or some species derived from it ..." is responsible for the photochemistry. Although S_2 itself is now also excluded, X is produced as a result of motion of the system on the same potential surface as S_2, and therefore is expected to exhibit some of the same chemical characteristics. Finally, we note that X has some zwitterionic character, and zwitterions have been proposed as intermediates in the intermolecular S_2-excited photochemical reactions of some thioketenes.[46,47]

Acknowledgment. The authors thank the Natural Sciences and Engineering Research Council of Canada for continuing financial support. We also wish to thank Dr. V. P. Rao for synthesizing a sample of the perdeuteriated adamantanethione and Dr. D. Sharma, Concordia University, for his cooperation in conducting lifetime experiments.

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Stereoselectivity of the Nucleophilic Addition of Organocopper Reagents to Chiral α,β-Unsaturated Carbonyl Compounds. Ab Initio Molecular Orbital Studies of Steric and Electronic Effects

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Abstract: Ab initio molecular orbital studies have been conducted on the conjugate addition of methylcopper to substituted enals. Transition structures have been located for the addition of methylcopper to (*E*)- and (*Z*)-2-butenal, and the effect of the methyl and hydroxyl substituents on the γ-carbon has been analyzed for both transition states. In the reaction with both (*E*)- and (*Z*)-2-pentenal, the most stable conformation in the transition state has the methyl group anti to the incoming nucleophile, with the *outside* position being preferred to the *inside* position. These conformational preferences are readily rationalized in terms of the relative steric encumbrance of the three positions. On the other hand, the conformational preference exhibited by the hydroxyl group is found to be dictated primarily by electronic factors. Thus, in the addition to both *E* and *Z* isomers of 4-hydroxy-2-butenal, the sterically unhindered anti position is the *least* favorable for the hydroxyl group. It is shown that electron-withdrawing groups in the anti position destabilize the transition state, whereas electron donors favor the anti position. From these calculations we have derived transition-state models that we have used to predict the diastereomeric excess of the addition to chiral 4-alkoxy α,β-unsaturated carbonyl compounds. *E* isomers prefer a conformation in which the alkyl and alkoxy group occupy the anti and inside positions, respectively, in the transition structure. In the *Z* isomers the favored conformation has the alkyl group outside the nucleophile and the alkoxy group inside; this conformation leads to formation of the other diastereoisomer. Good agreement with the observed stereoselectivity has been found in both cases. We have also performed model calculations that rationalize the stereoselectivity of the addition to *E* and *Z* isomers bearing an aryl group on the γ-carbon. These calculations suggest that the favored conformation in *E* isomers has the aryl and methyl groups in the anti and inside positions, respectively. In *Z* isomers, the aryl group lies *outside* and the methyl group *anti*, so that the same diastereomer is predicted to be the major product in both cases. This is also in agreement with recently reported experimental observations.

Several high-level theoretical studies of the addition of nucleophiles to carbonyl compounds have appeared in the recent literature. Many of these investigations deal with the stereochemical aspects of these reactions.[1] Theory is thus starting to catch up with a wealth of experimental evidence accumulated ever since Cram pioneered the field almost forty years ago.[2] Cram's rule and successive reinterpretations by Karabatsos,[3] Felkin,[4] and Anh[5] have become guidelines for the interpretation and prediction of the stereochemical course of the reaction. Recent evidence, both theoretical and experimental, provides strong support in favor of Felkin's and Anh's transition-state model (Figure 1).[6,7]

The closely related nucleophilic conjugate addition to chiral α,β-unsaturated carbonyl compounds, which is also widely employed in synthesis, has received relatively little attention from the theoretical point of view.[8,9] Addition to aldehydes or ketones on the one hand and conjugate addition to enals or enones on the other are obviously related. Thus, it is not surprising that the stereochemical course of conjugate additions to chiral substrates has often been empirically rationalized on the basis of "modified" Felkin–Anh models. The modification usually involves replacement of the C(R)=O group of Figure 1 with the conjugated C=C(R′)—C(R″)=O group, and the assumption that the substituents on C_γ are staggered[10] with respect to the forming C_β-nucleophile bond (Figure 2).

In spite of the similarities of the two reactions, it is difficult to speculate on the relative stabilities of various conformations for the transition states of conjugate addition reactions. This reaction is expected to have different steric requirements from

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[1] For a review, see: Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108.

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[3] Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367.

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[5] Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.

[6] Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. See also: Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *108*, 8107.

[7] (a) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. The issue, however, is still controversial. For a different interpretation, see: (b) Srivastava, S.; LeNoble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874.

[8] For a recent example of a study of nucleophilic attack on acrolein, see: Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.* **1986**, *51*, 2671.

[9] For a treatment of the regiochemistry of the addition reaction to conjugate systems, see: Loupy, A.; Seyden, J. *Tetrahedron Lett.* **1978**, 2571.

[10] The importance of staggering in nucleophilic and other types of addition reactions to double bonds has been discussed by Houk: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.

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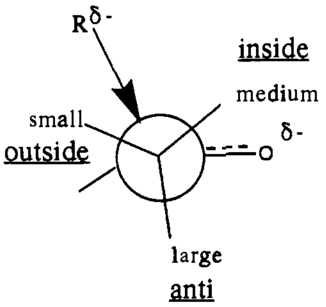

Figure 1. Preferred transition structure for the nucleophilic addition to chiral aldehydes and ketones (Felkin–Anh model). For the analogous case of conjugate addition, see Figure 10.

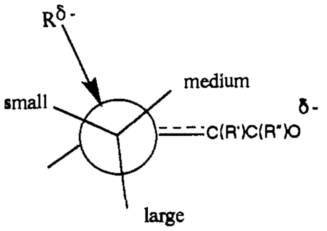

Figure 2. "Modified" Felkin–Anh model for the conjugate addition to chiral α,β-unsaturated carbonyl compounds.

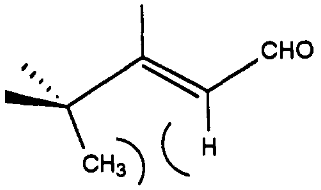

Figure 3. Schematic representation of the repulsive interaction between the C_α hydrogen and the in-plane methyl group in *E* enals.

the addition to carbonyl groups. Aside from considerations concerning the precise geometry of attack, which is not the same in the two cases,[6,11] the key issue to address is the preferred position of the "medium-sized" group M. In addition reactions to an aldehyde or ketone (see Figure 1), the *inside* position in Figure 1 is sterically less hindered than the *outside* position, as shown by Wu and Houk.[6] Moreover, electronic effects alone favor the inside position over the anti position in the transition state.[6] Qualitatively similar conclusions can be reached from an analysis of the ground-state conformers.[4] The most stable conformer of propionaldehyde has a methyl group eclipsed to the carbonyl group;[12] the conformer having a hydrogen eclipsed to the C=O bond is 1.45 kcal/mol higher in energy. These considerations reflect the "earliness" of the transition state in Figure 1 and provide some justification for the earlier model of Karabatsos, which was based on the preferred conformation of the reactant.[4]

Analogously, one is led to ask whether insight into the stereoselectivity of *conjugate* additions might not also be gained from the analysis of reactant conformations. In this context we must mention a recent investigation by Schreiber, et al.[13] These authors showed that the preferred ground-state conformation of (E)-β-ethylacrolein has the methyl group anticlinal to the C=C bond (that is, the torsional angle (H_3)C—C—C=C is about 120°). The conformation having the methyl group eclipsed to the C=C bond lies higher in energy by 0.64 kcal/mol. This reversal in trend from the propionaldehyde case is imputable to the steric interaction between the in-plane methyl group and the olefinic hydrogen on the α-carbon (Figure 3). A substantially larger destabilization of this conformation is expected for *Z* enals (or enones), in which the interaction between in-plane methyl group and the formyl (or alkanoyl) group (Figure 4) is clearly much more severe.

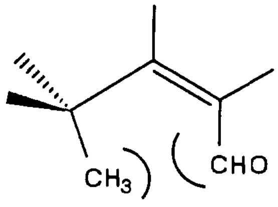

Figure 4. Schematic representation of the repulsive interaction between the formyl group and the in-plane methyl group in *Z* enals.

