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A Study on the Open Chain Model for Transition State Structures in the Nucleophilic Addition to β-Substituted Carbonyl Compounds and its Application to the 1,3 Asymmetric Induction

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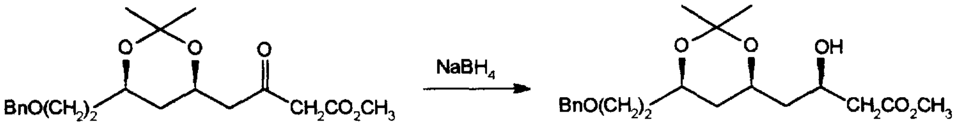
Abstract - By means of semi-empirical quantum-mechanical computations the minimum energy conformations of several β-substituted carbonyl compounds have been examined. On the basis of a unified model with different β-substituents, two of the possible six conformers are found to be the most probable as reactant-like transition state structures, in a non-chelating nucleophilic addition, offering the same π face of the carbonyl group. The applicability of a single model for tsuch reaction has been examined. The conformational models proposed well correlate the diastereoselection of the experimental reactions for most of the cases examined. © 1997 Elsevier Science Ltd.

The diastereoselective reduction of β-polar substituted carbonyl compounds received much attention in our research work in the last years.[1] More recently we found that the diastereoselective reduction of the following chiral β-ketoester (an intermediate in our synthetic approach to macrolide antibiotics) to the corresponding *syn-syn* triol, was better performed with $NaBH_4$ (see Scheme 1) with diastereoselective ratio of 95:5.

Scheme 1



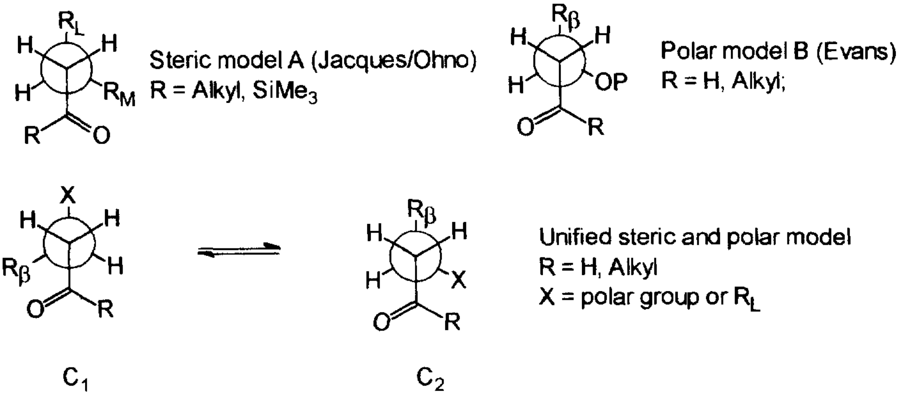
This result has suggested that, in non chelating conditions, the conformation of the starting ketones, resembling the probable transtition state structure, has great influence in directing the diastereoselective reduction.

Nucleophilic carbonyl addition reactions have been object of several efforts to develop transition state models accounting for the influence of proximal different substituents in the π-facial carbonyl selectivity. So far

Cram[2] and Felkin-Ahn[3] models were employed to investigate the effect of α or β-substituted carbonyl reaction with different nucleophiles. The chelate, metal centered, transition state organisation with α or β heteroatom substituents can be effectively utilized for the prediction of the diastereoselectivity in the nucleophilic addition reaction to the trigonal carbon center.[4] When chelate transition state models cannot be invoked, open chain models have been proposed to account for the β-substituent impact on the π-facial selectivity on the carbonyl moiety.[5] A steric model earlier proposed by Jacques[5a] was, more recently, confirmed by Ohno[5e] (see model A in figure 1). A revised polar transition state model has recently proposed by Evans for the 1,3 asymmetric induction in aldol type reactions[5f-g] and in the reduction of β-polar substituted ketones.[5h] (see figure 1, model B). In all the quoted models, staggered instead of eclipsed conformations between the Cα and the carbonyl group have been proposed according to the Felkin assumption.[3a]

Our propose in this work was: 1. to investigate the open chain transition state structures introducing a general single model for the nucleophilic addition reaction to β-substituted carbonyl compounds in a non chelating process, 2. to explain the experimental results on the diastereofacial selectivity in the nucleophilic addition for different reactions and substrates to β-alkoxy or alkyl substituted carbonyl compounds.

