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1,4-Addition to α,β-Unsaturated Carbonyl Compounds Bearing a γ-Stereocenter: a Molecular Mechanics Model for Steric Interactions in the Transition State.

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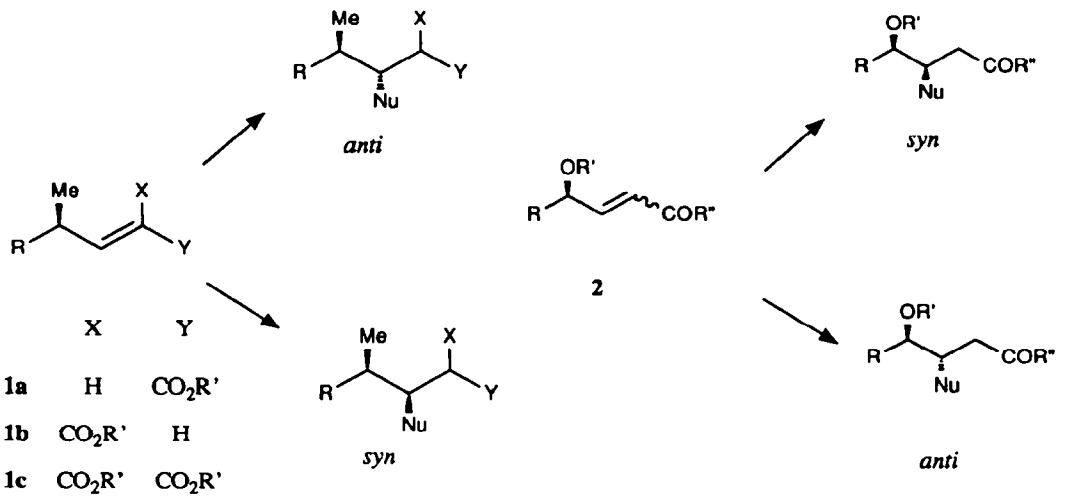
Abstract. A molecular mechanics model for the transition state of Michael additions to α,β-unsaturated carbonyl compounds was built. MM2 parameters were developed on the basis of the transition structure calculated *ab initio* by Weinstein and coworkers for the fluoride anion reaction with acrylic acid. Modeling the addition to γ-substituted crotonates provided a way of evaluating the steric interactions occurring between the γ-substituents and the incoming nucleophile and/or the double bond substituents. These calculations can be useful for discriminating between the various models which have been proposed to rationalize the stereoselectivity of Michael additions.

In recent years a great deal of experimental evidence has been accumulated regarding the stereoselectivity of conjugate additions to α,β-unsaturated carbonyl compounds bearing a γ-stereocenter. Recent work by Yamamoto[1a] and Honda[1b] has shown that alkyl copper reagents add to unsaturated esters of type **1a-c** with *anti* selectivity, regardless of the double bond configuration (Scheme 1). On the other hand, dialkyllithiumcuprates react with E and Z enoates **1a** and **1b** to give *anti* and *syn* products respectively.[1a] This behavior has been ascribed by Yamamoto to the involvement of single electron transfer processes.[1a] As for Grignard reagent additions, the stereochemical outcome of the reaction appears to depend on the steric bulkiness of the reagent itself.[1c]

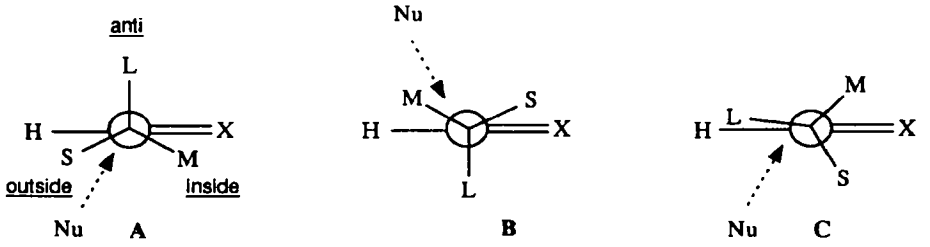
Even more puzzling are the results regarding γ-oxygenated α,β-unsaturated carbonyl compounds **2**.[2] In this case the stereochemical outcome of the reaction has been shown to depend on the nature of the nucleophile: *syn* compounds are obtained upon addition of alkoxides,[2a] amines,[2b] and alkyllithium reagents,[2c] whereas the addition of $(vinyl)_2CuLi$ gives *anti* compounds.[2d] For $BuCu\text{-}BF_3$[2e] and allylsilane-$TiCl_4$[2f] reactions the outcome is controlled by the double bond configuration. The nature of the alkyl group of the organometallic reagent is also influential.[2g] Moreover, chelation control has been suggested by Larchevêque in the organolithium and Grignard reagent additions to γ-alkoxy Z enoates.[2h] In order to rationalize this mass of data, various and often contrasting models (most of them "modified" Felkin-Ahn[3]) have been proposed.[1,2] Only recently Morokuma and Dorigo [4] reported an *ab initio* study of MeCu addition to chiral enals that, for the first time, deals with the nature of steric interactions and electronic effects of alkyl and alkoxy γ-substituents in the transition state of conjugate additions. Their report has prompted us to disclose our results in this area.