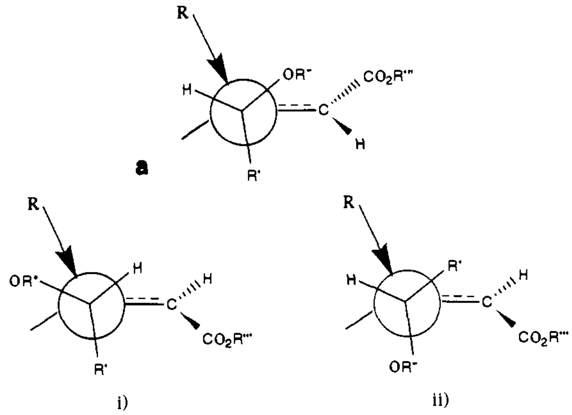

Figure 5. (a) Proposed[17] transition structure for the conjugate addition of alkylcopper–Lewis acid reagents to (E)-γ-alkoxy α,β-unsaturated esters. (b) i. Proposed[17] transition structure for the conjugate addition of alkylcopper–Lewis acid reagents to (Z)-γ-alkoxy α,β-unsaturated esters. ii. Alternative transition structure leading to the same product.

On the basis of these considerations alone, therefore, the preference for either the inside or outside position in the transition state could depend on the double-bond configuration. Recent experimental work by Yamamoto and co-workers[14] has shown that (E)-α,β-unsaturated esters probably react via the "modified" Felkin–Anh transition state shown in Figure 2. These authors have observed the same stereochemistry in the reaction of *Z* esters and α,β-unsaturated diesters; however, earlier work by Kingsbury and co-workers[15] had shown that the conjugate addition of Grignard reagents to the diesters proceeds either with low stereoselectivity or with the preferential formation of the "anti-Felkin–Anh" (or "anti-Cram") product.

Of equal or even greater interest, especially in natural product chemistry, is the addition to oxygenated substrates. Although dialkylcuprates are usually the reagents of choice,[16] alkylcopper–Lewis acid systems have also been used in conjugate addition reactions to γ-oxygenated α,β-unsaturated carbonyls.[17] A systematic study by Yamamoto[17] has shown that the stereoselectivity of the addition to (E)-γ-alkoxy α,β-unsaturated esters can be rationalized by the transition structure shown in Figure 5a, in which the alkyl and alkoxy group occupy the anti and inside position, respectively. The *Z* esters give mainly the opposite diastereomers, which can be interpreted in terms of either of the two transition structures shown in Figure 5b. The authors favored the first of these two, which has the alkyl and alkoxy groups in the *anti* and *outside* position, respectively. Which group occupies which position is actually an argument of interest and also of

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[11] In particular, the calculated angle of attack of the methyl group of methyllithium onto ethylene is larger (ca. 120°): Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821. See also: Schleyer, P. v. R.; Kos, A. J.; Kaufmann, E. *Ibid.* **1983**, *105*, 7617.

[12] Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035.

[13] Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274.

[14] (a) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1572. (b) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Am. Chem. Soc.* **1988**, *110*, 617.

[15] Kruger, D.; Sopchik, A. E.; Kingsbury, C. A. *J. Org. Chem.* **1984**, *49*, 778.

[16] For a review, see: Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

[17] Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464.

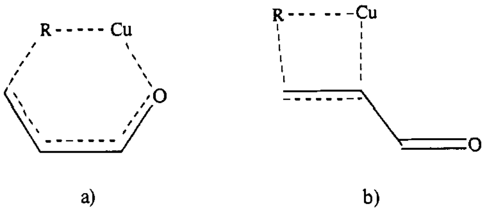

Figure 6. (a) Six-membered cyclic transition structure for the addition of methylcopper to acrolein. (b) Four-membered cyclic transition structure. See ref 25 for full details.

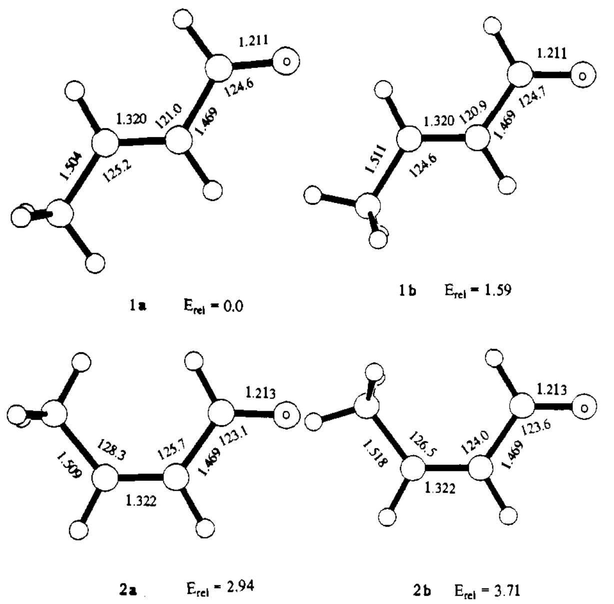

Figure 7. Optimized geometries (HF/3-21G) of: **1a**, eclipsed conformation of (*E*)-2-butenal; **1b**, staggered conformation of (*E*)-2-butenal; **2a**, eclipsed conformation of (*Z*)-2-butenal; **2b**, staggered conformation of (*Z*)-2-butenal. Bond lengths are given in angstroms, angles in degrees, and relative energies in kcal/mol.

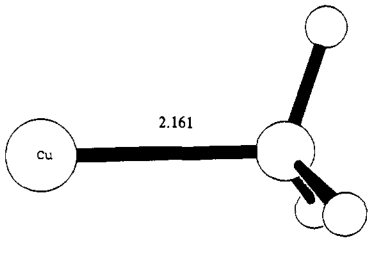

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Figure 8. Optimized geometry (HF/3-21G) of methylcopper (**3**). The bond length is expressed in angstroms.

controversy in related processes. Thus, for the addition reactions of dialkylcuprates (which however may operate via electron transfer[18]) to *Z* substrates, Yamamoto and co-workers favor the conformation shown in Figure 5bi; Marshall[19] and Roush[20] typically observe opposite stereoselectivity, and Roush[20] has suggested that the transition structure should have the alkoxy group anti and the alkyl group outside with respect to the nucleophile.[21]

In this paper we describe calculations aimed at establishing the nature of the steric and electronic effects of alkyl and alkoxy substituents on the transition states. This paper is divided into 10 sections. The first of these gives a description of the computational methods employed and the assumptions or approximations introduced in our calculations. In the second section, we describe calculations on the addition of methylcopper to (*E*)- and (*Z*)-crotonaldehyde (2-butenal). The third and fifth sections describe calculations on the preferred conformations of γ-methyl and γ-hydroxyl substituents in the transition states for addition to the *E* and *Z* isomers, respectively. The fourth section is directed to the analysis of nucleophile–substrate interactions in the transition states. This analysis allows us to rationalize the conformational preference of a substituent in terms of its steric and electronic properties. In the sixth, seventh, and eighth sections we derive stereoselectivity models for the nucleophilic addition to γ-alkoxy-α,β-unsaturated carbonyl compounds having a chiral C_γ center. Likewise, the ninth and tenth sections describe models that rationalize the stereoselectivity of nucleophilic additions to γ-aryl α,β-unsaturated carbonyl compounds. The sense and magnitude of stereoselection predicted on the basis of these models are found to be in good agreement with those observed experimentally.