Figure 1



Results and Discussion

We worked out on the assumption that the transition state of such reactions are reactant-like.[6] As above pointed out, staggered conformations (Felkin) between the Cα and the trigonal carbon are more like to be involved than the eclipsed (Cram). We also prefer the Newman projection along the Cα-Cβ bond, keeping fixed the staggered conformation on C=O-Cα and rotating Cα–Cβ for a generic β-alkoxy or Cl or alkyl carbonyl compounds, which can be more helpful for the prospective.

In order to work on a single simple model, we have assumed that the X (polar) substituent can be replaced by the R_L substituent, in the case of β-substituted alkyl compounds (figure 1, rotamer models C_1-C_2 see below for detailed explanation). The earlier approaches by Jacques/Ohno and Evans (models A and B) assumed to substitute the OP (polar) group with the R_M group. Both approaches can be used in the same sense to the same final diastereoselective products: we prefer our model also because both the X polar group (for electrostatic reason of dipole orientation) and the R_L group (for steric reason in "non bonded interaction") have the same role in determining the more stable rotamer (see below).

Calculations on several trial substrates[7] (by force field and semi-empirical)[8] are shown in Table 1. As shown the most stable conformers, of variable amount of energy, resonate between structures C_1 and C_2 in all the cases reported. Some considerations can therefore be made: 1. For β-substituted polar compounds (entry 1-5, X = OP or Cl) the structure C_2 seems to be mainly favourite[9] for stabilising electrostatic non bonded effect due to the spatial direction of the permanent dipole moments associated with C=O and Cβ-OP(Cl) bonds and with the two heteroatoms avoiding each other (stabilising gauche relationship). [10]

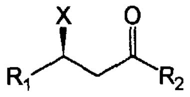
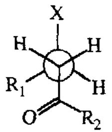
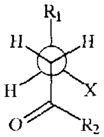
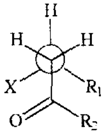
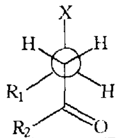
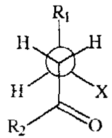
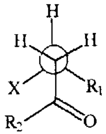
2. For β-substituted alkyl compounds (entries 6-13, X = larger alkyl group) the early proposed conformer C_1 (Jacques and Ohno, model A Fig. 1) appears as the most stable for a bulky R_2 carbonyl substituent (entries 6, 8, 12 and 13). In this conformer C_1 the destabilizing interaction between R_2 and the larger β-substituent are minimised. However when the R_2 carbonyl substituent is smaller (X = Me in entries 7, 9; X = H in entries 10-11) the stability appears governed by non-bonded interactions, where the C=O group and the R_L are in a gauche relationship. Therefore the conformer C_2 can now be considered as the most probable in a transition state like-structure for the nucleophilic addition to aldehydes (as already stated by Evans),[5g] and also to methyl ketones.

3. The proposed simple model, in both the C_1 or C_2 conformations, offers the same π-face of the carbonyl group to the nucleophile.

4. The opposite C_4 conformer with π-facial carbonyl (see Table 1) also possess the pseudo-eclipsed position between the Hβ and the carbonyl group (as for conformer C_2) but it has never been found as the most stable of the six conformers. However, in some cases, smaller energy differences are found (see, i.e. entries 3, 6, and 10), which can account for low diastereoselectivity in the nucleophilic addition.

In conclusion two main conformers appear as the most stable transition state structures of β-substituted carbonyl compounds and the results and prediction of 1,3 diastereoselective induction, in a nucleophilic non-chelating attack to the carbonyl group, can now be therefore examined.

Table 1

Compound				ΔE/kcal mol^{-1}					
									
Entry	**X**	**R$_1$**	**R$_2$**	**C$_1$**	**C$_2$**	**C$_3$**	**C$_4$**	**C$_5$**	**C$_6$**
1	OMEM	*i*-Bu	*i*-Pr	+5.7	**0.0**	+1.2	+2.5	+1.4	+0.7
2	OMEM	Me	*n*-Bu	+0.5	**0.0**	+2.3	+1.0	+2.4	+2.0
3	OTBS	Ph	Ph	**0.0**	+0.1	+5.1	+0.1	+2.1	+3.0
4	OTBS	*i*-Pr	*i*-Pr	+0.1	**0.0**	+1.0	+0.3	+2.3	+1.0
5	Cl	*i*-Pr	*i*-Pr	+2.8	**0.0**	+1.9	+1.8	+1.4	+1.4
6	Ph	Me	Ph	**0.0**	+3.0	+4.8	+0.1	+1.5	+4.8
7	Ph	Me	Me	+0.2	**0.0**	+4.1	+0.4	+1.4	+2.9
8	Ph	Et	*t*-Bu	**0.0**	+1.0	+7.5	+1.0	+1.0	+5.6
9	PMF	Me	Me	+0.2	**0.0**	+4.3	+1.6	+0.5	+2.8
10	Ph	Me	H	+0.5	**0.0**	+3.3	+0.1	+1.7	+2.0
11	Ph	*i*-Pr	H	+0.9	**0.0**	+6.4	+0.3	+1.9	+5.7
12	Ph	Me	SiMe$_3$	**0.0**	+6.2	+2.8	+0.8	+5.5	+2.2
13	*t*-Bu	Me	SiMe$_3$	**0.0**	+5.8	+3.1	+1.0	+5.1	+2.1

