is the smallest term; (ii) polarization undergoes variations smaller than 5 kcal/mol with the molecular conformation. If one of the fragments were, however, carrying a formal charge it would then be essential to include E_{pol} in the minimization process since its value could be of the same order of magnitude as the other contributions.[24]

The proton magnetic shielding constants were calculated according to a semiempirical methodology fully consistent with the SIBFA systematics.[19] The nuclear magnetic shielding is computed as the following sum of four terms

$$\sigma^T = \sigma^{RC} + \sigma^X + \sigma^E + \sigma^D$$

where σ^{RC} is a ring current contribution (due to benzene

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or naphthalene in this study), σ^{χ} the atomic magnetic anisotropy contribution, σ^{E} the polarization or electric field effect, and σ^{D} the dispersion contribution which attempts to take into account the (de)shielding due to electron correlation. For the σ^{RC} and σ^{χ} terms concerning a given proton, the summation runs over all the aromatic rings and non-hydrogen atoms of the molecule. The σ^{E} term, which is calculated as

$$\sigma^{E} = CE_{z}$$

is a function of E_z, the projection on the X–H bond of the electric field created at the middle of the bond by the set of multipoles used for E_{mtp} and E_{pol} energy terms. However, the multipoles located on the bonds involving the atom X carrying that proton are omitted in the summation. The neglect of the exchange or repulsion term, taken into account in the molecular energy, affects, for the present cases, the results to only a negligible extent since *ab initio* calculations have clearly established that its contribution is numerically significant only for protons engaged in strong hydrogen bonds.[25] It should be kept in mind that the computational procedure used here does not take into account the "local" contributions to σ^{T}, that is, those involving the electronic distribution of the proton under study. Therefore, as discussed previously,[19a] the calculated σ^{T} values cannot be compared to the measured chemical shifts. On the contrary, the theoretical results should be fully significant for chemical shift variations due to molecular conformation effects and to chemical substitution occurring at more than two bonds away from the proton considered.

Finally, the geometry used for 8-arylmenthol derivatives has been deduced from crystallographic data of 8-phenylmenthyl esters,[6b,9] while the crotonate moiety parameters were deduced from an X-ray study of its potassium salt.[26] For the cis and trans glyoxal conformers, we used the geometry reported by King.[27]

Results and Discussion

Asymmetric Crotonates. The results concerning asymmetric crotonates are gathered in Table 1 and the most stable conformations of those that have been experimentally studied are displayed in Figure 1. As can be seen from Scheme 1, in the "stacked" (S) conformation, the olefin moiety and the R group are face-to-face, while in the "trans" (T) conformation, R is switched with a methyl/hydrogen and in the "axial" (A) case, the C–R bond is parallel to an axial position on the cyclohexane ring. The tabulated results indicate that in all menthyl derivatives considered, the latter conformation lies higher in energy than the corresponding S and T conformers. Regarding the relative stability of stacked and trans-type structures, each compound has to be examined on its own.

The trans conformation of menthyl crotonate (HM, R = H) is the most stable by 2 kcal/mol ("stacked" being meaningless in the absence of any aromatic ring on the molecule), a result that is consistent with the slight de measured in this case. The energetic contributions detailed in Table 2 indicate that the trans-conformer stabilization is due to the repulsion (i.e. the steric constraints) decrease.

Table 1. Calculated Energy and Geometrical Parameter Values for Asymmetric Crotonate Conformational Optima $CH_3CH{=}CHCO_2R$*

R	conformer	dihedral angles[a]	E^b
menthyl (HM)	S	88/358/306/185/173/181	570.1
	T	88/357/167/181/174/181	**568.3**
	A	86/356/63/172/191/181	570.3
8-phenyl-menthyl (PM)	S	78/360/298/179/168/120/181	635.3
	T	79/1/177/189/178/64/181	**635.0**
	A	76/359/61/180/183/97/181	636.8
8-β-naphthyl-menthyl (NM)	S	79/359/299/180/168/298/181	**620.2**
	T	78/359/179/190/179/63/140	623.8
	A	77/359/65/182/187/101/24	624.9
8-(*p*-MeO-C_6H_4)-menthyl (POP)	S	80/360/301/183/169/114/180/90/300	**877.8**
	T	78/359/177/189/177/64/180/90/300	878.9
	A	76/359/59/179/182/96/180/90/300	880.6
8-(*m*-MeO-C_6H_4)-menthyl (MOP)	S	78/0/299/178/168/305/181/89/303	**877.4**
	T	77/359/177/189/178/64/181/89/300	878.7
	A	81/1/57/178/181/277/181/85/300	878.8
8-(*o*-MeO-C_6H_4)-menthyl (OOP)	S	78/2/302/181/170/300/180/110/314	**878.7**
	T	77/359/177/192/183/55/180/104/319	882.1
	A	77/352/68/184/174/281/180/245/49	889.9
8-(*p*-PhO-C_6H_4)-menthyl (PPP)	S	78/360/300/180/168/119/180/85/266	**877.3**
	T	78/359/177/189/178/64/180/269/268	878.4
	A	76/359/60/180/183/97/180/274/275	880.0
trans-2-benzylcyclohexyl (BC)	S	76/1/278/94	395.6
	T	77/0/199/268	395.6
	A	76/360/56/276	**395.4**
trans-2-phenylcyclohexyl (PC)	"exo"	78/360/236	**311.9**
	"endo"	297/1/236	317.5

[a] Dihedral angles ordering is shown in Scheme 4A. [b] In kcal/mol, in absence of intramolecular polarization. Boldface values represent the most-stable conformation.