Computational Methods and Assumptions

Ab initio restricted Hartree–Fock (RHF) molecular orbital theory was employed throughout.[22] For all atoms other than Cu, the 3-21G basis set[23] was used for geometry optimizations and most energy calculations; the energies of selected structures were calculated with the 3-21G basis set augmented with polarization functions on some of the heavy atoms. For the copper atom, an effective core potential[24] was used to describe the inner-shell electrons (up to 3p), while a (3s2p5d)/[1s1p1d] basis set was used to describe the remaining 11 electrons.[24] In our previous study on the regioselectivity of methylcopper addition to acrolein,[25] calculations with a double-ζ quality basis set for the valence electrons of copper gave results, in terms of both geometries and energies, very similar to those with a single-ζ basis set; the latter was therefore used in the present study. Substituted aldehydes were used as models for α,β-unsaturated carbonyl compounds, and monomeric methylcopper was used for simplicity in all our calculations. Although alkylcopper reagents exist as aggregates in solutions, our approximate treatment is reasonable, particularly in light of the calculated similarities in the activation energies and forming bond lengths in the addition of methyllithium monomer and dimer to formaldehyde.[26] Some assumptions were made possible by our previous calculations on the addition of methylcopper to acrolein.[25] There we showed that a six-membered cyclic transition state (schematically shown in Figure 6a) is greatly (14.4 kcal/mol) preferred to a cyclic four-membered transition state (Figure 6b) for conjugate addition. Experimental evidence in favor of a six-membered transition structure has also been uncovered recently.[27] In the present study, therefore, all calculations were carried out on six-membered transition structures only. Although only methylcopper was considered in our study, we believe that similar conclusions should apply to the reactions of other organometallic nucleophiles, such as Grignard reagents, that also give conjugate addition reactions.[28]

Some approximations were introduced in the optimization procedure for the location of the transition states for addition to (*E*) and (*Z*)-2-butenal. The C–H (10 in all) bond lengths were fixed: the C–H bond

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(18) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

(19) Marshall, J. A.; Trometer, D. J.; Blough, B. E.; Crute, T. D. *Tetrahedron Lett.* **1988**, *8*, 913.

(20) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231.

(21) Ziegler has pointed out that the nature of the alkyl group of the cuprate is also influential. In particular, allylic groups add to give stereochemistry opposite to that obtained with other alkyl groups: Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981**, *46*, 3874. A similar effect has been noted by Nicolau and co-workers: Nicolau, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224.

(22) The GAUSSIAN 82 program was used throughout: Binkley, J. S.; Frisch, M. J.; DeFrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, H. B.; Pople, J. A. GAUSSIAN 82, Department of Chemistry, Carnegie-Mellon University, Pittsburgh, PA.

(23) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(24) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270; *Ibid.* **1985**, *82*, 284. See also: Goddard, W. A., III; Kahn, L. R. *J. Chem. Phys.* **1972**, *56*, 2685.

(25) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 4635.

(26) Kaufmann, E.; Schleyer, P. v. R.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 5560. See also: Bachrach, S. M.; Streitweiser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3946.

(27) Yamamoto, Y.; Yamada, J.-i.; Uyehara, T. *J. Am. Chem. Soc.* **1987**, *190*, 5820.

(28) It is uncertain whether conjugate addition of Grignard reagents takes place via a cyclic six-membered transition structure or not. Stereochemical evidence in favor of this mechanism is described in: Marets, J. P.; Riviere, H. *Bull. Soc. Chim.* **1970**, 4320. For an opposite viewpoint, see: Klein, J. *Tetrahedron* **1964**, *20*, 465.

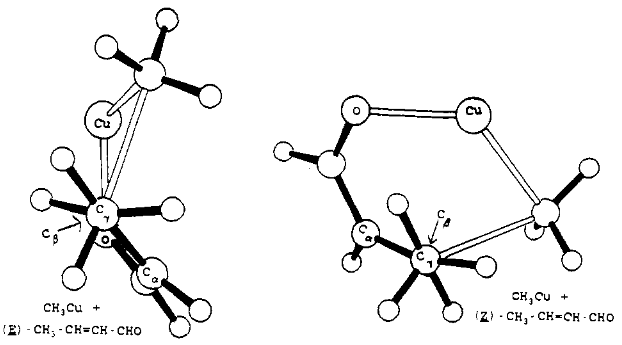
lengths of the β-methyl group were set equal to 1.0841 Å, which is the bond length in ethane (3-21G optimized structure[29]), while the remaining C–H bond lengths were set at the values that we had calculated (with full geometry optimization) for the addition of methylcopper to acrolein.[25] Our experience[25] shows that the changes in C–H bond lengths are very modest indeed. Full geometry optimization was carried out for the remaining (33) variables.

Energy calculations on 2-pentenal and 4-hydroxy-2-butenal (*E* and *Z* isomers in both cases) were performed on the geometries obtained for the addition reactions to 2-butenal, where each hydrogen of the enal methyl group was replaced, in turn, with a methyl (or hydroxyl) group. Geometry optimization was not performed. This implies that the fully optimized transition structures for addition to these molecules and to 2-butenal should be very similar. This is reasonable in light of theoretical studies on the related nucleophilic addition to carbonyl compounds,[6] which showed that transition structures for addition of sodium hydride to acetaldehyde and propanal are similar; however, in the addition to substituted enals, the conformation of the substituent on the β carbon is obviously of crucial importance. We have investigated this facet of the transition structure geometry in detail, as described in sections 3 and 5.

Results and Discussion

Nucleophilic Addition of Methylcopper to (*E*)- and (*Z*)-2-Butenal. We first investigated the structure of the reactants. Geometry optimization of (*E*)- and (*Z*)-2-butenal was performed at the HF/3-21G level; the optimized structures **1a**,**b** and **2a**,**b** are shown in Figure 7, together with the optimized geometry (**3**, Figure 8) of methylcopper (HF/3-21G-ECP(SZ)). This study and several calculations by Loncharich et al.[30] have shown that the preferred conformation of the C=C—C=O group of aldehydes is s-trans rather than s-cis. Therefore, the s-trans conformers were the only ones investigated for the two 2-butenal isomers. The terminal methyl group also exhibits conformational isomerism. As expected, the most stable structures (**1a** and **2a**) are the ones where one C–H bond is eclipsed to the C=C bond.[31] The difference in energy between the "eclipsed" and "staggered" conformers, however, is quite different in the two cases. The **1a**–**1b** gap of 1.59 kcal/mol is almost the same as in propene (2 kcal/mol);[32] however, the **2a**–**2b** energy separation is only 0.77 kcal/mol. This reflects the repulsion between the eclipsed C–H bond and the formyl group in **2a**, which partly offsets the electronic preference[31] for eclipsing.

The transition states **4** and **5** for the addition of methylcopper to the two stereoisomers of 2-butenal are shown in Figure 9. Both are similar to the structure calculated for the addition to acrolein, which we have discussed in detail in our previous paper. Here we summarize the main characteristics of both structures. The methyl group, as expected, attacks the β-carbon almost at right angles to the middle plane of the enal fragment; the C--C=C—C torsional angle is equal to -80° in both **4** and **5**. On the other hand, the Cu--O=C—C dihedral angle is rather small (32° in **4** and 31° in **5**), since the copper atom interacts more favorably with the in-plane lone pair of the carbonyl oxygen. The actual dihedral angle is the result of a compromise between this interaction and the necessity to maintain bonding with the methyl group in the transition state. The timing of the bond formation is also quite different: the metal–oxygen bond (2.01 Å long in **4** and 2.03 Å long in **5**) is only slightly stretched relative to the Cu–O bond in the enolate product, which is 1.883 Å long, whereas the methyl carbon–β-carbon bond is considerably elongated (2.30 Å in **4** and 2.32 Å in **5**). The calculated bond population ratio $n_{\mathrm{C-C}}/n_{\mathrm{Cu-O}}$ is of about 3:4. The importance of *electrophilic* oxygen–metal interactions in these transition structures for *nucleophilic* addition reactions has already been noted in a study of the addition of methyllithium and of its dimer to formaldehyde.[26] Both **4** and **5** can therefore be viewed as concerted but asynchronous transition states.[33,34] The actual forming C--C bond lengths are very similar in **4**, **5**, and the transition structure of the addition to acrolein, all being equal to about 2.3 Å. The activation energies were also found to be similar, being equal to 10.20 kcal/mol for the addition of methylcopper to (*E*)-2-butenal via **4** and 10.76 kcal/mol for the addition to the *Z* isomer via **5**. Each of these values is probably slightly higher than if full optimization of **4** and **5** had been performed.



