J. Org. Chem. **2000,** *65,* 7303−7309

A Quantum Mechanics/Molecular Mechanics Study of the Highly Enantioselective Addition of Diethylzinc to Benzaldehyde Promoted by (*R*)-2-Piperidino-1,1,2-triphenylethanol

Jordi Vázquez,† Miquel A. Pericàs,*,† Feliu Maseras,*,‡ and Agustí Lledós‡

Unitat de Recerca en Síntesi Asimètrica (URSA), Departament de Química Orgànica,
Universitat de Barcelona, c/ Martí i Franquès, 1-11. 08028-Barcelona, Spain, and Unitat de Química
Física, Edifici C.n, Universitat Autònoma de Barcelona, 08193-Bellaterra, Catalonia, Spain

mapericas@qo.ub.es

Received June 19, 2000

The enantioselective addition of diethylzinc to benzaldehyde mediated by (*R*)-2-piperidino-1,1,2-triphenylethanol has been studied with the IMOMM procedure, using a RHF description for the quantum mechanical part of the calculation and the mm3(92) force field for the molecular mechanics part. Both the sign and the value of the observed enantioselectivity are well reproduced by the calculations, the relative energies of the four possible transition states being as follows: anti-Si (0.0 kcal·mol^{-1}), syn-Re (2.7 kcal·mol^{-1}), anti-Re (4.7 kcal·mol^{-1}), syn-Si (5.9 kcal·mol^{-1}). These energies show a perfect correlation with the bond distance in the transition state between zinc and the methylene unit of the ethyl group being transferred.

Introduction

Over the last two decades, the increasing demand of enantiopure compounds for the pharmaceutical industry together with the raising of environmental concerns has fostered the development of enantioselective catalysis both as a discipline and a production methodology.[1]

In almost every case, the key species in the catalytic cycle involves a metal atom chelated by a polyfunctional organic molecule (a chiral ligand). This system offers neighboring sites for coordination of the substrate and reagent molecules and provides a low energy pathway for their reaction. In this supramolecular system, one of the most important roles of the chiral ligand is that of transmitting stereochemical information to the reacting molecules, so that diastereomeric transition states (TS's) involving enantiotopic groups or faces in the substrate molecule are energetically well differentiated.

For many catalytic processes, the use of different ligands belonging to the same family does not provoke any mechanistic change. Enantioselectivity, in turn, can be deeply modified by the nature of the employed ligand. In this respect, modularly constructed ligands are gaining progressive importance since (at least in principle) they can be structurally modified as to provide optimal enantioselectivity with any substrate participating in a certain reaction.

To achieve this goal, different approaches can be followed: (i) trial-and-error, (ii) combinatorial, and (iii) mechanism-guided. Whereas the trial-and-error approach has been classically followed, and combinatorial approaches in association with high throughput screening have already provided interesting results,[2] the problem can be most conveniently and economically tackled, when a clear mechanistic picture exists for the considered reaction, following a computer-assisted, mechanism-directed approach.[3]

This would involve the following stages: (a) Determining a reliable and cost-effective theoretical approach able to correctly predict the enantioselectivity of the reaction in a known, reference case, (b) analyzing the diastereomeric transition states for a *problem* example in order to identify structural factors in the considered ligand that could increase the gap between the lowest energy TS's leading to the enantiomers of the reaction product, (c) synthesizing the modified ligands suggested by the analysis in point b, and (d) testing the modified ligands in the reaction under study.

Our continued effort on the synthesis and evaluation of modular amino alcohols of high enantiomeric purity as all-purpose ligands for asymmetric catalysis[4] has recently led to the development of (*R*)-2-piperidino-1,1,2-triphenylethanol (**1**) as a very readily available, ex-

---

* To whom correspondence should be addressed. E-mail for F. Maseras: feliu@klingon.uab.es.

† Universitat de Barcelona.

‡ Universitat Autònoma de Barcelona.

(1) For a general account, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer, Berlin, 1999; Vols. I−III. For industrial applications, see: (b) Sheldon, R. A. *Chirotechnology: Industrial Synthesis of Optically Active Compounds*; Dekker: New York, 1993. (c) *Chirality in Industry*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds., Wiley: Chichester, 1992. (d) *Chirality in Industry II*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds., Wiley: Chichester, 1997.

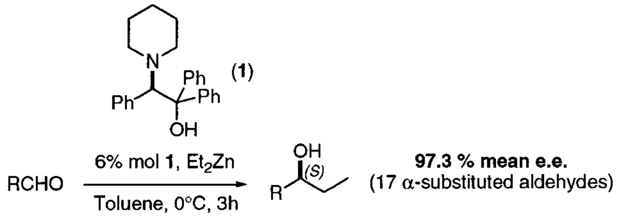
(2) For some recent examples, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63*, 5312. (c) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180. (d) Reetz, M. T.; Becker, M. H.; Klein, H. W. Stockigt, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1758.