The S and T conformers of 8-phenylmenthyl crotonate (PR, M = Ph) are found to be almost isoenergetic because of the opposite variations of the steric and electrostatic contributions on one hand and the dispersion contribution on the other (Table 2). If the theoretical ≈ 50:50 ratio for the stacked vs unstacked population in 8-phenylmenthyl crotonate is unable to account for the almost total diastereoselectivity reported by Oppolzer et al. in the 1,4-addition of phenyl cuprate[7a] to the only accessible face of this olefin, it provides figures in nice agreement with data obtained in the addition of diphenylmethylamine at this same position.[7b] The 60% de measured in favor of the *R* isomer in the latter case could be expected for a very high diastereofacial selectivity by the 50% of stacked conformer (thus leading to ≈50% *R* isomer) added to an almost statistical addition of this amino moiety on both faces of the crotonate by the other 50% of unstacked conformer (leading to ≈25% *R* + 25% *S* isomers). The resulting de would then be 50% in favor of the *R* isomer. Several examples of uncatalyzed cycloaddition reactions involving related compounds bearing the 8-phenylmenthyl group as chiral inductor are also reported to take place with a comparable de of 50–60%[4b–d,28] and support the present results.

(25) (a) Giessner-Prettre, C.; Ferchiou, S. *J. Magn. Res.* **1983**, *55*, 67. (b) Giessner-Prettre, C. *J. Biomol. Struct. Dyn.* **1984**, *1*, 233.
(26) Mc Gregor, D. R.; Speakman, J. C.; Lehmann, M. S. *J. Chem. Soc. Perkin Trans 2* **1977**, 1740.
(27) King, G. W. *J. Chem. Soc.* **1957**, 5054.
(28) (a) Gaonac'h, O.; Maddaluno, J.; Plé, G.; Duhamel, L. *Tetrahedron Lett.* **1992**, *33*, 2473. (b) Gaonac'h, O. Ph.D. Thesis, 1992, Rouen University (France). (c) Gaonac'h, O.; Maddaluno, J.; Marcual, A.; Duhamel, L. *Manuscript in preparation.*

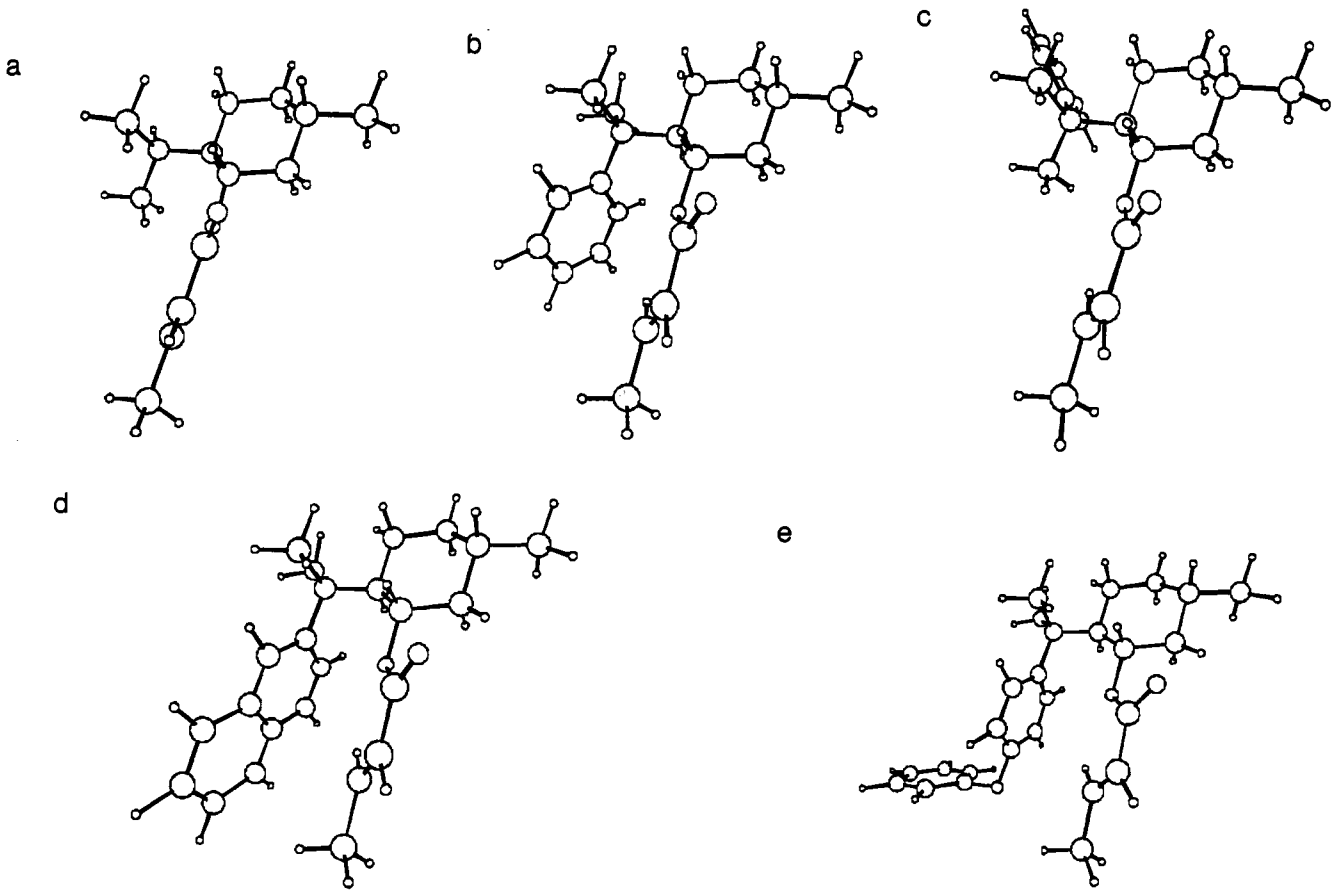
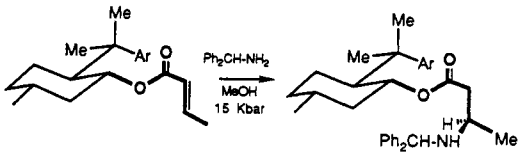