Scheme 1.



As Morokuma notes in his paper,[4] the major problem connected with "homologation" of the Felkin-Ahn model to 1,4-addition is related to the preferred position of the medium sized group M (Fig 1). In the addition to carbonyl compounds (Fig 1, X=O)[3] the outside position is the most sterically crowded, being the closest to the incoming nucleophile. This position is therefore occupied by the small substituent S, whereas M occupies the relatively unhindered inside position, as in A (X=O). On extending this picture to enones (X= CH-COR), the issue arises of whether the presence of the *cis* substituent (as opposed to the oxygen lone pair in carbonyls) reverses the situation by making the inside position much too crowded for M to occupy. This would cause transition structure B to be lower in energy and hence the reaction would occur on the opposite stereoface of the π system.

Figure 1.



Based on these considerations, a model analogous to **B** has been proposed to rationalize $(vinyl)_2CuLi$ addition to γ-alkoxy enones **2** (L=OR', M=alkyl chain, S=H),[2d] whereas the results of the addition of alkoxides to the same substrates[2a] and of alkylcopper reagents to esters of type **1** (L=Ph, M=Me, S=H)[1a] have been explained by transition structure **A**. Analysis of substrate conformations does not provide a clear-cut

discrimination between these two structures. In fact, at the ground state level the energy difference between the skew (H eclipsed) and syn (Me eclipsed) conformers of 2-pentenal is estimated by *ab initio* calculations with 6-31G* basis set and correction for electron correlation to be only 0.11 and 0.14 kcal/mol for the E and Z isomer respectively (the skew rotamer being the lower in energy).[5] The suggestion has also been put forth[1b] that *anti* selectivity in additions to **1** arises from transition structure **C** ("modified" Cram model[6]) that features staggering with respect to the C=CHCO group. At the ground state level, the staggered conformer of 2-butenal was found to be higher in energy than the eclipsed by 1.59 kcal/mol (E isomer) or 0.77 kcal/mol (Z isomer), as calculated *ab initio* with 3-21G basis set.[4] However, since correction for electron correlation was not included, these values are likely to be overestimated[7] and transition structure **C** should not be ruled out on this basis.

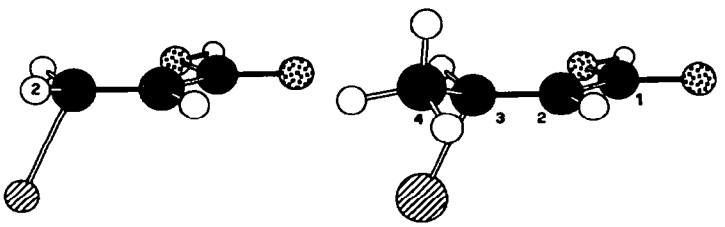
From the above discussion it is evident that one of the questions to be answered to rationalize the stereoselectivity of conjugate additions is connected with the relative steric hindrance of Nu and =X. Molecular mechanics calculations are well suited to evaluate steric interactions and, if applied to a transition state model, could help to gain some insight into this matter. We therefore applied this method to structure **4** (*vide infra*), which is intended to be a qualitative model for nucleophilic additions to crotonates. Of course such an approach considers only steric interactions and thus it is only expected to yield a qualitative picture, upon which additional effects due to counterion, solvent, dipole-dipole and stereoelectronic interactions, etc. will have to be superimposed. Nevertheless, we felt it could provide useful guidelines for the discussion of steric effects in 1,4-additions to α,β-unsaturated carbonyl compounds.