(3) For some examples, see: (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773. (b) Brandt, P.; Hedberg, C.; Lawonn, K.; Pinho, P.; Andersson, P. G. *Chem. Eur. J.* **1999**, *5*, 1692.

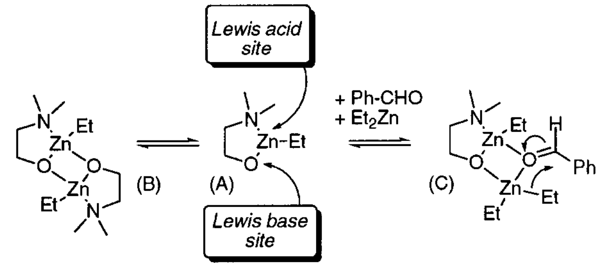
(4) (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970. (b) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. (c) Jimeno, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1999**, *40*, 777. (d) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969. (e) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902. (f) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **2000**, 165.

10.1021/jo000928+ CCC: \$19.00

Scheme 1



Scheme 2



tremely efficient controller for the enantioselective addition of diethylzinc to all kinds of α-substituted aldehydes (Scheme 1).[5] With this ligand as a starting point, we would like to identify possible structural modifications leading to improved enantioselectivities in the ethylation of α-unsubstituted aldehydes. We are thus at the outset of the mechanism-directed ligand engineering process we have discussed above.

We report here on the use of a recently developed, integrated ab initio plus molecular mechanics approach (IMOMM)[6] for the study of the possible transition states in the addition of diethylzinc to benzaldehyde promoted by **1** and on the successful prediction of the observed enantioselectivity of the reaction. This same method has been previously applied with success to the study of other enantioselective processes.[7]

Choice of the Theoretical Approach: Previous Studies on the Amino Alcohol Promoted Addition of Diethylzinc to Aldehydes. Experimental evidence indicates that the interaction between diethylzinc and an amino alcohol produces a chelated ethylzinc alkoxide (A), which is in equilibrium with a dimeric species (B).[8] Only the monomer is catalytically active, and the adjacent Zn and O ring atoms, displaying complementary Lewis acid and Lewis base characters, are believed to respectively coordinate one molecule of aldehyde and one molecule of diethylzinc to assemble the key species (C) where the ethyl group transfer occurs (Scheme 2).

Over the last years, several theoretical studies have been devoted to the mechanism of this reaction. In a pioneering effort, Yamakawa and Noyori studied at the RHF/3-21G/Zn level the 2-aminoethanol promoted addition of dimethylzinc to formaldehyde and established the preference for anti type TS's over syn type ones (Figure 1).[9]

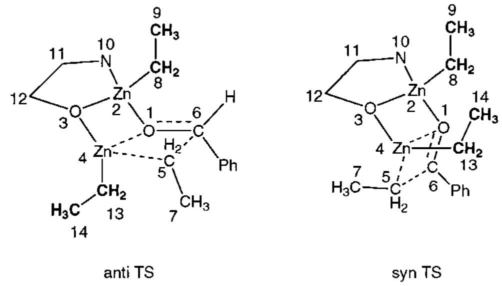


Figure 1. Schematic representation of the anti and syn transition states in the amino alcohol promoted addition of diethylzinc to benzaldehyde. Numbering is arbitrary and has been used in geometry discussions.

It is worth noting that each of these basic structures can give rise to two different transition states (Si and Re attacks) when a prochiral aldehyde is involved in the process.[10] A more complete study by the same group, performed at the same level of theory and also using DFT theory, analyzed and correctly predicted the sense of the enantioselectivity in the (2*S*)-3-exo-(dimethylamino)-isoborneol-induced addition of dimethylzinc to benzaldehyde.[11]

In turn, Houk and co-workers have reported a complete semiempirical PM3 study on the addition of dialkylzinc reagents (ZnMe$_2$ and ZnEt$_2$) to benzaldehyde catalyzed by different amino alcohols.[12]

If the analysis of the diastereomeric transition states in this reaction has to be used as a design tool, the right election of theoretical procedure becomes a critical question. While a complete ab initio analysis would be impractical in terms of cost when ligands incorporating very common, bulky structural elements (1,1′-binaphthalene-2,2′-diyl, diphenylmethyl, etc.) are involved in the study, the use of semiempirical approaches would be flawed by an imperfect description of the critical distances in the transition states as well as by a poor characterization of steric effects, and these factors could lead to an incorrect estimation of the effect on enantioselectivity of structural elements in the ligand.[13]

Integrated quantum mechanics/molecular mechanics (QM/MM) procedures appear in turn as the best suited for design purposes: The critical parts of the reacting system are accurately described at ab initio level, while the steric effects of the different structural elements constitutive of the ligands are well accounted for by the molecular mechanics treatment of this part of the system. As a consequence of this partition, the size of the molecules or supramolecular assemblies to which this methodology can be applied has practically no limit. One of these methods (ONIOM)[14] has very recently been applied to the study of dialkylzinc additions to benzaldehyde catalyzed by fenchone derivatives.[15] In the present article, we apply the closely related IMOMM method[6] to the reaction induced by a different amino alcohol, namely

---

(5) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078.