Figure 1. Most stable conformations of chiral crotonates for which experimental data are available: trans menthyl (a), stacked (b) and trans (c) 8-phenylmenthyl, stacked 8-β-naphthyl (d) and stacked 8-(*p*-phenoxyphenyl)menthyl (e).

Table 2. Contributions (in kcal/mol) of Main Components to Conformational Energy Minima of Chiral Crotonates. HM, PM, NM, POP, MOP, OOP, PPP, BC, and PC Refer to Menthyl, 8-Phenylmenthyl, 8-β-Naphthylmenthyl, 8-(*p*-, 8-(*m*-, 8-(*o*-Methoxyphenyl)menthyl, 8-(*p*-Phenoxyphenyl)menthyl, *trans*-2-Benzyl- and *trans*-2-Phenylcyclohexyl Crotonates, Respectively, under Their "Stacked" (S), "Trans" (T) or "Axial" (A) Conformations

	repulsion	dispersion	polarization	electrostatic	torsion	total[a]	exptl de (%)[b]
HMS	616.5	−65.3	−5.0	33.6	−14.8	565.1	10
HMT	614.8	−65.7	−5.2	33.9	−14.6	**563.1**	
PMS	726.7	−85.6	−5.8	8.7	−14.5	629.7	60
PMT	725.5	−82.6	−5.5	6.7	−14.5	**629.6**	
PPPS	951.1	−102.2	−5.8	42.8	−14.4	**871.5**	95
PPPT	949.3	−98.1	−5.8	41.8	−14.5	872.6	
NMS	722.3	−88.3	−5.7	0.7	−14.4	**614.5**	>99
NMT	721.5	−83.3	−5.6	−0.4	−14.5	617.6	
POPS	952.8	−100.3	−6.4	39.8	−14.4	**871.4**	
POPT	950.2	−96.1	−6.4	38.7	−14.5	872.5	
MOPS	953.3	−101.7	−6.5	40.2	−14.5	**870.8**	
MOPT	950.9	−96.4	−6.6	38.7	−14.5	872.2	
OOPS	959.5	−107.1	−7.0	39.2	−14.3	**870.2**	
OOPT	957.8	−101.9	−6.8	39.1	−14.1	874.0	
BCA	422.1	−47.6	−2.9	35.6	−14.7	**392.5**	
BCS	418.5	−46.5	−3.0	37.7	−14.1	392.6	
PCEX	320.2	−34.6	−2.2	41.0	−14.7	**309.7**	
PCEN	332.6	−40.4	−2.1	40.3	−15.0	315.4	

[a] Boldface values represent most-stable conformer. [b] Values are taken from ref 7b and refer to the following reaction:



In the case of the 8 β-naphthylmenthyl crotonate (NM, R = β-naphthyl) the stacked conformer is the most stable by 3.1 kcal/mol. This energetic gap is due to a particularly large value for the dispersion energy in the S form and

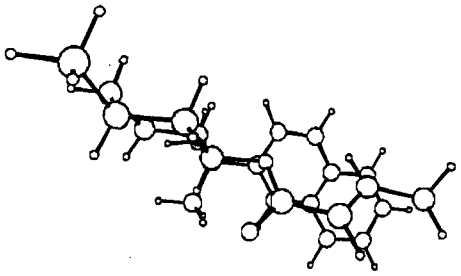


Figure 2. Side view of 8-β-naphthylmenthyl crotonate stacked conformer.

accounts for the very high level of diastereoselectivity reported in the first experimental application of this compound.[7b,29] The NM stacked conformation leads to a spectacular shielding of the β-olefinic carbon on which the addition reaction is to take place, as can be seen on Figure 2. It also agrees with the observed sense of asymmetric induction.