Results and discussion.

Standard MM2 force field parameters as implemented in version 2.5 of MacroModel[8] were used, except for bonds to the reaction core atoms. For these we followed Houk's approach[9] and developed a semiflexible MM2 model based upon the transition structure calculated at the 6-31++G level by Weinstein and coworkers[10] for the addition of F^- to acrylic acid (**3** in Fig 2). MacroModel is designed to include one user-defined atom Z0. We used it to describe the nucleophile and defined it as a methyl group by taking its van der Waals interaction terms from the AMBER[11] united atom CH_3 parameters. The "normal" bond lengths and angles were obtained from the *ab initio* optimized geometry. The stretching force constants were estimated by linear interpolation based on a scaling factor derived from the bond lengths of the transition structure and their relation to bond lengths in the product and the starting material. The calculated angle of attack was not allowed to vary. All other bending constants were set arbitrarily to be 10% less than the normal MM2 values. Stretch-bending terms were set to zero for all sp^2 carbons. Torsional parameters were added as were necessary to reproduce Weinstein's *ab initio* geometry. Substitution of H_2 (Fig 2) with a methyl group provided a model for addition to crotonates. Additional stretching and bending constants were dealt with as described above. The presence of the substituent at C_3 is expected to result in a deviation of the nucleophile trajectory from the plane perpendicular to the enone plane, away from the methyl group.[12] Torsional parameters involving C_4 (see **4** Fig 2) were therefore adjusted to maintain the trajectory deviation in the

range estimated by Heathcock for the addition to carbonyls (10° at 2.0 A distance).[12] Torsional parameters for the allylic substituents were all set to zero. The new parameters were varied to some extent in order to make sure that the qualitative results were not dependent on the exact value chosen for the parameter. The parameters were implemented in MacroModel[8] in the form of the special substructure reported in Table 1.

Figure 2.



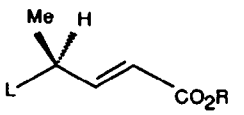
3 **4**

Table 1.

```
-3
C
9    Z0*C2=C2-C2(=O2)-O3
-2
1    1    2                    2.0000      3.0000
1    2    3                    1.3730      8.7000
1    3    4                    1.4160      7.9200
1    4    5                    1.2420      7.9000
1    4    6                    1.3800      6.0000
1    6   H2                    0.9540      5.0000
1   C3    2                    1.5100      4.4000
2   H1    2    3              119.8500      0.3200
2   H1    2   H1              116.6000      0.2900
2   H1    3    4              115.0000      0.3200
2    1    2   H1               86.3000      0.1000
2    1    2   H1               98.0000      0.2000
2    1    2   C3               94.0000      0.2000
2    1    2   C3              100.0000      0.2000
2    1    2    3              115.8000      3.0000
2    1    2    3               90.0000     10.0000
2    2    3   H1              120.8000      0.3200
2    2    3    4              124.0000      0.5400
2    5    4    6              116.8000      0.7000
2    3    4    5              127.0000      0.4100
2    3    4    6              115.9000      0.4500
2    4    6   H2              110.4000      0.2700
2   C3    2    3              119.0000      0.5000
2   C3    2   H1              116.0000      0.2000
4    1    2    3   H1           0.0000     -0.4000      0.6000
4    1    2    3    4           0.0000     -2.0000      0.0000
4   H1    2    3   H1           0.0000      1.0000      0.0000
```

```
4   H1    2    3    4          0.0000      1.0000      0.0000
4    2    3    4    5          0.9000      2.2000      0.0000
4    2    3    4    6          0.0000      2.2000      0.0000
4   H1    3    4    5          0.0000      1.1600      0.0000
4    3    4    6   H2          0.0000      1.0000      0.0000
4    6    4    3   H1          0.0000      2.2000      0.0000
4   C3    2    3   H1          0.0000      2.2000      0.0000
4   C3    2    3    4          0.0000      2.2000      0.0000
4   H1   C3    2    3          0.0000      0.0000      0.0000
4   H1   C3    2    1          0.0000      0.0000      0.0000
4   C3   C3    2    1          0.0000      0.0000      0.0000
4   C3   C3    2    3          0.0000      0.0000      0.0000
4   C2   C3    2    1          0.0000      0.0000      0.0000
4   C2   C3    2    3          0.0000      0.0000      0.0000
4    1    2   C3   O3          4.0000      0.0000      0.0000
4    3    2   C3   O3          0.0000     -1.0000      0.0000
5    2   00   00   00          0.0000      0.0000
5    3   00   00   00          0.0000      0.0000
5    4   00   00   00          0.0000      0.0000
-4
```

We then applied our model to chiral crotonates of type **5**.