(6) Maseras, F.; Morokuma, K. *J. Comput. Chem.* **1995**, *16*, 1170.

(7) (a) Ujaque, G.; Maseras, F.; Lledós, A. *J. Org. Chem.* **1997**, *62*, 7892. (b) Ujaque, G.; Maseras, F.; Lledós, A. *J. Am. Chem. Soc.* **1999**, *121*, 1317.

(8) Kitamura, S.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605.

(9) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327.

(10) The core geometry of these transition states (anti and syn) has been used in combination with AM1 geometrical optimization of substituents as a design tool for ligands derived from 3-phenyl-3-aminopropane-1,2-diol. See ref 3a.

(11) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128.

(12) Goldfuss, B.; Houk K. N. *J. Org. Chem.* **1998**, *63*, 8998.

(13) Note, however, that semiempirical approaches have shown to correctly predict the sign of enantioselectivity when a single ligand is considered. See refs 3a and 12.

(14) Dapprich, S.; Komáromi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. *J. Mol. Struct. (THEOCHEM)* **1999**, *461*, 1.

(15) (a) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77. (b) Goldfuss, B.; Steigelmann, M.; Rominger, F. *Eur. J. Org. Chem.* **2000**, 1785.

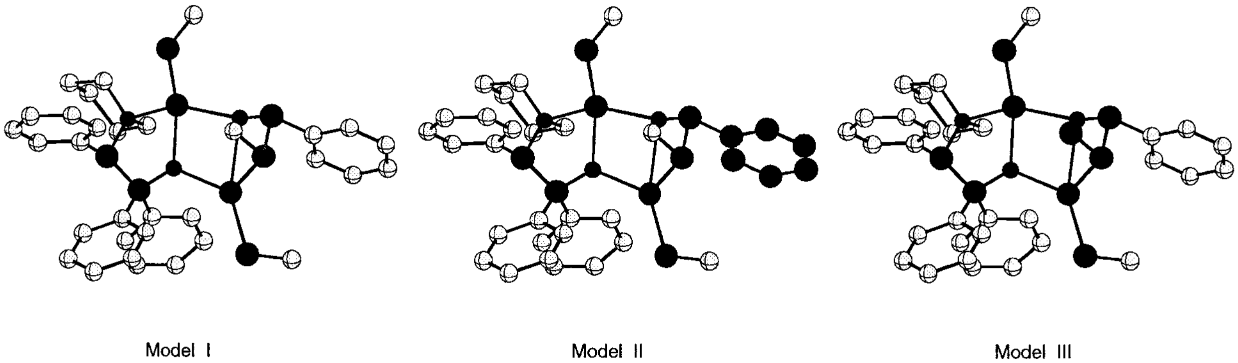


Figure 2. The three different QM/MM partitions tested for the IMOMM calculations. The QM region is always depicted in black. The drawings correspond to an anti-Si type transition state.

(*R*)-2-piperidino-1,1,2-triphenylethanol.[5] Other novelties with respect to the previous study are the use of a different force field in the MM region, the consideration of different QM/MM partitions, and the introduction of the complete ethyl substituents in the diethylzinc reagent which, as we will see later, is critical for an accurate description of the process.

Computational Details. IMOMM calculations were carried out with a program built from modified versions of the two standard programs Gaussian 92/DFT[16] and mm3(92).[17] The quantum mechanical (QM) part of the calculation used the restricted Hartree–Fock description with a valence double-ζ basis set for all atoms: LANL2DZ basis set for Zn,[18] and D95V for the rest.[19] This computational level is similar to the HF/3-21G method applied before in full QM calculations on a similar system,[11] where it was found to provide results similar to those of a much more expensive B3LYP/6-31G(d) description. The MM calculations used the mm3(92) force field.[20] van der Waals parameters for the zinc atom were taken from the UFF force field, and torsional contributions involving dihedral angles with the metal atom in the terminal position were set to zero.

All geometrical parameters were optimized except the bond distances between the QM and MM regions of the systems. The frozen values were 1.112 Å (C–H), 1.012 Å (N–H) in the QM part; and 1.499 Å (C_{sp^3}–C_{sp^2}), 1.525 Å (C_{sp^3}–C_{sp^3}), 1.448 Å (N–C) in the MM part. Transition states were located using analytical derivatives and approximate Hessians. In all cases, conformational isomerism arising from rotation of the ethyl groups was thoroughly investigated. Different partitions between the quantum mechanics (QM) and the molecular mechanics (MM) regions were considered, and they will be discussed in the next subsection.

