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The origin of the stereoselectivity in the asymmetric Michael reaction using chiral imines/secondary enamines under neutral conditions: a computational investigation

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Abstract

The diastereoselectivity in the asymmetric Michael reaction using chiral imines/secondary enamines under neutral conditions has been investigated with the help of AM1 calculations. The energetic differences between the two competing transition states involving enamino ketones **7d**, **7g** and methyl acrylate are in good agreement with the stereoselectivities observed with the corresponding chiral imines, derived from 1-phenylethylamine (de 95%) and from 1-cyclohexylethylamine (de 45%). The calculated transition structures indicate that steric factors govern the π-facial discrimination. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Some years ago, one of the most potent methodologies for the enantioselective construction of quaternary carbon centers was reported, based on the asymmetric Michael reaction using chiral imines under neutral conditions.[1] Thus, chiral imines **2**, derived from *racemic* 2-substituted-cyclanones **1** and optically active 1-phenylethylamine, reacted with electron-deficient alkenes **4**, to lead regio- and stereoselectively to Michael adducts **5** (Scheme 1).[1] However, a dramatic decrease of the stereoselectivity was observed, when the phenyl ring of the chiral auxiliary was replaced by a cyclohexyl group.

From the very beginning, it was postulated that the nucleophilic species in this Michael addition are, in fact, the *more* substituted secondary enamines **3**, in tautomeric equilibrium with imines **2**. Strong experimental evidences for a *cyclic transition state*, and for an *internal proton transfer* from the nitrogen atom of the enamine to the electrophilic alkene were obtained.[1a,2]

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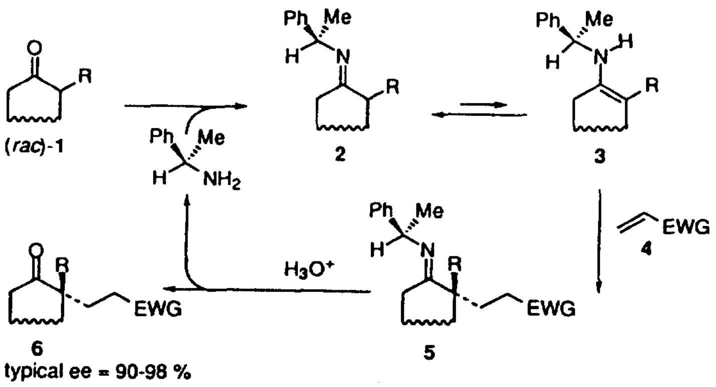
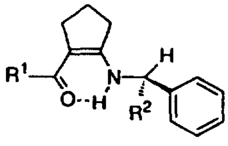


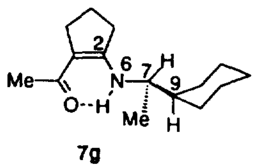
Scheme 1.

On the other hand, this process has been theoretically stimulated by *ab initio* SCF calculations, using propenal and ethyleneamine as prototype structures by Sevin et al. A *compact*, chair-like approach was found to be favored over a boat-like or a *linear* approach respectively, since being stabilized by MO interactions, and avoiding the formation of a thermodynamically disfavored *linear* zwitterionic intermediate.[3] However, further study of enamine structures having a pyramidal nitrogen atom, and the corresponding constrained transition structures at 3 Å, derived from the general substitution pattern, afforded no clear-cut conclusion about the origin of the remarkable stereoselectivity.[3] Recently, this process has been reinvestigated by Houk and Lucero on the basis of conformational transmission of chirality.[4] They found on a prototype system calculated at the RHF 6-31G* level that a transient *compact* zwitterionic intermediate is probably involved, and that for the transition state implicating the most stable half-chair of (*N*-1-phenylethylamino)cyclohexene and acrylonitrile computed with MM2, *axial* attack is 1 kcal/mol lower in energy than *equatorial* attack, a value consistent with the experimental data.