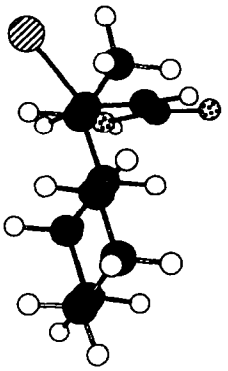
5a L=Cyclohexyl

5b L=tBu

5c L=Ph

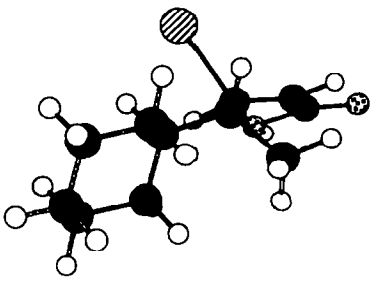
The first substrate we examined was **5a** (L=Cyclohexyl). Conformers for the addition to both π faces were generated at 30° resolution for the allylic bond by using the Multiconformer submode[13] of MacroModel, and were minimized by Batchmin. The resulting minima and their relative energies are reported in Fig 3. Conformations **6(i)-6(iii)** and **7(i)-7(iii)** lead to *anti* and *syn* products respectively. Their relative stability appears to be governed by the steric interactions with Z0. In fact, the lowest energy conformations for both structures (**6(i)** and **7(i)** in Fig 3) is the one in which the H (i.e. the smallest substituent) occupies the outside position, and therefore minimizes the steric repulsion with the incoming nucleophile. Conformer **6(i)**, in which the large cyclohexyl group is situated in the anti position, is more stable than **7(i)** by 1.0 kcal/mol. The model, therefore, correctly predicts the reaction to occur with *anti* selectivity.[1] Conformations **6(ii)** and **7(ii)** that feature the H in the inside position are only second best. The same trend is revealed by *ab initio* calculations. In fact, Morokuma found that the lowest energy conformation for the transition state of MeCu addition to a system having two methyl groups at C_γ has the two methyl groups anti and inside. The conformation of the isopropyl group that has the two methyls anti and outside is less stable by 1.49 kcal/mol.[4] It is worth noting that in our model the presence of the small group in the outside position seems to be an even more stringent requirement than positioning the bulky cyclohexyl group antiperiplanar to the incoming nucleophile (cf **7(i)** and **7(ii)** in Fig 3). The energy gap between the H inside and H outside conformer for each transition state shows some dependence on the size of the large group (L). In fact for **5b** (L=tBu) the H inside conformations are not found as minima and the predicted *anti*:*syn* ratio is increased. On the other hand, for **5c** (L=Ph) the energy gap is smaller (cf **8(i)-8(ii)** and **9(i)-9(ii)** in Fig 4), the H inside conformations are

Figure 3. Addition to **5a**



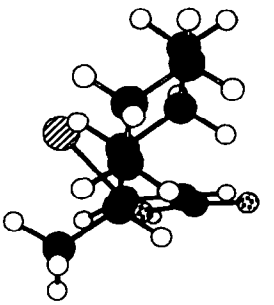
6(i)

0.0



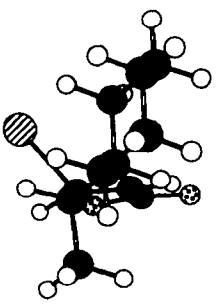
6(ii)

2.1



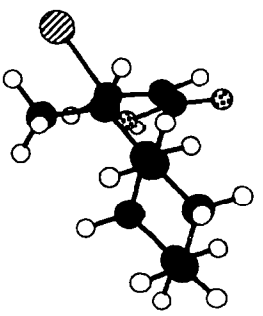
6(iii)

2.2 kcal/mol



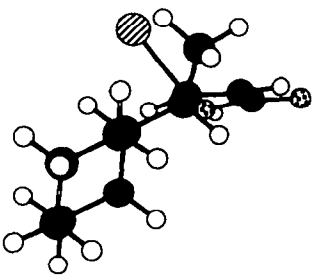
7(i)