In order verify the affidability of the stereochemical model we can now consider the diastereoselectivity experimentally found on a series of nucleophilic addition to β–substituted carbonyl compounds in non chelating conditions, such as: 1. Hydride addition (reduction) to β–alkoxy ketones (i.e. OR, Cl).[1b,5h] 2. Hydride addition (reduction) to β-alkyl ketones.[5a] 3. Organometallic addition to β–OTBS ketones.[11] 4. Organometallic addition to β–alkoxy acylsilanes.[5c] 5. Aldol-type addition to β-substituted aldehydes.[5f,g]

The experimental results and the analysis of the models for 1,3 asymmetric induction appear generally in good agreement. In Scheme 2 we present a summary of the level of diastereoselectivity which can be assumed for different reactions and conditions in a general nucleophilic addition to a β-substituted carbonyl compound. As shown, the proposed model provides an easy prediction of the diastereoselective induction, whatever is the X β-substituent or the R carbonyl substituent. The relative 1,3 configuration (*syn* or *anti*) depends only on the extended chain convention, on the configuration of the β-center and on the nature of both the nucleophile and R carbonyl substituent.

It should be pointed out that, although interactions between the incoming nucleophile and the carbonyl compounds can play some role in determining the diastereoselectivity ratio, the nature of the reagents (hydride, enolate or organometallic) does not appear to be so decisive to completely alter the π-facial selectivity.[12]

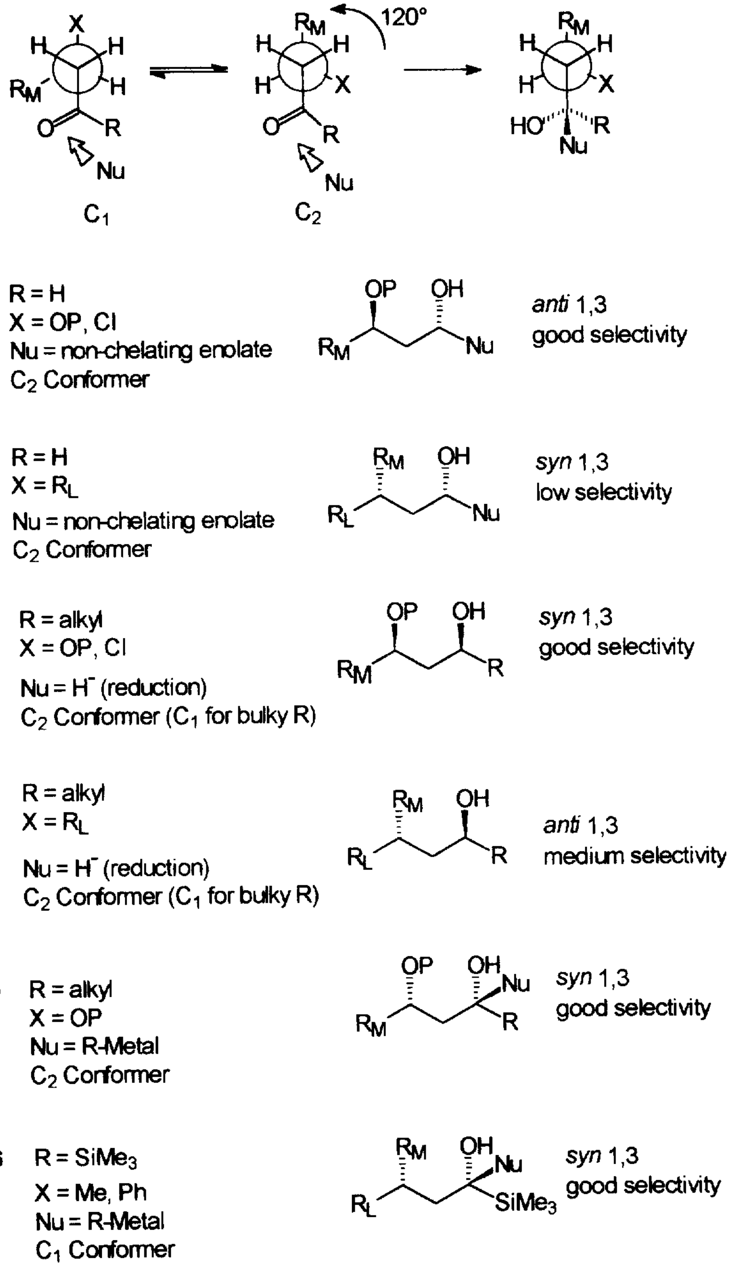
From the experimental results the better diastereoselective ratio has been found in the case of polar substituted aldehydes (case 1 for aldol condensation) or ketones (case 3 for reduction of ketones and case 5 for organometallic addition to ketones). This trend well agree with the energies found for the conformers C_1 or C_2, which appear quite different from that of the opposite π-facial conformer (see conformer C_4 in Table 1). Some small changes have been found for different OP substituent and also for the nature of the reducing agent in case 3.