In this article, we report on the results of quantum mechanical calculations related to the π-facial discrimination of chiral enamines **3**, by selecting methyl acrylate and enamino ketones **7d**,[1a] **7e** and **7g** as reactants, hence including both phenyl and cyclohexyl series. Unlike the above mentioned systems,[3,4] the conformationally mobile cyclohexene ring is changed for a planar cyclopentene nucleus, and the enamine nitrogen atom is now perfectly planar.[1a] Consequently in our model system, in contrast with previous studies,[3,4] the π-facial discrimination is purely governed by the chiral group of the enamino ketone partner. Proposed theoretical transition structures[5] were thus located, and an excellent agreement was obtained between calculated and experimental stereoselectivities.



7a: R^1 = MeO; R^2 = Me
7b: R^1 = pNO₂PhO; R^2 = Me
7c: R^1 = pNO₂PhO; R^2 = tBu
7d: R^1 = Me; R^2 = Me
7e: R^1 = Me; R^2 = tBu
7f: R^1 = MeO; R^2 = tBu

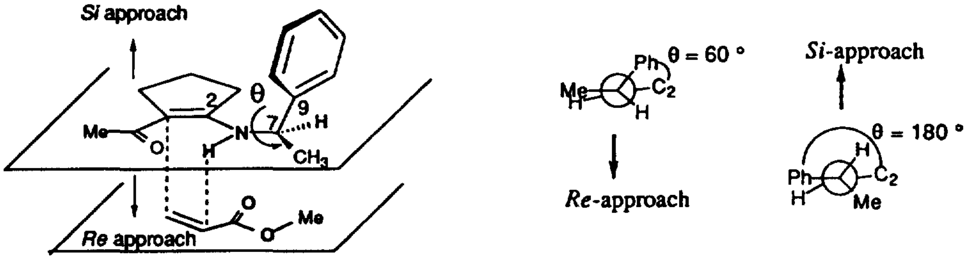


7g

2. Results and discussion

As a first step, the structures of constrained transition structures formed by methyl acrylate in close interaction with enamino ketones **7d**, **7e** and **7g** have been investigated by using the semi-empirical molecular orbital program MOPAC[6] at the RHF AM1 level.[7] Preliminary results for the two diastereomeric constrained transition structures of **7d** with methyl acrylate (*Re*-approach and *Si*-

approach) at 3 Å have shown that when methyl acrylate is approaching the *Re*-face (leading to the formation of the major diastereomer), at the relative minimum of energy, the enamino ketone adopts a conformation where θ=C2–N6–C7–C9 is about 60°. Conversely, when methyl acrylate is coming on the *Si*-face (leading to the formation of the minor diastereomer), the relative minimum corresponds to θ=180°: hence, for minimizing steric effects, the phenyl group is pushed away from its most stable position (81°, close to the corresponding angle value found in the crystal structure of enamino ester **7b**: 75°,[10] Scheme 2).[1a] The results are comparable with other enamino ketones **7e** and **7g**, for which only the constrained transition structures were calculated at 3.0 Å, where the dihedral angle θ is approximately 60° (*Re*-approach) or 180° (*Si*-approach). For **7g**, three additional 'sub-conformers': **7g$_1$**, (*anti*: H–C7–C9–H=180°), **7g$_2$** and **7g$_3$** (*gauche*: 60° and −60°) were generated (Table 1, Scheme 3).[11]



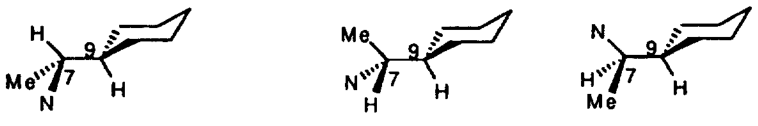
Scheme 2.

Between the competing diastereomeric constrained transition structures at 3 Å for **7d** and **7g** the conformational preferences lead to energetic differences of −0.9 and 0.2 kcal/mol, respectively. Those theoretical results, which correlate qualitatively with experimental data, prompted us to tentatively locate the corresponding proposed transition structures.[5–9] The formation enthalpies of all the considered proposed transition structures and the activation energies of the corresponding reactions are summarized in Table 1.[12] Taking into account the accuracy of the calculations, for the derivatives **7d** and **7g**, the energetic differences between the two competing proposed transition structures ($\Delta H_{Re}-\Delta H_{Si}=-2.2$ and 0.2 kcal/mol, respectively), are in good agreement with the related experimental results (de=95% and 45%, respectively).[1] Incidentally, it should be noted that no addition to methyl acrylate was observed under 'standard' experimental conditions for the hindered enamino ester **7f**.[1] A small increase in activation energy was indeed calculated for the related enamino ketone **7e** (Table 1), but not important