The results obtained for the two aryl compounds exhibit a common feature, *viz.* the repulsion and electrostatic contributions tend to stabilize the T conformer while the dispersion term favors the S one. The reverse situation occurs for the menthyl crotonate. The values of torsion and polarization contributions are much less sensitive to conformational effects. The importance of the variation of the electrostatic contribution suggests that the relative stabilities could be significantly altered by the presence of a polar substituent on the aromatic moiety of these compounds.

Computations on 8-(*p*-phenoxyphenyl)menthyl crotonate (PPP, R = *p*-PhO-Ph), of which the chiral moiety has been found highly efficient in at least two cases,[6e,7b] shows that the S conformer is the most stable by 1.1 kcal/mol. Examination of the values given in Table 2 indicates that the larger stabilization of the PPPS conformer with respect to the PPPT one, when compared to the corresponding PMS and PMT conformers, is not only due to an increase of the dispersion energy (−4 kcal/mol for PPP versus −3 kcal/mol for PM) but also to a more limited concomitant increase of the electrostatic repulsion (1 versus 2 kcal/mol).

This result prompted us to undertake comparable calculations for the different possible position-isomers of 8-(methoxyphenyl)menthyl crotonates, in which an OCH_3 is introduced on the phenyl ring, in order to further investigate the influence of the electrostatic forces on the conformation of 8-phenylmenthyl crotonates. The reason for the choice of a methoxy group as a substituent is twofold. The electrostatic effect should, for these molecules, be similar to that obtained for PPP while the increase in the dispersion contribution, possibly due to the extension of the aromatic system, should be of lesser importance in this case. On the other hand, experimental data on the closely related 8-(*p*- and 8-(*m*-methoxyphenyl)menthyl esters have shown that the introduction of the methoxy group on the aromatic ring has a moderate effect on these systems.[4a,5c]

The values for the three para, meta, and ortho 8-(methoxyphenyl)menthyl crotonate isomers (denoted as POP, MOP, and OOP, respectively) show that the presence of this substituent strongly favors the stacked isomers. The values reported in Table 2 indicate that, as expected, the introduction of a methoxy group tends to reduce the electrostatic repulsion that occurs in the stacked conformer. This is particularly striking for the OOP compound (Figure 3) and leads to a spectacular stabilization of the stacked OOPS conformer (3.8 kcal/mol). Interestingly, this particular compound has never, to the best of our knowledge, been prepared. We see also from Table 2 that the increase of the dispersion energy due to the presence of the methoxy group is as large as that produced by the *p*-phenoxy substituent.

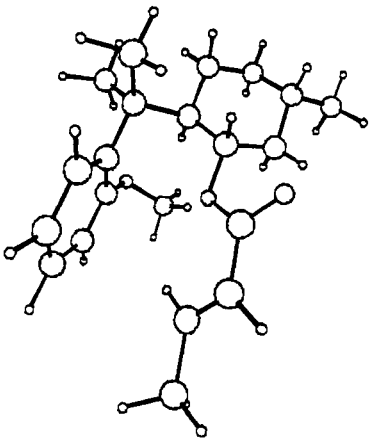
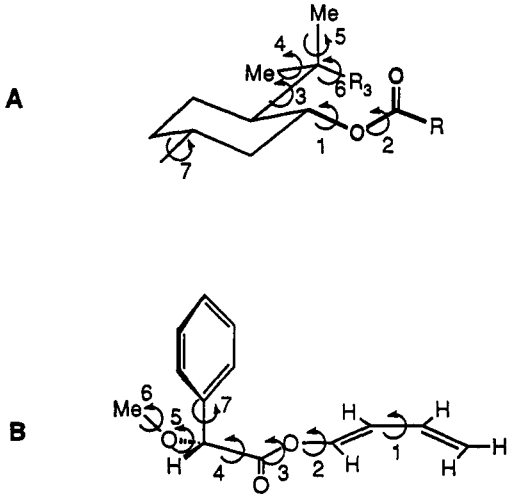


Figure 3. Most-stable conformation of 8-(*o*-methoxyphenyl)-menthyl crotonate.

Scheme 4



Other structural alterations have also been considered in an attempt to determine their relative influence on conformational preferences. The importance of the *gem*-dimethyl group had been experimentally evidenced[5c,7a] and has led us to investigate 2-benzyl-5-methylcyclohexyl (BC, X = Me, Y = Bn) and 2-phenylcyclohexyl crotonates (PC, X = H, Y = Ph) (Scheme 3). The values in Table 1 show that the three BC conformers are of comparable stabilities while a unique "exo" PC ester conformer (Scheme 3A) is found. This difference is due to a large increase in the repulsion contribution for the endo conformer. Accordingly, BC crotonate should be a poor partner for stereoselective reactions while the PC ester should prove interesting. There is no experimental data available, to our knowledge, for these chiral crotonates but the corresponding glyoxylates provide full support for these hypotheses (*vide infra*).

