

THEORETICAL EVALUATION OF STEREOELECTRONIC DIASTEREOFACIAL SELECTIVITY IN THE
CONJUGATE ADDITION OF CUPRATES TO 5-SUBSTITUTED CYCLOPENTENONES

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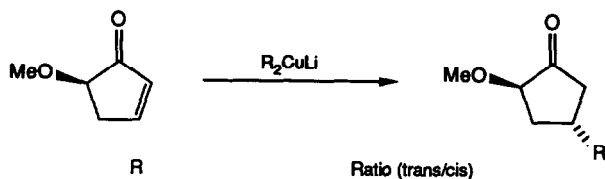
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Summary: The 53:1 preference for conjugate addition of Me_2CuLi anti to the methoxy of 5-methoxycyclopentenone has been evaluated with semi-empirical molecular orbital methods. The calculated preference for approach of a negative charge anti to the methoxy group is proposed to account for the observed diastereofacial selectivity.

In the preceding paper³ we described the remarkable diastereofacial selectivity observed in the conjugate addition of various cuprates to 5-substituted 2-cyclopentenones (Eq 1). Convinced that these results were due to an electronic bias exerted on the enone system, rather than a steric effect, computational work was performed in order to evaluate the effect(s) with the hope of developing an efficient computational model which would allow us to predict the direction and extent of this stereoselectivity, and to provide insight into the reasons for the observed selectivity. That steric effects do play a minor role in such additions is seen in the 3.5:1 ratio of diastereomers produced in the conjugate addition of lithium dimethylcuprate to 5-methylcyclopentenone.³ However, the high degree of selectivity seen with oxygenated substituents in the 5-position must be largely due to electronic effects.⁴



Me	53:1
Bu	13:1
Ph	7.3:1

To begin this study, we investigated the polarization of the enone π -system in 5-methoxycyclopentenone by the adjacent methoxy substituent to determine whether or not reaction with a negatively charged species was electronically preferred on one diastereotopic face over the other. Using MNDO,^{5,6}

a diffuse negative charge was brought up to the enone β -carbon along the Dunitz trajectory^{7,8,9} to each face of the MNDO-minimized cyclopentenone; the charge to β -carbon distance was optimized (energy minimum) at ca. 2.7 Å on each face¹⁰ and the energies of the optimized systems were compared. This model predicted anti addition to be favored over addition syn to the methoxy group by 2.1 kcal/mole. Furthermore, this model predicted that in the case of 5-acetoxy-2-cyclopentenone, anti addition was favored by only 1.2 kcal/mole. In the case of 5-methylcyclopentenone, little preference was predicted. In all cases, the full molecular geometry was optimized at each step. We emphasize that this model is simply describing the difference in the ability of the substituted cyclopentenone to stabilize a negative charge on either face of the enone system. While the mechanism of cuprate conjugate addition probably occurs via an electron transfer pathway,¹¹ there is presumably some ionic character to the reagent and the transition state. Since no attempts were made to locate a transition state along the reaction coordinate, these arguments describe a reaction proceeding under product development control.

Further MNDO calculations were performed on both the ground state system and on the reaction model. The preferred conformation in the ground state is calculated to be that rotamer in which the O-CH₃ bond is eclipsed with the ring C-H bond (Figure 1). Rotation about this C-O bond did not significantly alter the calculated ring geometry either in the ground state or in the reaction model. The unfavorable steric interactions of such a conformation may be overridden by a favorable interaction between the enone system and one of the ether oxygen lone electron pairs; we note that an oxygen lone pair is directed toward the enone π -system in this rotamer. This conformational preference was confirmed by ab initio molecular orbital calculations at the 3-21G level as single point calculations on the MNDO-minimized geometries using GAUSSIAN 82.¹² These rotamers were also examined in the computational reaction model for conjugate addition of a negative charge, both syn and anti to the methoxy group; in each case the minimum energy conformation was calculated (MNDO) to be essentially the same as in the ground state system. Calculations on 5-methoxy-5-methylcyclopentenone showed that the conformation preferred in the ground state system was that with the methyl group of the methoxy aligned nearly antiperiplanar to the carbonyl (Figure 1); here a 1,6-interaction between hydrogens is significantly more costly than the corresponding 1,5-interaction in 5-methoxycyclopentenone.¹³ The computational model predicted addition anti to the methoxy group to be favored over syn addition by 2.8 kcal/mol. The lowest energy rotational isomer in these calculations was the same as seen in the calculations on the ground state system, though the preference was less pronounced in the ground state.