Table 1

ΔH: Formation enthalpies of 7+methyl acrylate at 3.0 Å and of the corresponding proposed theoretical transition structures are in kcal/mol. AE=difference between the sum of the enthalpies of the optimized reactants in the ground state with the enthalpy of the corresponding most stable transition structure

Enamino ketones	**R^2**	**Reactants at 3.0 Å**			**AM1 - transition structures**			
		ΔH_{Re}	ΔH_{Si}	ΔH_{Re} - ΔH_{Si}	ΔH_{Re}	ΔH_{Si}	ΔH_{Re} - ΔH_{Si}	AE
7d	**Me**	-85.2	-84.3	-0.9	-61.9	-59.7	-2.2	-27.3
7g1	**Me**	-141.1	-140.4		-118.6	-117.7		
7g2	**Me**	-142.6	-142.8	0.2	-119.5	-119.7	0.2	-27.4
7g3	**Me**	-142.3	-140.8		-119.5	-118.8		
7e	***t*Bu**	-93.6	-93.4	-0.2	-72.1	-68.4	-3.7	-28.2



7_{g1} 7_{g2} 7_{g3}

Scheme 3.

enough to explain this lack of reactivity. In order to have an appreciation of the role of the chiral group in the stereochemical sense of the reactions and to understand the crucial difference between the phenyl and the cyclohexyl series, the relative stabilization energies were analyzed. The energy of each reactant moiety was evaluated by removing the atoms of the partner followed by single-point calculations, without altering the proposed transition structures geometry (Table 2).

Table 2
ΔH: Formation enthalpy of transition structures (7+methyl acrylate) in kcal/mol. a: Formation enthalpy of the enamine moiety in the transition structures in kcal/mol. b: Formation enthalpy of the acrylate moiety in the transition structures in kcal/mol

Enamino ketone	**Transition structure** $\Delta H_{Re} - \Delta H_{Si}$	**Enamino ketone moiety** $\Delta H_{Re} - \Delta H_{Si}$ [a]	**Acrylate moiety** $\Delta H_{Re} - \Delta H_{Si}$ [b]	**Remaining interaction energy**
7d	-2.2	-0.7	-0.6	-0.9
7_{g2}	0.2	0.1	0.1	0

For **7d**, the enamino ketone and the acrylate moieties in the *Re* transition structure are more stable than those in the *Si* transition structure by 0.7 and 0.6 kcal/mol, respectively, while for **7g**, the relative stabilities of the enamino ketone and the acrylate moieties in the *Re* and *Si* transition structures are quite comparable. The proper interactions between **7d** and the acrylate on the *Si* face are more important than on the *Re* face: this fact finds expression in the remaining energy difference (0.9 kcal/mol). For **7g**, this energy difference is nil. The AM1 optimized transition state geometries for **7d** and **7g** are shown in Fig. 1. At first sight, it is obvious that steric factors govern the geometry of these transition structures. The interactions due to the chiral group in the *Re* and *Si* transition structures of **7d** and **7g**, which allow better understanding of these energy differences, are featured by dotted lines in Fig. 1. As a matter of fact, in the *Si* transition structure of **7d**, on one hand, one hydrogen atom of the phenyl ring of the chiral group is close to one hydrogen atom of the methyl group of the acrylate (2.19 Å) and on the other hand, one hydrogen atom of the methyl of the chiral group is close to one hydrogen atom of the five-membered ring (2.02 Å). The rotation around the N6–C7 axis which could lower one interaction will unavoidably raise the other one. In comparison, in the *Re* transition structure of **7d**, the interactions of the chiral group with the five-membered ring as well as with the acrylate are less important than those in the *Si* transition structure. On the contrary, in both *Re* and *Si* transition structures of **7g**, these steric contacts are comparable. Indeed, in the *Re* transition structure of **7g**, one hydrogen atom of the cyclohexyl ring of the chiral group is close to one hydrogen atom of the five-membered ring (2.12 Å), and one hydrogen atom of the methyl of the chiral group is close to one hydrogen atom of the methyl group of the acrylate (2.25 Å). In the *Si* transition structure of **7g**, two hydrogen atoms of the cyclohexyl ring of the chiral group are close to one hydrogen atom of the methyl group of the acrylate (2.29, 2.38 Å), and one hydrogen atom of the methyl of the chiral group is close to one hydrogen atom of the five-membered ring (2.13 Å). The difference between the *Re* transition structures of **7d** and **7g** is that the steric interactions of the