Definition of the QM Region in the Calculations. The IMOMM method describes properly the steric effects of atoms in the MM region, but neglects their electronic effects.[21] Because of this, the partition of the system between the QM and MM regions is critical for the outcome of the calculations. The larger the QM region, the more accurate the results, but the more expensive the calculations. In fact, the best would be a full high-level QM calculation on the system under study, but this would require a total of 508 basis functions, and a systematic search of a series of transition states with that many basis functions involved is currently beyond our reach.

Table 1. Relative IMOMM Energies (kcal·mol^{-1}) with Respect to Anti-Si of the Four Possible Transition States Computed with Each of the QM/MM Partitions Shown in Figure 2

	model I	model II	model III
anti-Si	0.0	0.0	0.0
anti-Re	3.2	5.4	4.7
syn-Si	4.6	3.7	5.9
syn-Re	2.7	2.3	2.7

The first QM/MM partition considered (presented in Figure 2 as model I) limited the QM description of the catalytically active, chelated alkylzinc alkoxide to $Zn(OCH_2CH_2NH_2)(CH_3)$, that of the diethylzinc to $Zn(CH_3)_2$, and that of the benzaldehyde substrate to H_2CO. This partition reduces the size of the QM region to an affordable amount of 169 basis functions. The four distinct transition states corresponding to the four traditional anti-Si, anti-Re, syn-Si, and syn-Re interaction modes were fully optimized with this model. Their relative IMOMM energies are collected in Table 1. It can be seen that the most favorable path corresponds to the anti-Si arrangement. The preference for an anti geometry is in agreement with the results of AM1 calculations for a similar system with a frozen core,[3a] and with the RHF results reported by Yamakawa and Noyori on a smaller but similar system.[11] Most importantly, the predicted sign of enantioselectivity is in agreement with experimental observations with the same ligand/substrate system.[5] Apparent discrepancies between these results and those by Goldfuss and Houk[12,15] on a number of other ligands simply reflect that the preference for a given geometry type in the transition states is greatly dependent on ligand type.

The reliability of the QM/MM partition applied was evaluated through additional IMOMM calculations with different partitions. These are also shown in Figure 2. The extensions considered to the QM region were in the region closer to the bond being formed, because this is in principle the area more sensitive to electronic effects. This region is in the vicinity of carbon atom C5, which is being transferred with its hanging methyl group (C7)

---

[16] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Foresman, J. B.; Robb, M. A.; Head-Gordon, M.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople J. A. *Gaussian 92/DFT* (Gaussian Inc., Pittsburgh, PA, 1993).

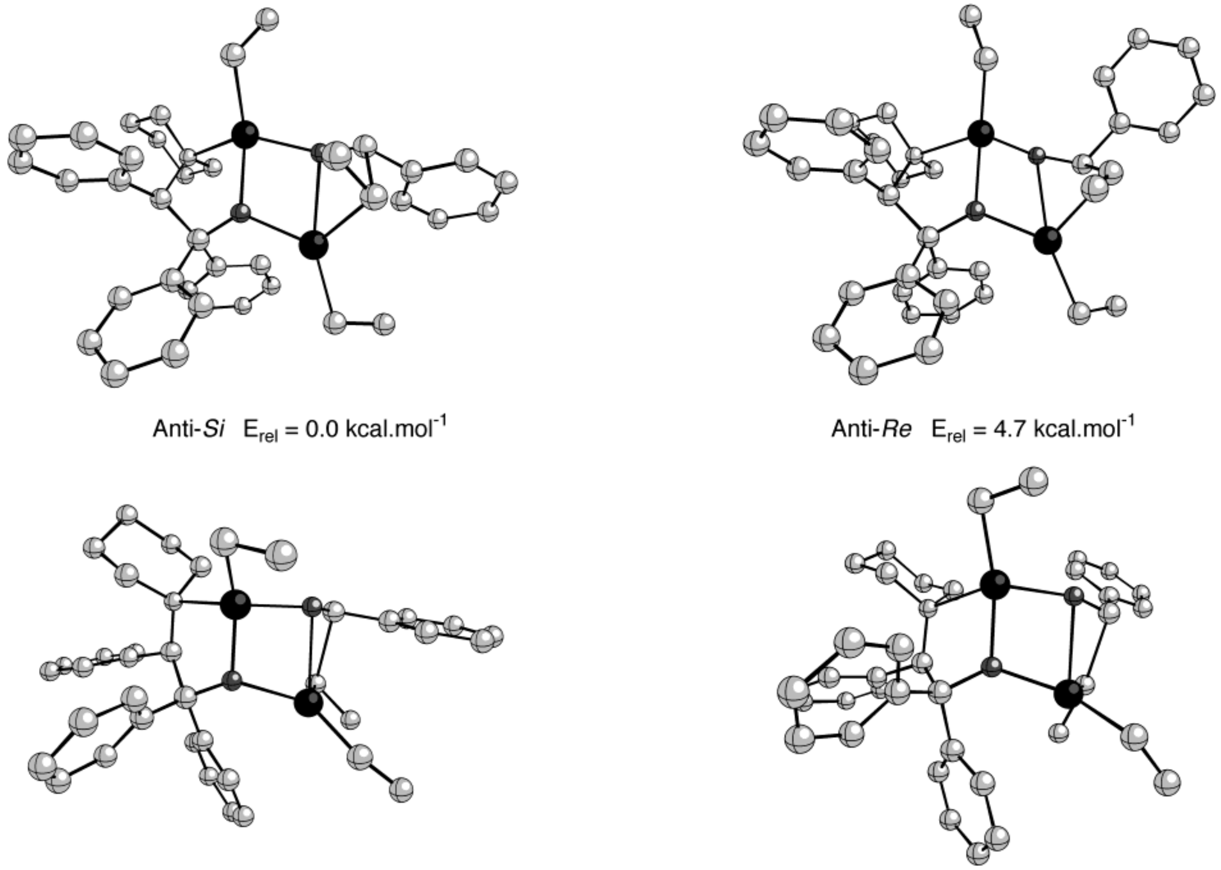
[17] Allinger N. L. mm3(92); QCPE: Bloomington IN, 1992.