1.0



7(ii)

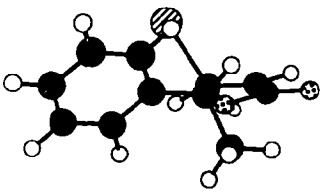
1.7



7(iii)

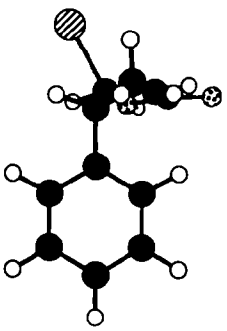
1.8 kcal/mol

Figure 4.



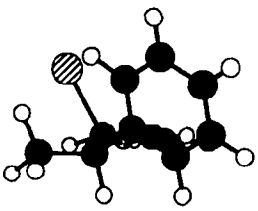
8(i)

0.0



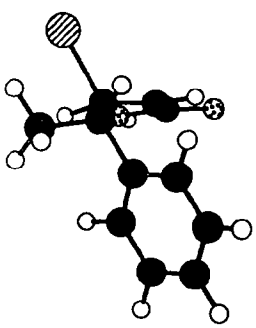
8(ii)

0.3



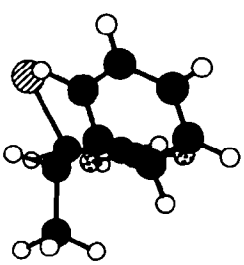
8(iii)

1.6 kcal/mol



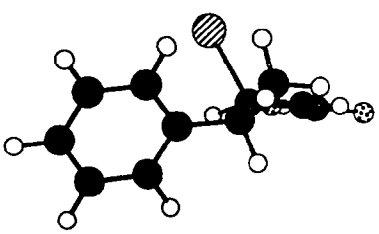
9(i)

0.2



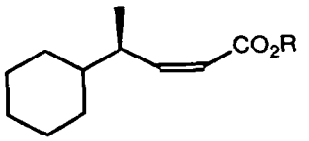
9(ii)

0.7



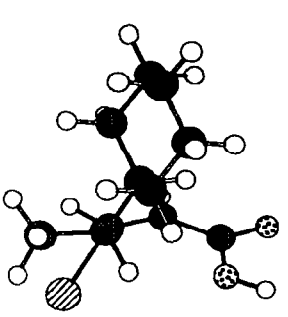
9(iii)

1.8 kcal/mol



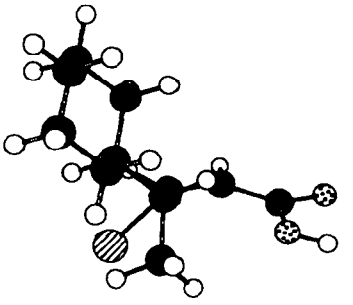
10

Figure 5



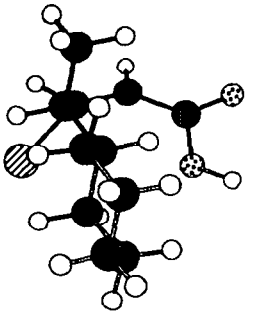
11(i)

0.0



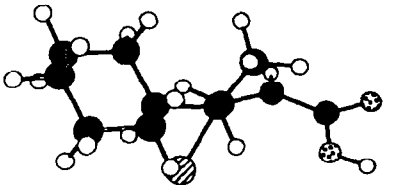
11(ii)

0.6



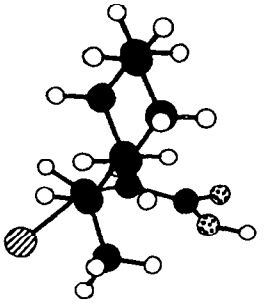
11(iii)

3.2 kcal/mol



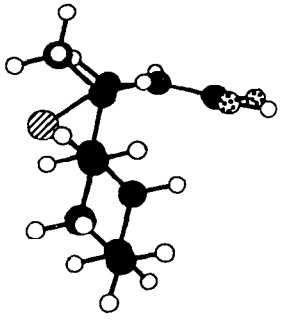
12(i)

0.7



12(ii)