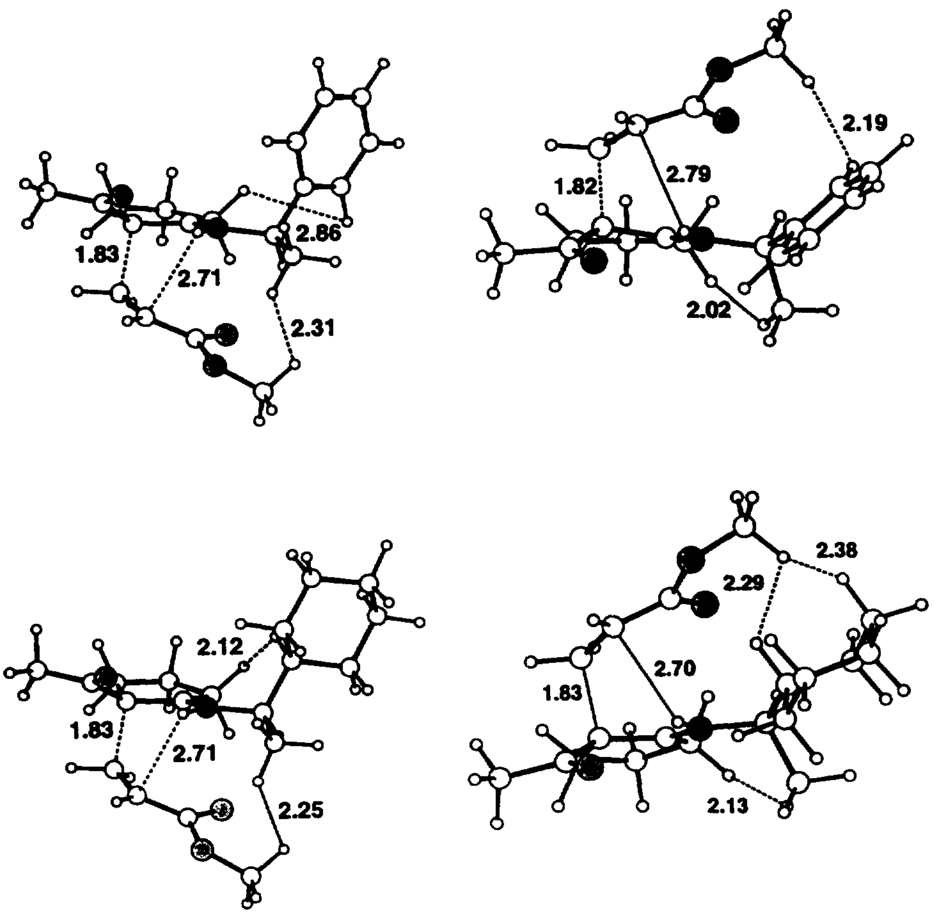


Fig. 1. AM1 transition structures for **7d** and **7g**+methyl acrylate; top left: **7d** *Re*-approach, top right: **7d** *Si*-approach, bottom left: **7g** *Re*-approach, bottom right: **7g** *Si*-approach. The interatomic distances (dotted lines) are given in Å

five-membered ring are much more important with the sp^3-hybridized carbon-atoms of the cyclohexyl ring than with the sp^2-hybridized carbon-atoms of the phenyl ring of the chiral group.