4 E = 10.20

5 E = 10.76

	4	5
C=O	1.274	1.273
C(O)-C_α	1.383	1.388
C_α=C_β	1.400	1.401
Cu--O	2.010	2.028
C--C_β	2.305	2.321
C_β-C_γ	1.513	1.525
O=C-C_α	125.0	125.2
C_β=C_α-C(O)	121.2	122.9
Cu--O=C	112.4	109.3
C--C_β=C_α	115.2	116.0
C_γ-C_β=C_α	118.7	121.6
O=C-C_α=C_β	8.7	10.9
Cu--O=C-C_α	32.0	31.5
C--C_β=C_α-C(O)	-79.6	-80.4
C_γ-C_β=C_α-C(O)	173.2	45.8

Figure 9. Optimized (see text) transition structures (HF/3-21G) for the addition of methylcopper to (i) (*E*)-2-butenal (**4**) and (ii) (*Z*)-2-butenal (**5**). Both structures are viewed along the C_β–C_γ bond. Relevant bond lengths (angstroms), bond angles (degrees), and torsional angles (degrees) are given. The energies (kcal/mol) of **4** relative to (**1a** + **3**) and of **5** relative to (**2a** + **3**) are also shown.

The angle of nucleophilic attack (115° in **4** and 116° in **5**) is somewhat larger than that characteristic of nucleophilic attack on carbonyl compounds.[1,35] A similar value (120°) has been calculated for the C--C=C angle in the reaction of methyllithium with propene.[11] In our case, the large C--C=C angle is probably a consequence of the appreciable bonding maintained between the methyl group and the copper atom in the transition state. A decrease in the C--C=C angle would, in turn, force the C=O--Cu angle to get smaller; since the O--Cu bond is already quite strong in both transition structures, this bending motion is energetically expensive. In addition, the CH_3–C_α repulsion in conjugate additions may be larger than the CH_3–O repulsion in additions to carbonyl groups, owing to the more diffuse nature of carbon orbitals. This factor would also lead to a larger angle of attack than in the addition to carbonyl groups.

Where **4** and **5** differ significantly is in the conformation of the methyl group at C_β. In **4**, the methyl group is almost ideally staggered with respect to the incoming nucleophile, as the figure eloquently shows. Here the relief of torsional interactions with

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(29) Whiteside, R. A.; Frisch, M. J.; Pople, J. A. *The Carnegie-Mellon Quantum Chemistry Archive*, Department of Chemistry, Carnegie-Mellon University, Pittsburgh, PA.

(30) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(31) For a discussion of the preference for eclipsing to C=C bonds, see: Hehre, W. J.; Pople, J. A.; Devaquet, A. J. P. *J. Am. Chem. Soc.* **1976**, *98*, 664. Pross, A.; Radom, L.; Riggs, N. V. *J. Am. Chem. Soc.* **1980**, *102*, 2253.

(32) Moller, K. D.; DeMeo, A. R.; Smith, D. R.; London, L. H. *J. Chem. Phys.* **1967**, *47*, 2609.

(33) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209.

(34) The wave function for the transition state of addition to acrolein[25] was verified to be UHF-stable. In other words, each MO of the transition state contains one pair of electrons, and there exists no lower energy solution in which α-spin and β-spin MOs are different. This suggests that these reactions do not proceed via open-shell species, such as a diradical or diradicaloid intermediate.

(35) Burgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

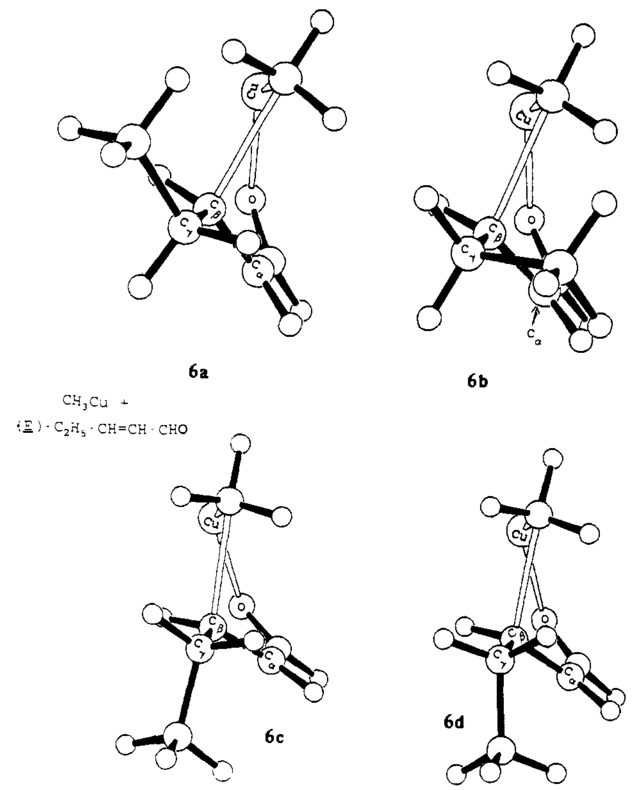

Figure 10. Approximate (see text) transition structures (HF/3-21G) for the addition of methylcopper to (*E*)-2-pentenal: **6a**, outside conformation; **6b**, inside conformation; **6c–d**, anti conformation. The rotational angle ϕ is equal to zero (by definition) in **6a–c**, and it is positive for an anticlockwise rotation about the C_β–C_γ bond. In **6d**, $\phi = +20°$.

the forming bond, which is at the basis of the Felkin–Anh model,[5,6] is once again of paramount importance. On the other hand, good staggering cannot be achieved in transition structure **5**; this would bring the inside hydrogen into a region which is sterically very encumbered, owing to the cis formyl group and, even more so, the copper ion. Consequently, the methyl group assumes a conformation such that the inside hydrogen is almost eclipsed to the C=C bond, which in turn brings the outside hydrogen closer to the nucleophile.

Effect of Substituents on the γ-Carbon of 4. (a) Effect of a Methyl Group. **4** and **5** may be regarded as the "parent" transition states for 1,4-addition to *E* and *Z* enals. Most molecules of interest in synthetic organic chemistry have complex substitution patterns, and a knowledge of the steric and electronic effects of such substituents would be desirable. In particular, we were interested in the conformational preference of a given substituent at the γ-carbon atom in the transition structures. From the steric point of view, the anti position appears to be the least hindered just by inspection of **4** and **5**, and the outside position seems in turn less hindered than the inside position, at least in the addition of the *Z* isomer. The electronic effect, not surprisingly, is more difficult to assess. Previous theoretical studies on the related nucleophilic additions to carbonyl compounds have discussed in detail the electronic characteristics of substituents and how their conformational preferences depend on the nature of the transition structures.[6,36,37]

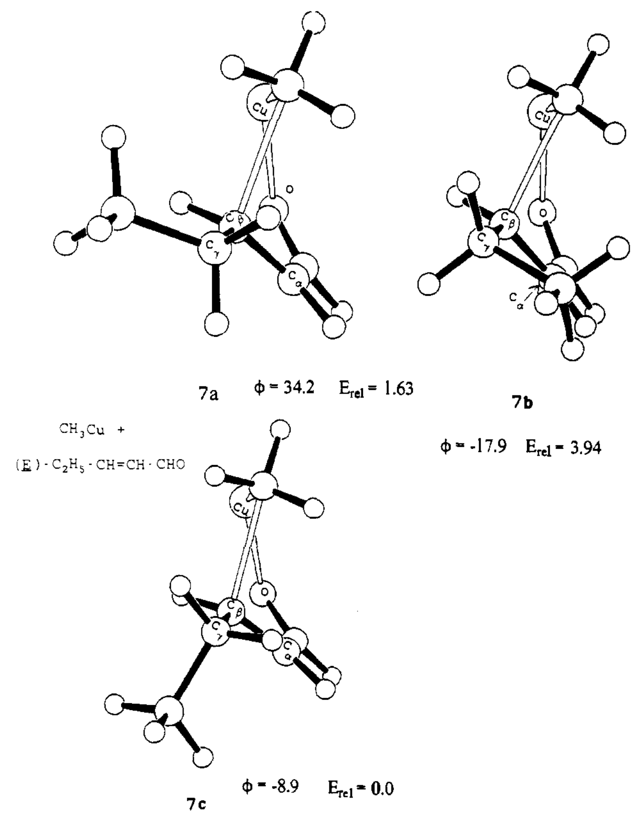

Figure 11. Local conformational minima (HF/3-21G) for the transition structures for the addition of methylcopper to (*E*)-2-pentenal: **7a**, outside conformation; **7b**, inside conformation; **7c**, anti conformation. **7c** is the global minimum. Relative energies (kcal/mol) and ϕ values (degrees) are also shown.