[18] Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270.

[19] Dunning, T. H.; Hay, P. J. in *Modern Theoretical Chemistry*; Schaefer, H. F., Ed.; Plenum: New York, 1976; Vol. 3, p 1.

[20] Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.

[21] Maseras, F. *Top. Organomet. Chem.* **1999**, *4*, 165.



Anti-*Si* E_{rel} = 0.0 kcal.mol^{-1}

Anti-*Re* E_{rel} = 4.7 kcal.mol^{-1}

Syn-*Re* E_{rel} = 2.7 kcal.mol^{-1}

Syn-*Si* E_{rel} = 5.9 kcal.mol^{-1}

Figure 3. Molecular structures and relative energies of the located transition states. Hydrogen atoms have been omitted for clarity.

from the metal center Zn4 to the aldehyde carbon C6. Because of this, model II was an extension of model I where the phenyl group attached to C6 was added to the QM region. Similarly, in model III, the extension consisted of the methyl group (C7) attached to C5. The relative energies obtained with the three different models are collected in Table 1, and one can see that differences between different models are rather small. It is particularly reassuring that the nature of the two transition states determining the sign of the enantioselectivity (i.e., the most stable ones of Si and Re types) is always the same, with anti-Si being the most stable, and syn-Re following ca. 2.5 kcal/mol above.

These observations are confirmed by the inspection of the three different sets of optimized geometries. In particular, the bond distances of the carbon atom (C5) being transferred change very little. For instance, the Zn4−C5 and C5−C6 distances in the anti-Si structure are 2.269, 2.327 Å with model I; 2.289, 2.323 Å with model II; and 2.268, 2.312 Å with model III. The geometrical parameter most sensitive to the selected model is the Zn4−C5−C7 angle. In particular, its mean value changes from 87° with model I to 96° with model III. This geometrical difference might be related to the formation of a spurious agostic interaction in the QM part of the calculation between the C5−H group replacing the C5−C7 bond and the Zn4 center, an interaction which is lost when the full C-Me group is introduced in the QM region. It is worth noting that this agostic interaction can only be shown by the aforementioned angular distortion since the C5−H distance, which should be elongated by the agostic interaction, is frozen in the IMOMM calculation. This distortion, however, appears to be not very important from the energetic point of view. In summary, the three QM/MM models applied yield very similar results in practice. The extension of the QM region in areas further apart from the reaction centers has not been considered, because the effect ought to be even smaller. In the rest of the article we will discuss only the results obtained with model III, because they are free of the potential problem with the spurious agostic interaction without representing much additional computational effort with respect to model I. On the other hand the additional computational cost derived from using model II does not appear to be justified; although the inclusion of the phenyl ring of benzaldehyde in the QM region should allow a more accurate description of the loss of conjugation during addition, this only seems to affect the energies of the most energetic transition states which have no influence on enantioselectivity.

IMOMM Analysis of the Enantioselectivity of the Ethylation Process. We have represented in Figure 3 the optimized structures of the most stable conformers of the four possible diastereomeric transition states for the addition process, with the QM part defined by model III, along with their corresponding energies.