1.8



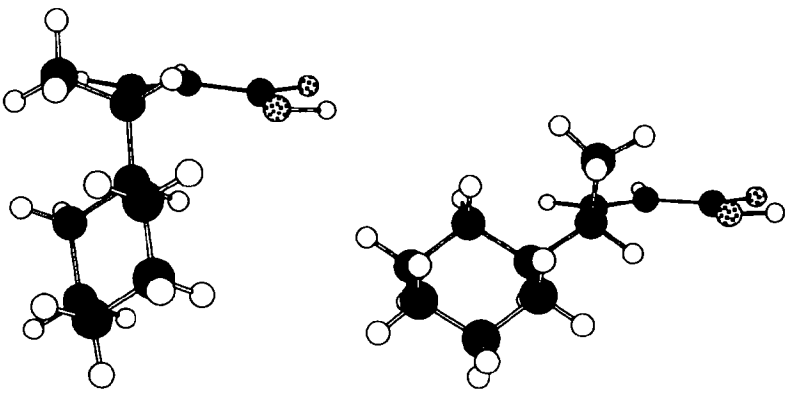
12(iii)

4.3 kcal/mol

the lowest in energy, and the predicted *anti:syn* ratio is reduced. It is interesting to note that Morokuma's calculations show a tendency for the phenyl group to occupy the outside position rather than the anti one, at least for addition to Z-enoates. This finding was interpreted as an electronic effect due to the -I nature of aryl groups.[4] Our model cannot possibly account for such an effect and thus seems to suggest that some steric factor is also operating (see **8(i)**, Fig 4).

For Z enoates the steric requirement of the $CHCO_2R$ residue appears to determine the relative stability of the transition structures. In fact the lowest energy conformation for both transition states leading from **10** (Fig 5) to the *anti* or *syn* compound features the small group in the inside position (**11(i)** and **12(i)**, Fig 5). It is interesting to note that this situation closely parallels the conformational preference of the substrate ground state (Fig 6), as calculated by molecular mechanics with standard MM2 parameters.

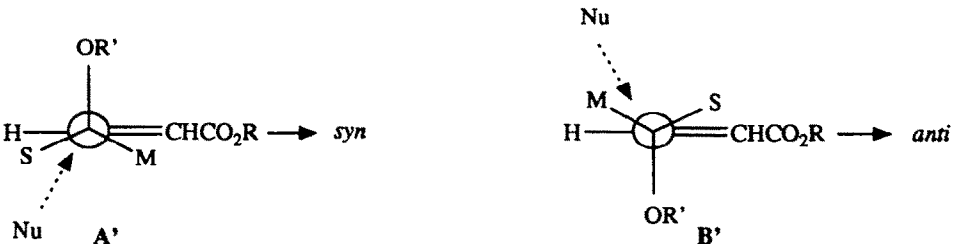
Figure 6.



The dominant steric influence of the enone residue is also apparent in conformer **11(ii)**. This structure, in which the bulky cyclohexyl group is antiperiplanar to the $CHCO_2R$ residue, is only 0.6 kcal/mol less stable than the absolute minimum, even if the nucleophile is situated in a very crowded environment. The model predicts the addition to occur with low *syn* selectivity, i.e. the stereochemical outcome of the reaction depends on the configuration of the double bond. Comparison between **12(i)** and **11(i)** suggests the latter to be preferred because it minimizes the steric hindrance around the nucleophile. The energy gap, therefore, is likely to increase with the steric bulkiness of Z0. Experimentally, it has been found that bulky Grignard reagents[1c] and dialkyllithiumcuprates[1] react with Z enoates to give *syn* compounds. This is not the case for alkylcopper reagents[1a] which, however, give a reduced *anti:syn* ratio with Z enoates compared to E enoates.[1b]

In the case of nucleophilic additions to γ-alkoxy enoates a Felkin-like model is generally assumed, and the two structures to be compared are **A'** and **B'**(Fig 7) where the alkoxy group takes the anti position for electronic reasons.[3] Torsional parameters for the allylic oxygen were therefore introduced to reproduce this electronic preference (see Table 1).

Figure 7.