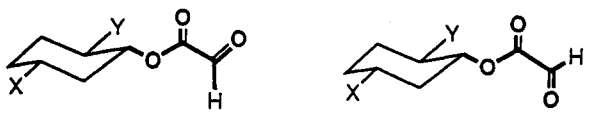
(29) For other applications of this chiral auxiliary to Michael addition reactions involving organometallic species, see ref 7c and Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427.

Table 3. Experimental[a] and Calculated Relative NMR Shielding Values [Δ(δ)] for the Protons in the Ethylenic Moiety of 8-Arylmenthyl Crotonates with Respect to Menthyl Crotonate (calculations performed on the stacked (S) and/or trans (T) conformations)

		HM	PM	NM	PPP
H(α)	exptl	0.0	0.51	0.91	0.48
	calcd	0.0 (T)	0.58 (S), −0.06 (T)	0.99 (S)	0.46 (S)
H(β)	exptl	0.0	0.52	0.89	0.46
	calcd	0.0 (T)	0.69 (S), −0.08 (T)	0.88 (S)	0.23 (S)
Me[b]	exptl	0.0	0.15	0.64	0.09
	calcd	0.0 (T)	0.20 (S), −0.03 (T)	1.05 (S)	−0.20 (S)

[a] Taken from ref 7b. [b] Average values for the three protons.

Scheme 5



A B

Computations of magnetic nuclear shielding constants have been carried out for the crotonate moiety protons of the compounds for which NMR spectra have been recorded.[7b] In Table 3 are presented the measured chemical shift differences [Δ(δ)] of these same protons between 8-arylmenthyl and menthyl crotonates.[30] They are reported together with the corresponding data calculated for the most stable conformation(s) of these compounds. Considering the theoretical values for the stacked conformations of arylmenthyl crotonates, it appears that, as expected, the aromatic ring(s) induce(s) a significant upfield shift for the protons considered. Moreover, the reasonable quantitative agreement between calculated and measured Δ(δ) gives good support to the theoretical conformations. However, in the case of phenylmenthyl crotonate itself, the negligible energy difference found between the S and T conformers suggests that both forms are present in solution. The values in Table 3 concerning this compound tend to confirm this assumption since experimental data may be accounted for with reasonable accuracy by a weighted average between the two threshold conformations.

Asymmetric Glyoxylates. Chiral glyxoylates,[5b,c,6a,b,10a] phenylglyoxylates,[6c,9,15g,h,31] and pyruvates[9,10c,15h] have been widely studied in asymmetric addition and ene reactions. Glyoxylates have also been submitted to an extensive structure–selectivity correlation study by Whitesell's group.[5c] The availability of this homogeneous set of experimental results, including proton NMR data, and the high level of selectivity obtained in several cases prompted us to extend our study to some of these compounds.

The configuration of the chiral centers experimentally obtained in these particular cases is consistent with a cisoid arrangement of the carbonyl groups of the reagent rather than a transoid one (Scheme 5). This result has been interpreted for phenylglyoxylate by the stabilizing interaction between the phenyl HOMO and the glyoxal LUMO.[8] However, the results obtained for menthyl glyoxylate show that the reaction occurs on the cisoid form of the glyoxal moiety, even in the absence of this interaction. This led us to evaluate the energy difference between the cisoid and transoid forms of the methyl glyoxylate at the SCF level using the 6-31G** basis set.[32] The transoid conformer is found to be more stable than its cisoid counterpart by only 1.3 kcal/mol. It can therefore be expected that the long-range interactions between the glyoxal moiety and the substituted cyclohexane ring tend to invert the relative stability of conformers, as experimentally found. In relation to this problem, it is worth noting that the computations, which have been carried out for both cisoid and transoid conformers, show that the former is the more stable in all cases. The analysis of both sets of results indicates that the stabilization of the cisoid form is due to the electrostatic contribution. Nevertheless, for the sake of conciseness, we will report here only results dealing with the cisoid derivatives. Table 4 and Figure 4 show that the results concerning the glyoxylates lead to conclusions almost identical to those drawn for the corresponding crotonates. As in the previous case, an overall correlation between the preference for the stacked conformers and the measured de is noticed. Albeit not as good as that concerning crotonates, this correlation is significant since we do not take into account the organometallic intermediate involved in the reaction under study. Worthy of note are the cases of MOP, BC and PC glyoxylates, for which no experimental data on corresponding crotonates are available. The results concerning BC glyoxylate (Table 5), similar to those obtained for the BC crotonate, illustrate the essential contribution of the *gem*-dimethyl group to the stability of the 8-phenylmenthyl ester stacked conformation.