From a geometrical point of view, these supramolecular species present a significant difference with the corresponding structures involving conformationally rigid ligands, like DAIB.[11] In that case, it is observed that anti

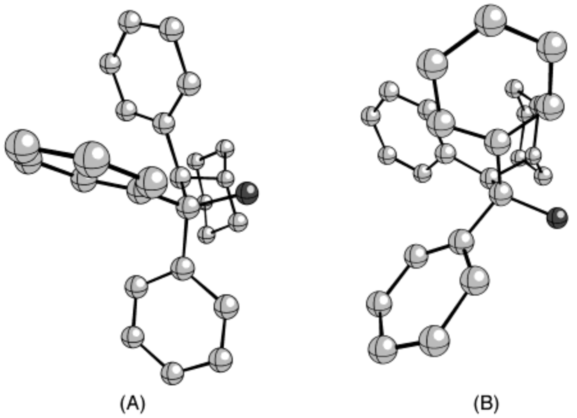


Figure 4. The ligand fragment in anti (A) and syn (B) transition states.

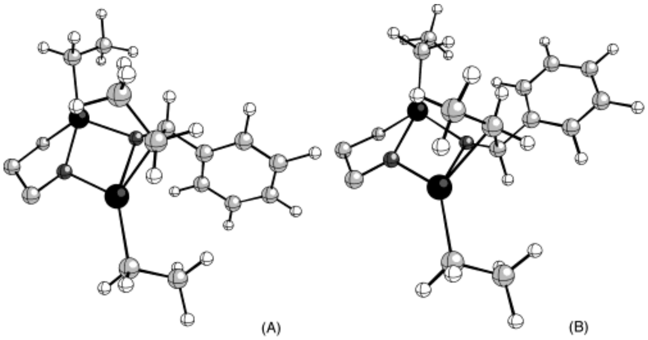


Figure 5. Anti-Si (A) and anti-Re (B) transition states in the addition of diethylzinc to benzaldehyde. Substituents in the ligand moiety have been omitted for clarity.

type TS's are generically more stable that syn type ones, and this fact has been attributed to a minimization (in anti structures) of strong interactions occurring in syn TS's between the alkyl groups substituents of the zinc atoms. In the present case, in turn, the conformation of the ligand fragment is smoothly adapted to the TS type: In anti structures, the H−C11−C12−O3 moiety is antiperiplanar, while in syn structures the aforementioned unit presents a gauche arrangement as shown in Figure 4. It is interesting to note that the ligand portion of these molecular assemblies is completely transferable (i.e., superimposable) between transition states of the same type.

Let us do now a comparative analysis of the structures of the same type. Among those of anti type, the anti-Si is the most stable one. In this assembly, the three ethyl groups are in such an arrangement that their mutual steric interactions are minimized. That arrangement has necessarily to be very favorable, since it is able to overcome a close contact (2.236 Å) between one of the H atoms at C5 and one of the ortho hydrogen atoms in the benzaldehyde fragment. These characteristics can be properly appreciated in Figure 5, where the anti structures have been represented with suppression of the ligand fragment for clarity. In the anti-Re structure, which is considerably (4.7 kcal·mol^{-1}) less stable, the change in orientation of the benzaldehyde molecule has provoked a rotation of ca. 43° in the ethyl substituent at the 5/4 ring junction. After that, no close contacts can be detected in the molecule.

A question arises on why such an important energy difference exists between these diastereomeric structures,

Table 2. Partition of the IMOMM Relative Energies (kcal·mol^{-1}) of the Four Possible Transition States into Quantum Mechanics (QM) and Molecular Mechanics (MM) Parts[a]

	QM	MM	IMOMM
anti-Si	0.00	0.00	0.00
anti-Re	3.01	1.63	4.66
syn-Si	7.29	−1.43	5.86
syn-Re	5.87	−3.23	2.65

[a] All energies are relative to that of the most favorable transition state (anti-Si).

and a possible explanation can be provided as follows: As we will see again later, a very clear preference exists in the studied reaction for an attack trajectory of 111−112° (C5−C6−O1 angle). In the anti-Si structure, attack following the optimal trajectory can take place without any deformation in the ring system. In the Re type structure, conversely, unfavorable steric interactions would arise between the ethyl and phenyl groups if no distortion took place. To avoid them, the ethyl group rotates 43° away as already discussed. To the same end, also the benzaldehyde molecule rotates (by ca. 53°). Since the preferred attack trajectory is maintained, an important deformation occurs at the critical four-membered ring where the reaction events take place (The O1−C6−C5−Zn4 dihedral angle has increased from 33.8° to 62.7°). All together, the geometrical deformations in the anti-Re structure we have just discussed have to be responsible for the energy difference between the two anti type transition states. We have summarized in Table 2 a partition of the energy differences between the diastereomeric TS's into QM and MM parts. It is interesting to see that, in line with the preceding discussion, both terms are in favor of the anti-Si TS.