Table I. Energies (E_{rel}, kcal/mol) of Outside, Inside, and Anti Methyl Group Transition-State Conformers in the Addition of Methylcopper to (*E*)-2-Pentenal and Corresponding ϕ Values[a]

outside		inside		anti	
ϕ	E_{rel}	ϕ	E_{rel}	ϕ	E_{rel}
0	16.63	-30	4.70	-20	0.40
20	3.22	-20	3.97	-10	0.01
30	1.81	-10	4.26	0	0.26
40	1.86	0	6.92	10	1.31
50	2.30	10	12.70	20	3.16
				30	5.51

[a] See text and Figure 10 for the definition of ϕ. All energies are relative to the energy of the global minimum **7c** (Figure 11).

Let us now discuss the results of our calculations in which one of the enal methyl group hydrogen atoms is replaced with a methyl group.[38] We will first consider transition structure **4**, for addition to the *E* isomer. Replacement of each of the three hydrogen atoms gave three structures (**6a**, **6b**, and **6c** in Figure 10) which are approximate models for the transition states for conjugate addition to 2-pentenal, in which the methyl group of the enal occupies the outside, inside, and anti positions, respectively. The energies of **6a–c** were calculated. Next, we mapped the potential energy surface corresponding to rotation about the C_β–C_γ bond by varying simultaneously each of the three dihedral angles (one C—C_γ—C_β=C and two H—C_γ—C_β=C angles) at 10° intervals and calculating the energy of the newly obtained rotamer. For convenience, we define at this point a rotational angle ϕ, which is defined to be 0° in each of the three reference structures **6a**, **6b**, and **6c**. In any other rotamer, ϕ is defined as the smallest difference between the value of the C–C_γ–C_β–C_α dihedral angle in that rotamer and its values in **6a**, **6b**, and **6c**. For example, the value of ϕ in **6d**, where the methyl group is in the anti position,

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(36) Cieplak has suggested that nucleophilic attack should occur anti to the best electron donor: Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. Evidence exists both in favor of this hypothesis (see ref 7b) and against it (ref 6, 7a).

(37) Hehre and co-workers have successfully interpreted the stereochemistry of a number of nucleophilic and electrophilic addition reactions to unsaturated systems in terms of an electrostatic model. For an example related to the present discussion, see: Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399.

(38) The optimized structure (HF/3-21G) of the methyl group in ethane[29] was used. The methyl group was constrained to be staggered with respect to the C_β–C_γ bond.

is equal to +20°, since the C–C_γ–C_β–C_α torsional angle here (−45.6°) is 20° larger than it is in **6c** (−65.6°—the sign of the dihedral angles is defined so that ϕ is positive for an anticlockwise rotation).

With this procedure, we were able to locate approximately three local rotational minima. To obtain the minimum-energy value of ϕ more accurately, the points in the vicinity of the approximate local minimum were then fitted to a parabola. The three rotational minima thus obtained are shown in Figure 11. These correspond to values of ϕ of 34.2° (**7a**) for the outside conformer, −17.9° (**7b**) for the inside conformer, and −8.9° (**7c**) for the anti conformer. The relative energies of these and several other points (for different values of ϕ) are given in Table I.

Before we discuss in detail the results of our calculations, we will comment briefly on the above procedure. It is clear that geometry optimization would locate the three local minima with greater accuracy. However, aside from the computational expense involved (split-valence basis set geometry optimization, even partial, of a system having 8 heavy atoms (one of them a transition metal), 11 hydrogen atoms, and no symmetry is an unenviable task), locating the local minima alone was not sufficient. It was also necessary to calculate the energies of other points, displaced from each local minimum, to obtain a measure of the steepness of the potential well for each minimum. The reason for this is that, in a system where there are *two* substituents at C_γ, any conformational minimum could conceivably correspond to a value of ϕ different from all three given in Figure 11. We shall show that this is indeed the rule, rather than the exception. It is therefore indispensable to know the energy of several rotamers as well as the three conformational minima, particularly if these minima happen to lie in shallow potential energy wells.

Let us now return to Figure 11. The global minimum is **7c**, the anti conformer, which is 1.63 kcal/mol more stable than the outside conformer **7a** and 3.94 kcal/mol more stable than the inside conformer **7b**. The preference for **7c** over the other two is certainly due, at least in part, to the fact that the anti position is the least hindered sterically. It is remarkable, however, that the anti conformer is less stable than the inside conformer in the addition of sodium hydride to propionaldehyde.[6] This effect was interpreted by Wu and Houk[6] in terms of the electron-donating effect of the methyl group: an anti methyl group is expected to destabilize an electron-rich, nucleophilic transition state. The difference between this result and our finding in favor of the anti conformer suggests differences in the electronic nature of the two transition states. We will return to this point in greater detail when we consider the effect of a hydroxyl group.

The structural differences in **7a–c** are also noteworthy. Whereas **7b** and **7c** exhibit good staggering of the ethyl group relative to the forming nucleophile–C_β bond, **7a** shows rather poor staggering. In this conformation, the large repulsive interaction between the negatively charged methyl "anion" and the hydrogen atoms of the outside methyl group must be relieved. Our calculations show that the energy of this conformation decreases considerably (14.95 kcal/mol from **6a** to **7a**) as this group swings away from the incoming nucleophile, and that the conformational minimum is obtained for a rather large value of ϕ. In fact, while **7a** is more stable than the inside conformer **7b**, **6a** is less stable than **6b** by 9.71 kcal/mol.

(b) Effect of a Hydroxyl Group. A similar procedure was used to determine the conformational preference of a hydroxyl group (this serves as a model for the electronically similar—but computationally expensive—alkoxy group). The local rotational minima **8a–c** in which the hydroxyl group[39] occupies the outside, inside, or anti positions are shown in Figure 12. ϕ is equal to 12.9° for the outside conformer (**8a**), −12.4° for the inside conformer (**8b**), and 3.1° for the anti conformer (**8c**). The global conformational minimum is **8a**, which is 0.63 kcal/mol more stable than **8b** and 2.78 kcal/mol more stable than **8c**. In Table II we give the energies of these and other rotamers.

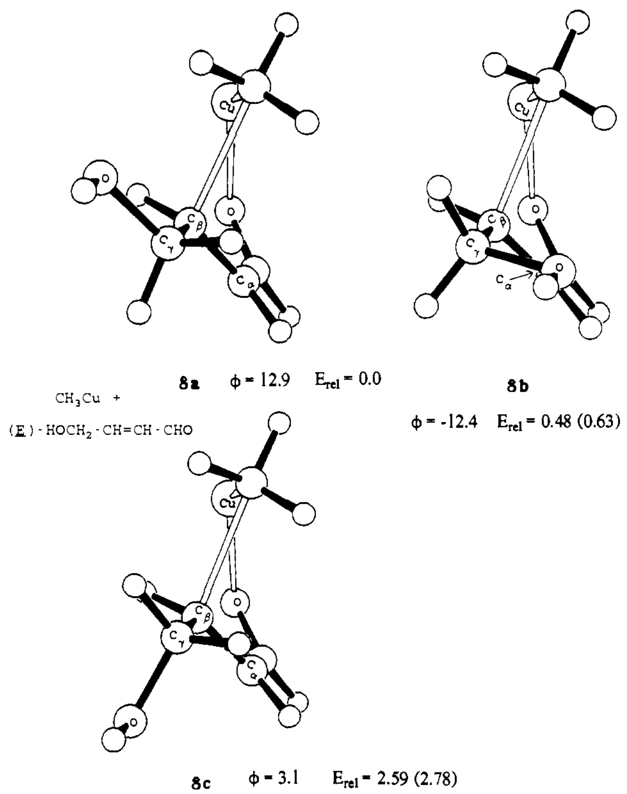

Figure 12. Local conformational minima (HF/3-21G) for the transition structures for the addition of methylcopper to (*E*)-4-hydroxy-2-butenal: **8a**, outside conformation; **8b**, inside conformation; **8c**, anti conformation. **8a** is the global minimum. HF/3-21GP (HF/3-21G) relative energies (kcal/mol) and ϕ values (degrees) are also shown.