Table 4. Calculated Energy and Geometrical Parameter Values for Asymmetric Glyoxylate Conformational Optima CHOCOOR*

R	conformer	dihedral angles[a]	E[b]
menthyl (HM)	S	77/1/306/185/173/181	567.9
	T	77/1/166/180/174/181	**566.4**
	A	76/1/65/172/192/181	568.2
8-phenylmenthyl (PM)	S	82/359/302/182/169/117/180	**633.0**
	T	77/0/178/189/177/64/180	**633.0**
	A	76/0/53/175/177/270/180	635.0
8-(*p*-MeO-C_6H_4)-menthyl (POP)	S	83/356/302/182/169/117/181/80/59	**877.0**
	T	76/2/176/190/178/64/181/77/50	877.6
	A	75/2/60/179/183/96/181/279/301	879.4
8-(*m*-MeO-C_6H_4)-menthyl (MOP)	S	83/359/302/181/170/120/181/88/63	**876.1**
	T	77/2/177/189/178/64/181/79/59	877.2
	A	78/5/60/179/184/279/181/80/60	877.8
8-(*o*-MeO-C_6H_4)-menthyl (OOP)	S	84/356/304/182/172/295/181/110/312	**876.6**
	T	75/1/178/197/182/56/180/106/318	879.7
	A	76/359/302/198/167/88/181/112/88	886.8
trans-2-benzylcyclohexyl (BC)	S	81/359/296/113	392.6
	T	77/0/194/74	**392.2**
	A	76/0/52/90	392.4
trans-2-phenylcyclohexyl (PC)	"exo"	79/0/237	**308.8**
	"endo"	296/2/234	315.8

[a] Dihedral angle ordering is shown on Scheme 4A. [b] In kcal/mol, in absence of intramolecular polarization. Boldface values represent most-stable conformer.

(30) See ref 19b for preliminary results. Finding a more stable conformation for NMS led us to recalibrate eq 3 of the latter paper. Values reported here have been calculated using the following formula:

$$\sigma^D = \sum_P \sum_P (-1/r_{Hp}^{10} + 1.5/r_{Hp}^{8} - 2/r_{Hp}^{6})$$

(31) Hamon, D. P. G., Holman, J. W., Massy-Westropp, R. A. *Tetrahedron* **1993**, *49*, 9593.

(32) Pietro, W. J.; Francl, M. M.; Hehre, W. J.; De Frees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039.

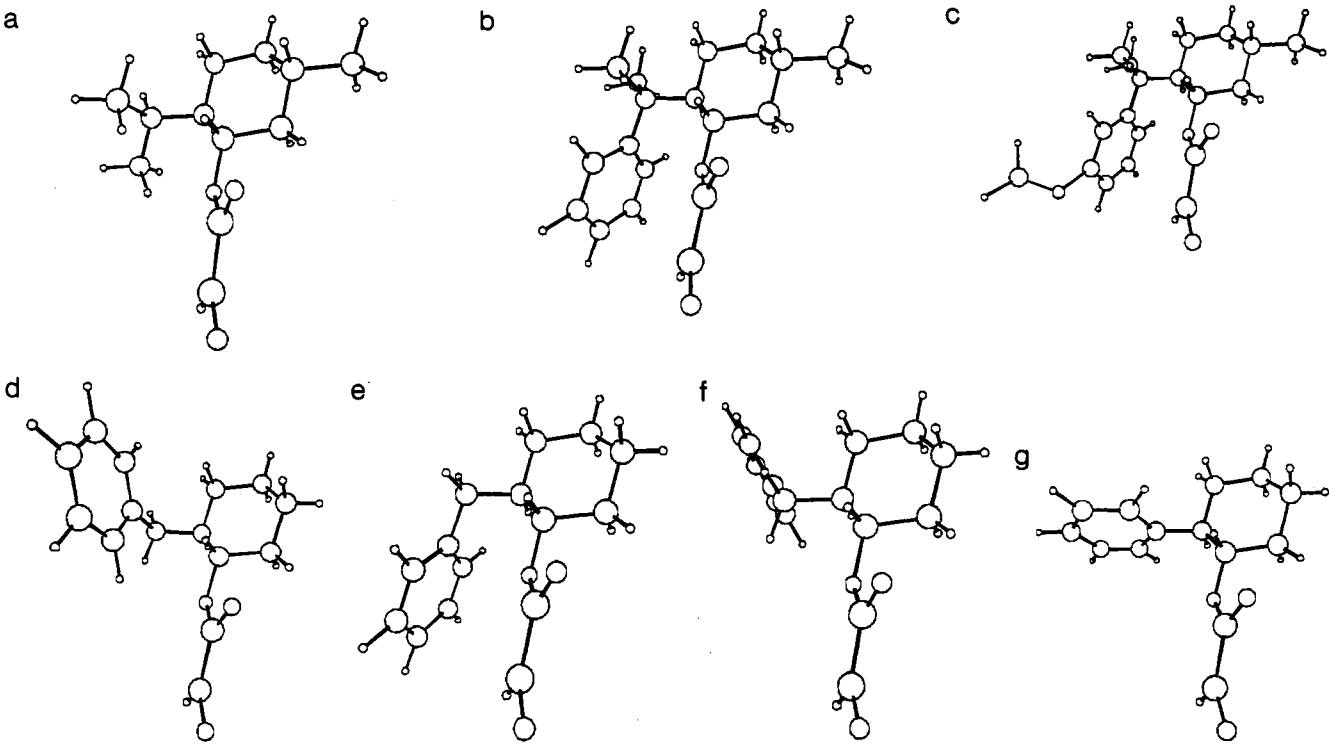
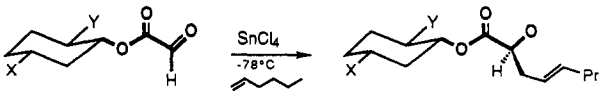