It is evident that the polar interaction between the β-substituent and the carbonyl group plays a fundamental role in determining the relative conformers energy. On the contrary the substitution of the β-polar group with an alkyl group appears quite disrupting any interaction between the β-group and the carbonyl function. The low diastereoselectivity observed in these cases (case 2 for aldol condensation, and case 4 for hydride reduction), agree with the energies found for conformers C_1 and C_2 similar to those of the opposed C_4 conformer (see Table 1).

An indicative exception to this trend was found for organometallic addition to β-alkyl acylsilanes [5e] (case 6), with a good level of diastereoselectivity. Significantly these experimental results well agree with the calculated energies of conformer C_1. In this last case the role of the R carbonyl substituent appears evident, where R is able to determine a reasonable level of diastereoselectivity also in respect to the size of the other β-substituents.

In conclusion a general good agreement has been found between the calculated energies of the most stable conformers in a reactant-like transition state for nucleophilic addition of β-substituted carbonyl

Scheme 2


X
H
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O
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O
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H
H
H
X
HO
R
Nu
1
R = H
X = OP, Cl
Nu = non-chelating enolate
C_2 Conformer
OP
OH
R_M
Nu
anti 1,3
good selectivity
2
R = H
X = R_L
Nu = non-chelating enolate
C_2 Conformer
R_M
OH
R_L
Nu
syn 1,3
low selectivity
3
R = alkyl
X = OP, Cl
Nu = H^- (reduction)
C_2 Conformer (C_1 for bulky R)
OP
OH
R_M
R
syn 1,3
good selectivity
4
R = alkyl
X = R_L
Nu = H^- (reduction)
C_2 Conformer (C_1 for bulky R)
R_M
OH
R_L
R
anti 1,3
medium selectivity
5
R = alkyl
X = OP
Nu = R-Metal
C_2 Conformer
OP
OH
Nu
R_M
R
syn 1,3
good selectivity
6
R = $SiMe_3$
X = Me, Ph
Nu = R-Metal
C_1 Conformer
R_M
OH
Nu
R_L
$SiMe_3$
syn 1,3
good selectivity

compounds and the trend of several experimental reactions. This way a good level of confidence can be invoked in the prediction of the effect of the 1,3 asymmetric induction in such reactions, and this work nicely complements previous work by Evans[5f,g] on aldol type additions.

The study on more generally α and β substituted ketones and the relative transition state structures could open the way to a more deep insight the stereochemical outcame of the nucleophiilic addition to carbonyl compounds.

Acknowledgements

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6. This assumption (which Evans et al. also formulated for the calculations on aldol type nucleophilic addition)[5g], and the kinetic control of the reaction imply that the nature of the nucleophiles should not be decisive for the trend of the diastereoselectivity.

7. We have also performed calculations on models for the aldol type reaction (entries 10-11), which have been anticipated by Evans[5g] and our data are in good agreement with those published.
8. MM+ Force Field was used for molecular mechanics and Polak-Ribiere algorithm with gradient calculations was adopted for geometry optimization. Semi-empirical electronic total energy estimate and refinement of the geometry were performed with AM1 or PM3 parameter set, depending on the availability of parameters for metal atoms.
9. The slight preference ($\Delta E = 0.1$ kcal mol^{-1}) for structure C_1 for entry 3, appears mainly depending from the bulky phenyl substituents.
10. The data confirm the prevision of Evans,[5h] on his proposed model for diastereoselective reduction of β-alkoxy ketones.
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12. It has been found that more sterically demanding hydride donors, in the reduction of β-susbtituted ketones, have improved the diastereoselective ratio .

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