Table II. Energies (E_{rel}, kcal/mol) of Outside, Inside, and Anti Hydroxyl Group Transition-State Conformers in the Addition of Methylcopper to (*E*)-4-Hydroxy-2-butenal and Corresponding ϕ Values[a]

outside		inside		anti	
ϕ	E_{rel}	ϕ	E_{rel}	ϕ	E_{rel}
0	1.11	−20	0.87	−10	3.01
10	0.06	−10	0.65	0	2.79
20	0.33	0	1.31	10	2.84
30	1.94	10	3.09	20	3.16

[a] All energies are relative to the energy of the global minimum **8a** (Figure 12).

The most striking feature of this set of calculations is that the anti position (see **8c**), which sterically is the least hindered, is also the least favorable. It is true that the hydroxyl group is smaller than the methyl group, but this would suggest that the energetic preference for the anti position should simply decrease somewhat relative to the case of methyl substitution. This effect is evident, for example, in the small preference (relative to the case of methyl substitution described previously) for the outside over the more crowded inside position. The fact that the outside and inside positions become more favorable than the anti position suggests that electronic factors, rather than steric, determine the conformational preference of the hydroxyl group and possibly the methyl group too.

These findings could conceivably result from the use of a relatively small basis set (3-21G). Wiberg has pointed out[12,40] that polarization functions on the heavy atoms are required to obtain accurate rotational barriers about single bonds in α,β-unsaturated carbonyl compounds. We considered the possibility

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(39) The optimized geometry (HF/3-21G) of the hydroxyl group in methanol was used.[29] Since the hydroxyl group serves as a model for alkoxy groups, the H–O–C–C dihedral angle was constrained to be 180°, so as to mimic the preferred conformation of the C–O–C–C group of alkyl ethers. A similar approach has been described in: Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257.

(40) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935.

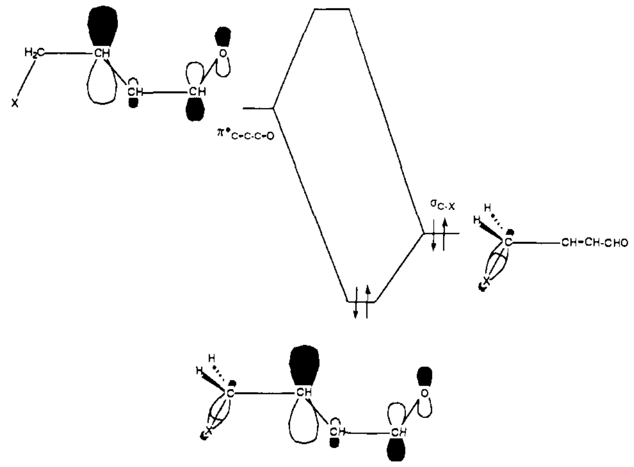


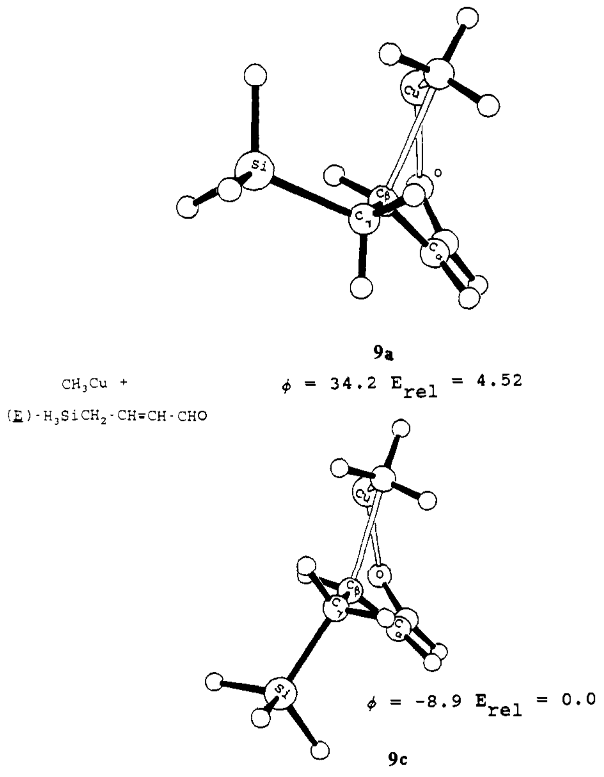
Figure 13. Schematic representation of the two-electron orbital interaction between the $\sigma_{C_\gamma-X}$ orbital and the $\pi^*_{C=C-C=O}$ orbital of an α,β-unsaturated carbonyl compound.

that the relative energies of **8a–c** would also depend on the particular basis set employed, especially due to the presence of a polar single C–O bond in these structures. The energies of **8a–c** were thus recalculated by using the 3-21G basis set augmented with d polarization functions[41] (hence denoted 3-21GP) on the carbon and oxygen atoms. The relative energies of the three conformers were found to be very similar to those obtained with the 3-21G basis set: **8a** was calculated to be 0.48 kcal/mol more stable than **8b** and 2.59 kcal/mol more stable than **8c**. Thus, the 3-21G basis set appears to be reliable for our purposes, at least for calculations on the *E* isomers.

We can now formulate a postulate that defines the effect of a substituent on the γ-carbon atom: *An electron-withdrawing group in the anti position is disfavored because it destabilizes the transition structure by removing electron density from the enal fragment*; *an electron-donating group in the anti position is favored both for steric reasons and because it stabilizes the enal fragment*.

This postulate is in agreement with the observed destabilization caused by the electron-withdrawing hydroxyl group, and the stabilization by the electron-donating methyl group in the anti position. This last statement implies that a C–C bond is a better donor than a C–H bond, in agreement with computational[6] and experimental[42] evidence mainly due to Houk. As is evident from **4** and **5**, the dominant interaction in the transition state occurs between the carbonyl oxygen and the copper atom. The metal–oxygen bond in the transition state is quite strong, whereas the nucleophile–carbon bond is still long and weak. An electron-withdrawing group can thus destabilize this structure by removing electron density from the enal oxygen; an electron-donating group should instead stabilize it by enhancing the electron density. Hehre and co-workers have likewise emphasized the importance of electrostatic interactions in determining the reaction stereoselectivity.[37]

Similar conclusions on the effect of an electron donor may also be reached by the following argument, based on perturbation molecular orbital theory, which focuses on the substituent effect on the enal moiety. This fragment has a low-lying LUMO (π^* orbital), even more so in the transition structure than in the ground state, due to the lengthening of the C=O and C_β=C_α bonds and the shortening of the (O)C–C_α bond. If C_γ bears an electron-donating group (X in Figure 13), the interaction of the high-lying $\sigma_{C_\gamma-X}$ orbital with the low-lying π^* orbital stabilizes this fragment by an amount inversely proportional to the energy gap.[43] This interaction is obviously more effective if the σ orbital is perpendicular to the C=C—C=O group or anti to the nucleophile.



9a

ϕ = 34.2 E_{rel} = 4.52

ϕ = -8.9 E_{rel} = 0.0

9c

Figure 14. Model transition structures for the addition of methylcopper to (*E*)-4-silyl-2-butenal: **9a**, outside conformer; **9c**, anti conformer. Relative energies (kcal/mol) and ϕ values (degrees) are also shown.

The substituent effects present in our transition structures are similar to those that characterize *electrophilic* additions to C=C bonds of simple olefins.[44] For example, the stereoselectivity of osmylation of chiral allylic alcohols has been rationalized in terms of a transition structure in which attack of the electrophile takes place anti to the allylic C–C bond rather than anti to the C–O bond.[45] A similar conformation of the allylic substituents of a diene is preferred in the Diels–Alder addition of electron-deficient alkenes[46] and in nitrile oxide cycloadditions.[47] Once again, this similarity reaffirms the importance of the electrophilic interaction involving the enal oxygen and the copper center.