Figure 4. Most-stable conformations of chiral glyoxylates for which experimental data are available: trans menthyl (a), stacked 8-phenylmenthyl (b), stacked 8-(*m*-MeO-phenyl)menthyl (c), axial (d), stacked (e), and trans (f) 2-benzylcyclohexyl and 2-phenylcyclohexyl (g).

Table 5. Contributions in kcal/mol of Main Components to Conformational Energy Minima of Chiral Glyoxylates. HM, PM, POP, MOP, OOP, BC, and PC Refer to Menthyl, 8-Phenylmenthyl, 8-(*p*-, 8-(*m*-, 8-(*o*-Methoxyphenyl)menthyl, *trans*-2-benzyl- and *trans*-2-Phenylcyclohexyl Glyoxylates, Respectively, under Their Most Stable Conformations ("stacked" (S), "trans" (T) or "axial" (A))

	repulsion	dispersion	polarization	electrostatic	torsion	total[a]	exptl de (%)[b]
HMS	617.6	−64.4	−4.7	29.2	−14.5	563.2	33
HMT	615.6	−64.3	−4.8	29.4	−14.4	**561.6**	
PMS	726.7	−82.8	−5.1	3.4	−14.3	**627.9**	99.8
PMT	726.6	−81.3	−5.0	2.3	−14.6	628.0	
POPS	952.4	−96.6	−6.0	35.1	−13.9	**870.9**	
POPT	952.2	−94.8	−6.0	34.4	−14.2	871.6	
MOPS	952.3	−96.9	−6.2	35.1	−14.3	**870.0**	>90
MOPT	952.2	−95.0	−6.0	34.3	−14.2	871.2	
OOPS	959.6	−104.0	−6.7	33.7	−12.7	**869.9**	
OOPT	958.6	−100.4	−6.4	34.5	−13.0	873.4	
BCA	422.8	−46.4	−2.6	31.1	−15.2	**389.8**	
BCT	418.3	−42.3	−2.5	31.2	−15.0	**389.8**	20
BCS	418.7	−44.2	−2.6	33.2	−15.1	390.0	
PCEX	321.2	−33.6	−1.7	36.3	−15.2	**307.0**	>90
PCEN	335.0	−39.8	−1.7	35.9	−15.4	314.0	

[a] Boldface values represented most-stable conformer. [b] Values are taken from ref 4c and refer to the following reaction:



The values reported in Table 5 put clearly in evidence that, as previously, the dispersion term which favors the S conformation is counterbalanced by the electrostatic forces. However, for the glyoxylates, the electrostatic repulsions occurring in the stacked conformer are smaller than in the crotonates. This result may be attributed to the existence, as postulated by Runsink et al.,[9] of a dipole-induced-dipole stabilizing contribution in the stacked conformations of 8-aryl menthyl glyoxylates. Noteworthy is the case of OOP in which both electrostatic and dispersion contributions stabilize the stacked form (by 3.5 kcal/mol), a result that tends to confirm that an *o*-MeO-substituted phenylmenthyl ester should be a particularly efficient substrate for diastereoselective reactions.

We see from the values of the chemical shift variations reported in Table 6 that the theoretical results run parallel to experiment. However, for this series of compounds, theory tends to underestimate the upfield shift of the aldehydic proton resonance produced by the aromatic ring. We wish to point out that, in the case of BC, the agreement between calculated and measured $\Delta(\delta)$ is considerably improved if one considers the average value (0.21 ppm)

Table 6. NMR Shieldings (σ^T, in ppm) and Relative Chemical Shifts ($\Delta(\delta)$, upfield > 0) for the Aldehydic Proton of Menthyl (HM), 8-Phenylmenthyl (PM), 8-(*m*-MeO-Phenyl)menthyl (MOP), 2-Benzylcyclohexyl (BC), and 2-Phenylcyclohexyl (PC) Glyoxylates in Their Most Stable Stacked (S), Trans (T), or Axial (A) Conformations

	HMT	PMS	PMT	MOPS	BCS	BCT	BCA	PCEN
σ^T	1.42	2.03	1.32	2.08	2.17	1.40	1.33	1.69
$\Delta(\delta)$ calcd	0.00	0.61	−0.10	0.66	0.75	−0.02	−0.09	0.27
exptl[a]	0.00	0.80		0.83		0.12		0.39

[a] Values taken from ref 5c.

Table 7. Conformational Parameters and Energy Components (in kcal/mol) of the Two Most Stable Conformations of Butadienyl *O*-Methylmandelate

	conformational parameters[a]	repulsion	dispersion	polarization	electrostatic	torsion	total
A	0/180/0/303/195/181/107	683.8	−51.4	−4.0	−18.8	−44.7	**564.6**
B	0/180/0/128/196/181/99	683.8	−51.7	−4.1	−17.8	−44.8	565.4

[a] Dihedral angle ordering is shown on Scheme 4B.