The syn type structures (Figure 6) look very similar except for the orientation of the benzaldehyde molecule, and only a closer inspection evidences some differences at the level of the ethyl group being transferred. The syn-Re structure appears to be essentially free of close contacts and is in fact the most stable of the whole set when only the MM part is considered. The most noticeable characteristic of this structure is the peculiar orientation of the ethyl groups in the Et_2Zn moiety, which are found in a synperiplanar face-to-face arrangement, sterically confined between one of the phenyl groups of the ligand and the phenyl group of benzaldehyde. A space-filling representation of this transition structure illustrating this characteristic is given in Figure 7.

In the syn-Si structure (the most unfavorable one in the whole set), the transferred ethyl group is no longer confined and adopts a very different arrangement; the C7−C5−C6 angle has increased from 127 to 207° (−153°), so that an inversion of configuration has taken place at the transferred carbon.[22] This important geometrical change does not appear to be forced by geometrical constraints. The higher energy of this TS probably reflects its degree of advancement along the reaction coordinate, since the main component in its relative energy is of QM origin (Table 2). With respect to the syn-Re one, the energy difference seems to be partially due to the existence of a close-contact (2.193 Å) between an ortho hydrogen atom in benzaldehyde and an axial

---

[22] For a recent example of a theoretical study predicting inversion of stereochemistry at nucleophilic carbon, see: Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294.

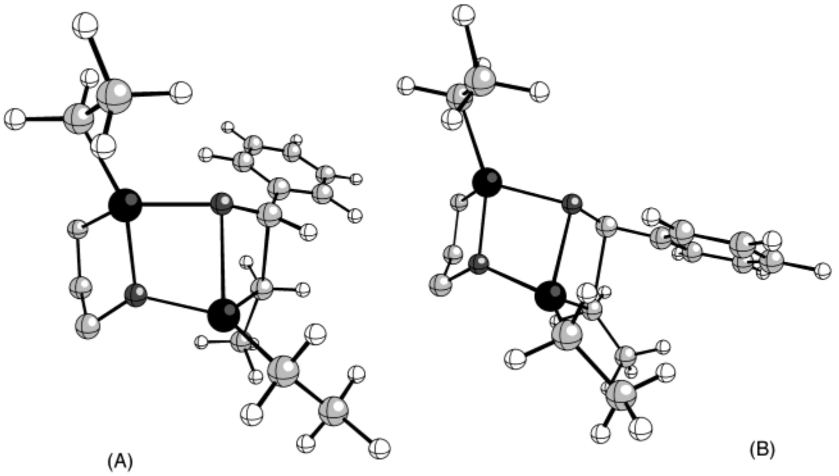


Figure 6. Syn-Si (A) and syn-Re (B) transition states in the addition of diethylzinc to benzaldehyde. Substituents in the ligand moiety have been omitted for clarity.

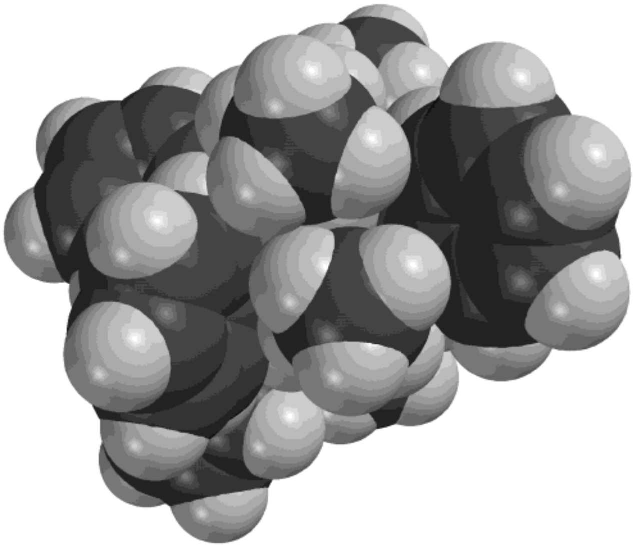


Figure 7. A space-filling model of the syn-Re transition state showing the confinement of the diethylzinc moiety between phenyl ring of ligand and substrate.

hydrogen atom in the piperidine ring. Avoidance of this interaction does not seem to be compatible with the maintainment of a reasonable trajectory of attack.

Since, as we have discussed, the conformational flexibility of our ligand does not warrant an analysis of enantioselectivities merely based on the anti/syn nature of the transition states, it is reasonable to collectively analyze all four possible transition states for the reaction. Given that the maximal structural variability of the transition states is concentrated at the four-membered ring where the reaction events occur, we have attempted to correlate the energy of the transition states with the geometry of this part of the molecules, as shown in Table 3.