CALCULATED GROUND-STATE CONFORMATIONS



Figure 1

Calculations were also performed on a model reaction involving conjugate addition of a hydride ion to 5-methoxycyclopentenone. At a fixed distance of 4.0 Å from the enone β -carbon, there was essentially no diastereofacial preference. As the hydride was brought closer (in 0.5 Å increments)

the preference for addition anti to the methoxy group increased to a maximum of 2.4 kcal/mol at 2.5 Å. Further approach of the hydride resulted in a calculated decrease in diastereofacial preference to only 0.4 kcal/mole at a distance of 1.5 Å as the corresponding enolate began to be more fully formed; the same enolate results from addition of a hydride either syn or anti to the methoxy group.

The 5-membered ring of 2-cyclopentenone has been shown experimentally to be planar.¹⁴ Calculations confirm both this observation and the expectation that 5-methylcyclopentenone not deviate much from planarity.¹⁵ In such a planar system, the substituent at the 5-position is oriented away from the ring (ca. 120° dihedral angle)¹⁶ and one would not expect to see any significant steric impediment to favor diastereofacial selectivity in approach to the β-carbon of the enone. Yet, modest diastereofacial selectivity is seen in the reactions of 5-methylcyclopentenone, despite the fact that the methyl group is presumed to be electronically inert. The experimental work of S. G. Smith¹⁷ and the computational work of Whangbo¹⁸ on cuprate conjugate addition reactions suggest a transition state in which the square planar lithium dimethylcuprate dimer¹⁹ chelates with the enone oxygen via lithium, as the alkyl group is transferred to the β-carbon. This transition state requires that the organometallic reagent approach in an endo fashion; it is thus reasonable that some diastereofacial selectivity is seen in conjugate addition reactions to 5-methylcyclopentenone. Our experimental results with 5-methoxycyclopentenone certainly must reflect the steric requirements of such a transition state as well as an inherent electronic bias due to the polarization of the enone by the oxygen substituent. An additional preference might arise from electrostatic repulsion between the oxygen lone pairs and the electron-rich cuprate reagent. Thus, while there is a baseline steric bias favoring anti addition, the electronic effect favoring anti addition is greater in magnitude and can be reasonably well predicted with the use of model semi-empirical calculations.

In many ways, the effect we have observed is a vinylogous extension of the antiperiplanar effect in nucleophilic additions to the carbonyl group observed experimentally and interpreted theoretically by Ahn and Eisenstein.²⁰ That this effect could be extended (in the case of 1,2-addition) to electrophilic and radical attack on π-systems was demonstrated by Houk *et al.*²¹

Finally, the computational prediction, in the case of 5-methoxycyclopentenone, seems to be in accord with the postulate that the orbitals of the enone system are interacting in some manner with the C-O σ-bond orbitals. As the substituent on oxygen is changed from alkyl to acyl, the energy of the C-O σ*-orbital is raised. This is likely to make such interactions less favorable.²² It is reasonable that the key interaction in the transition state is between the σ-orbital of the bond being formed and the C-O σ*-orbital; such throughbond interactions are well known in many types of organic reactions.²³ Experiments designed to distinguish between these potential explanations are currently underway in our laboratories.

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1. Camille and Henry Dreyfus Teacher-Scholar, 1978-1983; National Institutes of Health (National Cancer Institute) Career Development Award; and J. S. Guggenheim Foundation Fellow, 1985-1986.
2. Dana Faculty Fellow, Bowdoin College.

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