To confirm that an electron donor prefers the *anti* position, the methyl group in structures **7a** and **7c** was replaced with a silyl group, and the energies of the two resulting structures (**9a** and **9c**, Figure 14) were calculated. **9c** was found to be preferred over **9a** by 4.52 kcal/mol, a large increase over the 1.63 kcal/mol energy gap between **7a** and **7c**. This does not seem to be due to a destabilization of **9a** owing to a simple steric effect. Even though the silyl group is obviously larger, the C–Si bond (ca. 1.9 Å) is longer than the C–C bond (ca. 1.5 Å), so that the silyl hydrogen atoms in **9a** are actually further from the incoming nucleophile than the methyl hydrogen atoms in **7a** (the shortest H–H distance is 2.074 Å in **7a** and 2.211 Å in **9a**). The electronic effect of the silicon–carbon bond, a much stronger donor[48] than the carbon–hydrogen and carbon–carbon bonds, is considered to be the driving

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[41] The exponent of the d polarization function is equal to 0.8. Five d orbitals are used in the atomic orbital basis.

[42] Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 1189.

[43] Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223; Salem, L. *Ibid.* **1968**, *90*, 553.

[44] A similar suggestion on the role of electrophilic interactions in the reactions of nucleophiles has been made in: Kahn, S. D.; Dobbs, K. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 4602.

[45] Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.

[46] Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257, and references therein. See also: Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225.

[47] Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3380.

[48] The stabilization of β-silyl carbocations is well-known. Moreover, Hehre and co-workers have shown that the preferred conformation of allylsilanes has a similar conformation of the Si—C—C=C group (nearly 90°) to that of **9c**: Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650.

Table III. Fragment Deformation Energy (DEF), Total Interaction Energy (INT), and Individual Energy Components of INT in **6a**–**9a** and **7c**–**9c** (kcal/mol)[a]

transition struct	DEF_A	DEF_B	INT	ES	EX	OM
6a	0.95	12.69	−6.02	−74.57	148.69	−80.14
7a	1.89	12.69	−21.95	−68.06	114.95	−68.92
7c	0.0	12.69	−21.69	−67.32	113.18	−67.55
8a	−1.15	12.69	−24.60	−66.88	114.03	−71.75
8c	0.0	12.69	−23.16	−67.28	114.14	−70.02
9a	5.16	12.69	−21.91	−68.95	116.63	−69.59
9c	0.0	12.69	−21.27	−67.76	113.70	−67.21

[a] Here A is the enal moiety, B methylcopper. All calculations are done at the HF/3-21G level.

force behind the stabilization of **9c**.

It is nevertheless clear that the preference for the less encumbered anti position could be, in general, a simple steric effect, although this does not explain the destabilizing effect of an anti hydroxyl group. The calculations described thus far cannot determine the relative importance of the various components of the interaction energy. To this end, we performed an energy decomposition analysis[49] of several transition structures. The results of this analysis are discussed below.

Energy Decomposition Analysis of the Nucleophile–Enal Interaction. The interaction between two transition structure "fragments" can be expressed as the sum of several terms,[49] the most important being an electrostatic component (ES), an orbital mixing (charge transfer and polarization) term (OM), and an exchange term (EX). The energy of a transition structure relative to the reactants depends on the magnitude of each component and on the energy required to distort each reactant into its geometry at the transition state (DEF[49]). Thus, when comparing two transition structures, we can readily identify which energy component(s) is (are) mainly responsible for the difference in energy between them. The theory has been described in detail elsewhere;[49] here we recall the main points. The total interaction energy INT between two fragments A and B is expressed[49b] as

$$\mathrm{INT} = \mathrm{ES} + \mathrm{EX} + \mathrm{CTPLX(A{\to}B)} + \mathrm{CTPLX(B{\to}A)} + R$$

ES is a purely electrostatic term that represents the interaction energy between two fragments when neither orbital mixing nor electron exchange is allowed. The second term, EX, represents the effect of allowing electron exchange and is generally dominated by the repulsion generated between the filled orbitals of A and those of B. The remaining terms can be categorized as orbital mixing (OM) terms. The CTPLX(A→B) term is obtained by subtracting ES and EX from the energy in which the interactions between filled A orbitals and vacant B orbitals, filled orbitals on both fragments, and filled and vacant B orbitals are incorporated. This term may therefore be called the "donative interaction" from A to B. The other term, CTPLX(B→A), is completely analogous. Finally, *R* is a residual term that arises from cross terms involving the other components, and it is generally small.[25] We shall hence denote the sum (CTPLX(A→B) + CTPLX(B→A) + *R*) as OM.

Table III summarizes the results of the calculations performed within this framework at the HF/3-21G level on **6a**, **7a**–**9a**, and **7c**–**9c**. In Table III, DEF normally[49] represents the energy of the individual reactant fragments in the transition state relative to the undistorted reactants. This would require the optimization of the geometry of the ground-state enal moiety in each case. In practice, all that is needed to compare two conformers of each pair (for example, **7a** and **7c**) is the difference in the values of DEF. Thus, the DEF_A values in the table are calculated by arbitrarily setting the energies of the anti conformers (**7c**–**9c**) to zero and calculating the relative energies of the outside conformers (**6a**–**9a**).

In **6a**, all the energy components are much larger than in all the other structures considered. This is usually the case in a structure where some nonbonded atoms lie very close to one another; in **6a**, these are the hydrogen atoms of the two methyl groups. The destabilization due to steric repulsion (incorporated in the term EX) is dominant, so that the resulting INT term is rather small.

Table IV. Individual Energy Components of OM in **8a** and **8c** (kcal/mol)[a]

transition struct	CTPLX(A→B)	CTPLX(B→A)	*R*
8a	−44.29	−21.14	−6.32
8c	−43.02	−20.71	−6.29

[a] Here A is the enal moiety, B methylcopper. All calculations are done at the HF/3-21G level.

When the substituent is an electron-releasing group (as in **7a**–**c** and **9a**–**c**), the values of INT are similar for the outside and anti conformers, and the difference in energy between the two transition structures is determined essentially by the difference in DEF_A. A logical interpretation of this result is that the outside conformers are sterically more hindered (at least when the outside heavy atom is tetracoordinated), and that the ensuing destabilization (cf. **6a**) has to be relieved at the expense of achieving a high-energy conformation of the enal fragment. In fact, inspection of **7a** and **9a** shows that the C–C (C–Si) bond is almost eclipsed to the C_β–H bond. This interaction is certainly more severe than the interaction involving the anti C–C (C–Si) and the C(O)–H bond in **7c** and **9c**. In **9a** and **9c**, the difference in DEF_A is so high that an additional factor must be operative; this is the preference for a C–Si bond to lie perpendicular to a C=C bond, demonstrated by calculations by Hehre and co-workers on allylsilanes.[48]

The destabilization of the anti position in **8c** is less simple to rationalize. There are two contributing factors to the preference for **8a** over **8c**, namely, DEF_A and INT. Most likely, DEF_A is smaller in **8a** because the C_γ–O and C_β=C_α dipoles are counteraligned; in **8c** they form an angle of about 62°. The larger difference, however, is in the INT values. INT is substantially stronger in **8a**, as a consequence of a larger (more negative) value of OM in **8a** than in **8c**. This finding prompted us to probe more closely the origin of this difference in OM values by calculating the CTPLX(A→B) and CTPLX(B→A) terms for **8a** and **8c**. The results are shown in Table IV. Both terms favor **8a**, especially CTPLX(B→A), which represents donation from the filled orbitals of methylcopper to the vacant orbitals of the 4-hydroxy-2-butenal. Nonetheless, some caution is required in the interpretation of this last result, since the individual CTPLX terms and the residual term *R* depend on the level of the calculation.

Finally, additional evidence of the role of the copper center in determining the nature of the transition structure—and therefore the conformational preference of a substituent—was deduced from calculations on **8a′** and **8c′**, obtained from **8a** and **8c** by removing the copper center. The charge of each system was set to −1 in these calculations. It was found that **8c′** is favored over **8a′** by 0.35 kcal/mol. This represents a 2.94 kcal/mol "swing" from the preference for **8a** over **8c**. Although **8a′** and **8c′** are not optimized, this finding clearly demonstrates the importance of the copper–oxygen interaction.