Moreover, in these proposed transition structures, the C–C forming bond is 1.83 Å, and the hydrogen atom borne by the nitrogen atom is not far from the C2′ carbon atom of the acrylate (2.71 Å). It is noteworthy that, in line with our results, Houk et al. found a C–C forming bond of 1.87 Å and a C–HN distance of 2.55 Å in the RHF 6-31G* calculated transition structure for the reaction of (*N*-methylamino)cyclohexene with acrylonitrile.[4] The finding that the calculated energies of the transition structures correlate nicely with the experimental results, on one hand, and that the 6-31 G* and AM1 transition structures are quite similar on the other hand, makes the geometry of the transition structure trustworthy. These results are consistent with a fast internal, but stepwise proton transfer, and therefore the present Michael reaction can be interpreted in terms of an 'aza-ene-like' process, with steric factors dictating the stereoselectivity.

3. Conclusion

The origin of the π-facial discrimination in the asymmetric Michael addition of chiral imines/secondary enamines has been investigated by computational modeling. A good agreement was obtained between the stereoselectivities calculated with the help of AM1 procedure (Fig. 1) and the experimental values in both phenyl and cyclohexyl series, thereby providing feedback information about the reliability of the proposed theoretical transition structures developed here. These transition structures indicate that steric factors are responsible for the experimentally observed stereoselectivity, and also support satisfactorily another striking feature of this Michael addition, namely the *internal proton transfer* from the enamine to the electrophilic partner.

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References

1. *Reviews*: (a) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.(b) d'Angelo, J.; Cavé, C.; Desmaële, D.; Dumas, F. *Trends in Organic Chemistry*, Pandalai, S. G., Ed.; Trivandrum: India, 1993, Vol 4, pp 555–615.
2. (a) Ambroise, L; Desmaële, D.; Mahuteau, J.; d'Angelo, J. *Tetrahedron Lett.* **1994**, *35*, 9705–9708. (b) Cavé, C.; Desmaële, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 4361–4368.
3. Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.* **1986**, *51*, 2671–2675. See also: Sevin, A.; Maddaluno, J.; Agami, C. J. *J. Org. Chem.* **1987**, *52*, 5611–5615. Sevin, A.; Masure, D.; Giessner-Prettre, C.; Pfau, M. *Helv. Chim. Acta* **1990**, *73*, 552–573.
4. Lucero M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 826–827.
5. They were located at the RHF AM1[7] levels with the help of the procedures NLLSQ and SIGMA[8] in the MOPAC[6] package: all variables were optimized by minimizing the sum of the squared scalar gradients;[9] final values of the gradient norms were <1 kcal/Å, and each transition state had one negative eigenvalue in the Hessian matrix as required.
6. Stewart, J. J. P. MOPAC, Quantum Chemistry Program Exchange, University of Indiana, Bloomington, USA, Program 455.
7. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
8. Bertels, R. H.; Report CNA-44, 1972, University of Texas, Centre for numerical analysis.
9. McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625–2633.
10. (a) Chiaroni, A.; Riche, C.; Guingant, A.; d'Angelo, J. *Acta Cryst. C* **1993**, 1406–1409. (b) d'Angelo, J.; Guingant, A.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.* **1989**, *30*, 2645–2648.
11. For **7d**, the potential barrier of rotation around the C7–C9 bond has been evaluated. In the preferred conformation, the phenyl plane is eclipsing the C7–H bond. The torsion angle N6–C7–C9–C10 is −121.3°, while in the crystal structure, the corresponding angle is −138.5°. While for **7d** and **7e**, only one degree of freedom allows us to describe the conformational space, for **7g**, we must take into account the rotation around the single bond C7–C9. See also: Haviari, G.; Célérier, J.-P.; Petit, H.; Lhommet, G.; Gardette, D.; Gramain, J.-C. *Tetrahedron Lett.* **1992**, *33*, 4311–4312.
12. In order to confirm the orientation of the approach of methyl acrylate towards the C1 carbon of the enamine which is defined by the dihedral angle β=C1′–C2′–C1–C2, the *Re* TS of **7d** has been selected for an exploratory scanning at the AM1 level of the other possibilities of *Re* transition states. The corresponding enthalpies of formation obtained for (a) $\beta=-60°$, boat-like, −60.2 kcal/mol, (b) $\beta=60°$, chair-like, −61.9 kcal/mol, (c) $\beta=180°$, extended, −54.7 kcal/mol, clearly favours the chair-like conformation for the TS, as proposed by Sevin et al.[3]