A geometrical characteristic that deserves a comment is the preference for a certain type of trajectory of attack. Thus, the C5−C6−O1 angle remains essentially constant over the four TS's (111.2−112.6°), while the Zn4−C5−C6 angle shows a very limited variation (anti: 72.8−74.9°; syn: 68.2−70.0°). We thus make the interpretation that other geometric characteristics vary as to allow fulfillment of these angle values.

Table 3. Relative Energies (kcal·mol^{-1}) and Relevant Geometrical Parameters (Å and Degrees) of the Four Possible Transition States in the Addition of Diethylzinc to Benzaldehyde

	Anti-Si	Syn-Re	Anti-Re	Syn-Si
relative energy	0	2.7	4.7	5.9
O1−Zn4	2.604	2.386	2.818	2.439
Zn4−C5	2.268	2.291	2.312	2.331
C5−C6	2.312	2.360	2.218	2.293
C6−O1	1.283	1.283	1.296	1.282
C5−C6−O1	112.6	112.4	111.7	111.2
Zn4−C5−C6	74.9	70.0	72.8	68.2
C6−C5−C7	106.1	127.0	147.6	−153.4
O1−Zn2−O3−Zn4	24.2	24.5	37.4	14.8
O1−C6−C5−Zn4	33.8	−25.1	62.7	−43.9
Ar−C6−C5−C7	158.0	8.2	143.0	−152.8

Another important general point is on compactness and flexibility of the 5/4/4 ring system core of the transition states. In agreement with the findings of Noyori and Yamakawa, the O1−Zn4 distance representing the common edge of the four-membered rings is shorter in syn transition states than in anti type ones. For the ligand under study (Table 3), the differences are more important than for DAIB,[11] so that the tricyclic ring system appears to be more flexible (i.e., more tolerant to geometrical distortion) in anti TS's than in syn ones.

Very interestingly, two different parameters among those collected in Table 3 experience a completely parallel evolution with the relative energy over the whole considered set of transition states. In first place, the Zn4−C5 distance increases with the energy of the transition states, suggesting that the most energetic TS's are also the most advanced ones. Second, the value of the C6−C5−C7 angle notably increases with the energy of the TS's, exhibiting a wide variability from 106.1° in the anti-Si TS to −153.4° (or 206.6°) in the syn-Re one. It is important to realize that this parameter is not a true bond angle, since the C5−C6 distance is in the TS 60% longer than its normal bond length, but it seems to possess an important diagnostic value. Although the existence of similar tendencies should be investigated with other ligands before a general interpretation is provided, the present results are clearly illustrative of the importance of including in the calculations a complete representation of the zinc substituents while studying the present alkyl transfer process.

Conclusions

In summary, we have shown that the IMOMM procedure correctly predicts the sign of the enantioselectivity in the additions of diethylzinc to benzaldehyde mediated by (*R*)-2-piperidino-1,1,2-triphenylethanol (**1**). From a qualitative point of view, the predicted enantioselectivity assuming a Boltzmann distribution at room temperature (97.9%)[23] shows an excellent coincidence with the observed one at 0 °C (98%). This close coincidence tends to indicate the validity of the IMOMM method as a potential design tool for the development of new, more efficient ligands.

The geometrical analysis of the located transition states for the considered reaction shows that, contrary to an extended opinion, conformationally flexible ligands able to adapt their geometries to both anti and syn type transition states, can originate very high enantioselectivities. With these ligands, no intrinsic preference appears to exist for a certain type (syn or anti) of transition state.

In the system under study, the vehicles for transmission of stereochemical information from the ligand to the reaction centers are to a large degree the nontransferred ethyl groups bonded to zinc, which show a great conformational variability over the four considered transition states. This observation, together with the small difference in size between the resulting molecular systems, tells in favor of do not using dimethylzinc as a model for diethylzinc in theoretical studies on the amino alcohol promoted ethylation of aldehydes.

The studied reaction has illustrated a clear preference for a very precise trajectory of attack of the ethyl group to the carbonyl group. The bicyclic 4/4 core system of the transition states has shown to be flexible (mostly in the anti type ones) and to experience deformation as to allow maintenance of that preferred trajectory.

If the enantioselectivity of the reaction had to be increased, the syn-Re transition state should be destabilized. The suggestion that perturbation of the peculiar conformational arrangement exhibited by that structure (Figure 7) could be effective to this end is in the basis of investigations now underway in our laboratories.

Acknowledgment. Financial support from MEC (grants PB98-1246 and PB98-0916-CO2-01) and DURSI (grants 1998SGR00005 and 1999SGR00089) is gratefully acknowledged. We also thank CESCA-CEPBA for the use of their computational facilities.

JO000928+

---

[23] This result should be taken with precaution, since the calculated energy differences between transition states are not $\Delta\Delta G^{\ddagger}$ values.