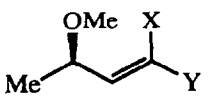
Starting conformers for the addition to **13** were generated at 30° resolution and minimized with Batchmin. Structures **14** and **15** (Fig 8) were found, **14** being more stable by 2.1 kcal/mol. This model, therefore, predicts the formation of *syn* compounds upon addition of nucleophiles to γ-alkoxy E enoates, and is thus suited to rationalize the stereochemical outcome of organolithium[2c] and alkoxide[2a] reactions, but does not explain the results obtained upon cuprate[2d] and alkylcopper[2e] addition. In these cases chelation of the metal by the γ-alkoxy group could be occurring,[14] or, as suggested by Morokuma's calculations, the addition could be dominated by the metal-carbonyl oxygen interaction.[4] In the latter case the stereoelectronic requirements of the process would be more similar to those that characterize electrophilic additions to double bonds, i.e. the allylic CO bond would lie close to the π bond plane, rather than perpendicular to it.[15]

For Z enoates, chelation control by the γ oxygen is strongly suggested, from both experimental[2h] and theoretical[4] results. Larchevêque and coworkers recently showed that, if chelation is inhibited, *anti* selectivity is observed upon organolithium and Grignard reagent addition. Modeling addition to **16** (see Fig 9), indeed, shows that the transition structure **17**, which leads to the *anti* isomer, is slightly favored over **18**, which leads to the *syn* one. Here again for Z enoates the selectivity appears to be dictated by the steric bulk of the $CHCO_2R$ residue, which forces the hydrogen to occupy the inside position.

Conclusions.

A molecular mechanics model for the transition state of nucleophilic 1,4-addition to γ-substituted crotonates was developed. The scope of the model is limited to the evaluation of steric interactions between the C_γ-substituents and the incoming nucleophile and/or the double bond substituent.

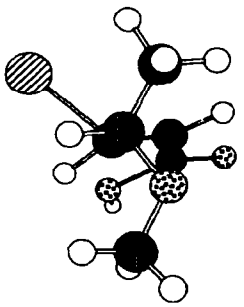
The model shows that for E enoates with two γ-hydrocarbon substituents the dominant steric interaction is between the nucleophile and the γ-substituents: the lowest energy conformations leading to both *anti* and *syn* products feature the smallest group (S) in the outside position. Reactions with nucleophiles are predicted to occur preferentially through a transition structure analogous to **A** (Felkin model[3]) and give *anti* compounds. This is in qualitative agreement with the available experimental results.[1] A dependence of the stereoselectivity on the size of the large γ-substituent is also predicted. For Z enoates the presence of the *cis* substituent appears to determine the steric course of the reaction: the lower energy conformations for the transition state features S in the inside position. Low *syn* selectivity is predicted. This is in agreement with the

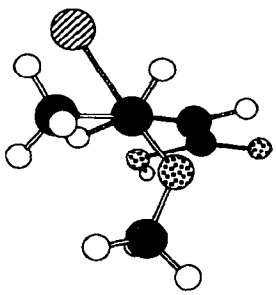


13 X=H, Y=COOR

16 X=COOR, Y=H

Figure 8. Addition to **13**

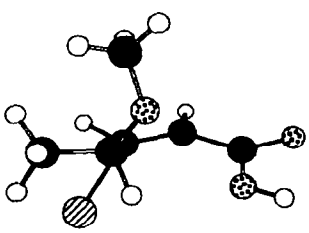


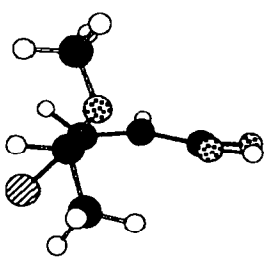


14 **15**

0.0 2.1 kcal/mol

Figure 9. Addition to **16**





17 **18**

0.0 0.4 kcal/mol

results obtained upon addition of bulky Grignard reagents[1c] and dialkyllithiumcuprates,[1] but not of alkylcopper reagents.[1a,b]

For γ-alkoxy E enoates the model suggests that a Felkin-like transition state model[3] can be used to rationalize organolithium[2c] and alkoxide[2a] additions (*syn* selectivity), but does not explain the stereochemical outcome of cuprate[2d] and alkylcopper[2e] reactions (*anti* selectivity). This could be due to chelation control by the γ-oxygen[14] or to stereoelectronic requirements different from those assumed in the Felkin model.[4,15] For γ-alkoxy Z enoates our Felkin-like model predicts a modest *anti* selectivity, which is in qualitative agreement with experimental results obtained under non-chelating conditions.[2h]

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