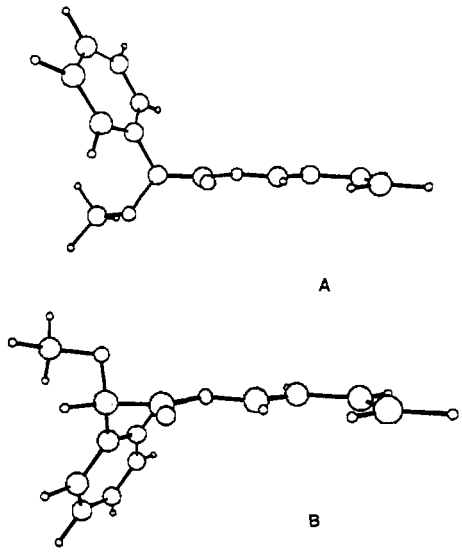


Figure 5. Two most-stable conformations of butadienyl *O*-methylmandelate (see Table 7 for energetic details).

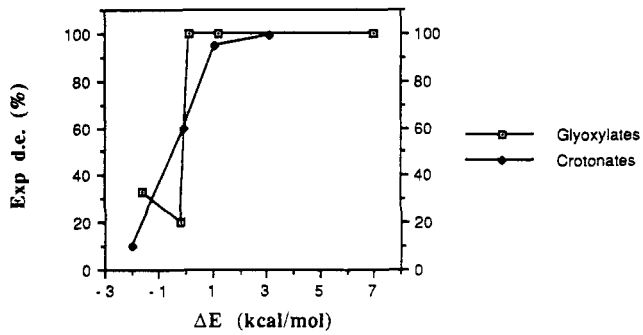


Figure 6. Correlation between the experimental de and the (de)stabilization of stacked conformers of chiral glyoxylates and crotonates.

instead of any of those calculated for the three isoenergetic conformers.

Butadienyl *O*-Methylmandelate. The results concerning butadienyl *O*-methylmandelate (Scheme 2) are reported in Table 7 and illustrated in Figure 5. They are consistent with those obtained by Houk et al.[13] using MM2. In agreement with these authors, we were unable to find any local minimum on the molecular potential energy surface corresponding to a conformation exhibiting a stacking phenomenon between aryl and diene moieties. These similarities in results derived from quite different molecular mechanics systematics, SIBFA and MM2, suggest that the relative role of the different contributions to the overall energy in this type of compound is correctly balanced. They tend to show in particular that the importance of the dispersion phenomenon is specific to the aryl menthyl derivatives. This last point is strengthened by the results concerning phenyl cyclohexyl esters. We obtain, for the glyoxylate, a conformation (Figure 4g) analogous to that of butadienyl *O*-methylmandelate. Hence, the "perpendicular model" proposed earlier by Thornton[14a] for the latter compound could also explain the selectivities measured in reactions involving the former one.

Conclusion

The most stable conformations of aryl menthyl conjugate esters obtained from SIBFA calculations exhibit a π−π stacking between the aryl and conjugated moieties of the molecules. This result, consistent with the initial experimental hypotheses,[1,4a] is also supported by the agreement obtained between measured and calculated NMR proton shifts. Those concerning benzyl cyclohexyl esters on the one hand and menthyl esters on the other show that the presence of the *gem*-dimethyl group is critically important for these inductors' efficiency. The overall correlation obtained between the energy stabilization of the stacked conformer and that of the trans/axial one (illustrated on Figure 6) tend to show that the small calculated energy differences are qualitatively fully significant. This correlation supports the hypothesis of the primary importance of chiral reactant's ground-state conformation. Considering the limitations of our theoretical approach, we could not reasonably expect more than a qualitative agreement. Improvements could be brought by (i) the use of a larger basis set in the *ab-initio* computations of the fragments; (ii) the introduction of a charge-transfer term;[33] (iii) the introduction of the $1/R^8$ and $1/R^{10}$ terms in the dispersion contribution computation;[34] (iv) the use of multipoles taking into account electron correlation.

This set of results suggests that, for this series of molecules, the stabilization of the stacked structure demands the occurrence of a π−π complexation and thus makes the presence of the aromatic ring essential, as previously mentioned by several authors.[5c,9,35] In addition, recent catalytic induction results[36] seem to indicate that

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the enantioselectivity due to a stacked arrangement of the chiral partner can occur for compounds very different from those considered in this study.

In the cases of phenyl cyclohexanol esters and butadienyl *O*-methylmandelate, the origin of diastereoselectivity cannot be simply related to preferred ground-state conformation. In such cases, explicit introduction of the relevant adducts can become essential.[13,37] Last but not least, the dispersion contribution that stabilizes the stacked conformation can be counterbalanced by unfavorable electrostatic forces. However our results concerning *o*-MeO-phenylmenthol esters show that an appropriate substitution may overcome such a repulsive interaction.

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