Effect of Substituents on the γ-Carbon of 5. (a) Effect of a Methyl Group. In this section we describe the effect of replacing a γ-hydrogen with a methyl or hydroxyl group in transition structure **5**, for addition to the *Z* enal. The same procedure that we have described in the preceding section was also applied here to obtain the conformational minima. We shall describe the effect of methyl group substitution first.

Structures **10a**–**c** (Figure 15) represent the three model transition structures in which the C_γ methyl group lies in the outside, inside, and anti positions, respectively. In Table V we give the energies of the rotamers we have calculated. The sign of ϕ is defined in the same way as in Figure 10—ϕ is positive for an anticlockwise rotation.

The global minimum is the anti conformer **10c** (ϕ = 1.0°); this result is in line with our previous discussion on the *E* isomer and suggests the same type of electronic control. This time, however, the preference over the outside conformer **10a** (ϕ = −41.0°) is

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(49) (a) Kitaura, K.; Morokuma, K. *Int. J. Quantum Chem.* **1976**, *10*, 325. (b) Kitaura, K.; Sakaki, S.; Morokuma, K. *Inorg. Chem.* **1981**, *20*, 2292.

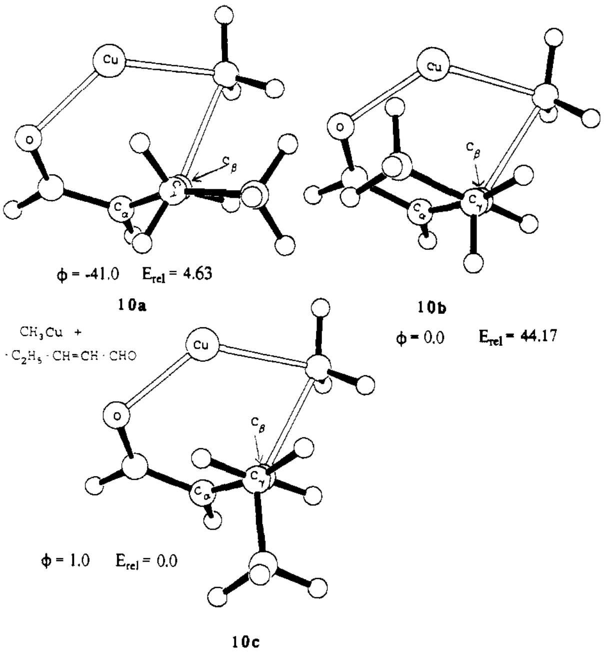

Figure 15. Local conformational minima (HF/3-21G) for the transition structures for the addition of methylcopper to (*Z*)-2-pentenal: **10a**, outside conformation; **10c**, anti conformation. **10b** (ϕ = 0°), which is not a conformational minimum (see text), is shown for comparison. **10c** is the global minimum. Relative energies (kcal/mol) and ϕ values (degrees) are also shown.

Table V. Energies (E_{rel}, kcal/mol) of Outside, Inside, and Anti Methyl Group Transition-State Conformers in the Addition of Methylcopper to (*Z*)-2-Pentenal and Corresponding ϕ Values[a]

outside		inside		anti	
ϕ	E_{rel}	ϕ	E_{rel}	ϕ	E_{rel}
-60	4.70	0	44.17	-40	6.12
-50	4.72	20	32.97	-30	3.82
-40	4.63	40	14.79	-20	1.86
-20	5.12	60	7.31	-10	0.51
-10	5.74			0	0.01
0	6.26			10	0.35

[a] All energies are relative to the energy of the global minimum **10c** (Figure 15).

Table VI. HF/3-21G energies (E_{rel}, kcal/mol) of Outside, Inside, and Anti Hydroxyl Group Transition-State Conformers in the Addition of Methylcopper to (*Z*)-4-Hydroxy-2-butenal and Corresponding ϕ Values[a]

outside		inside		anti	
ϕ	E_{rel}	ϕ	E_{rel}	ϕ	E_{rel}
-20	4.83	0	14.35	-20	7.86
-10	4.47	-10	11.74	-10	6.65
0	4.39	-20	7.97	0	5.97
10	4.56	-30	4.30	10	5.81
		-40	1.69		
		-50	0.31		
		-60	0.04		
		-70	0.86		

[a] All energies are relative to the energy of the global minimum **11b** (Figure 16).

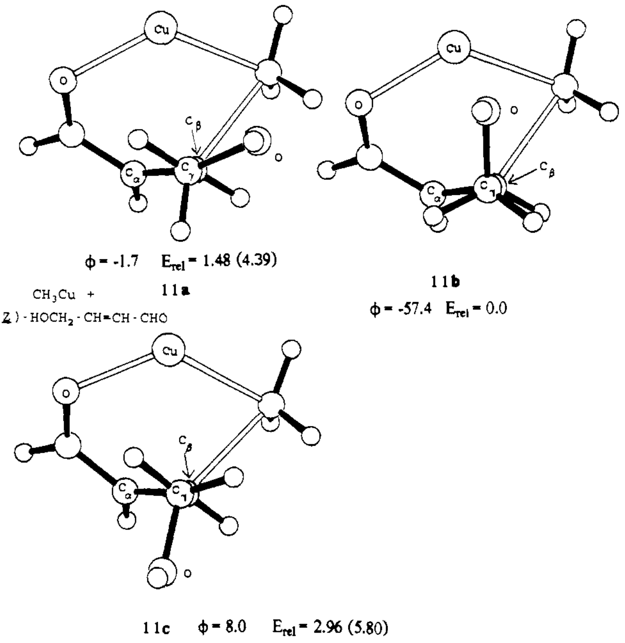

Figure 16. Local conformational minima (HF/3-21G) for the transition structures for the addition of methylcopper to (*Z*)-4-hydroxy-2-butenal: **11a**, outside conformation; **11b**, inside conformation; **11c**, anti conformation. **11a** is the global minimum. HF/3-21GP (HF/3-21G) relative energies (kcal/mol) and ϕ values (degrees) are also shown.

large (4.63 kcal/mol), and the destabilization of the inside conformer is enormous (**10b** is 44.17 kcal/mol higher in energy than **10c**). Indeed, **10b**, unlike the other structures discussed here, is not a local minimum; clockwise rotation about the C_β–C_γ bond by any amount causes the energy to decrease monotonically, until the anti conformation **10c** is reached. The dramatic magnitudes of these effects are readily rationalized in terms of the large steric destabilization of the inside and outside positions, particularly the former, which is a consequence of the large bulk of both the C=O group and the copper center. The inside methyl group is sandwiched between these two groups, and the methyl hydrogen atoms cannot avoid "bumping" into one or the other. The outside position is also more unfavorable, as can be appreciated by referring to the "parent" transition structure **5**. There, and in **10a**, the inside hydrogen has to rotate away from the copper center, causing the outside hydrogen or methyl to swing toward the nucleophile, in a more crowded environment.

(b) Effect of a Hydroxyl Group. The same procedure was used to analyze the effect of a hydroxyl group, and it gave an altogether different result. Table VI shows the energies of all the rotamers calculated. The inside position (see **11b** in Figure 16; ϕ = −57.4°) was found to be markedly favored (by 4.39 kcal/mol) over the outside position (**11a**; ϕ = −1.7°), with the anti conformer (**11c**; ϕ = 8.0°) being the worst (5.80 kcal/mol less stable than **11b**).

The preference for the outside over the anti conformer can be readily rationalized in terms of our previous postulate, but the strongly favored inside conformer owes its stability to a different interaction, namely, coordination of the oxygen atom to the copper center. The metal is thus chelated by the two oxygen atoms in **11b**. For this coordination to be achieved, the hydroxyl group must swing through a wide arc toward the metal center—ϕ in **11b** is equal to −57.4°.

It is however well-known that the strength of electrostatic interactions of this kind is strongly basis-set dependent; for example, hydrogen bond strengths are overestimated by basis sets which do not include polarization functions.[50] We considered that the 3-21G basis set might not be adequate for the analysis of the interaction implied in **11b**, although we had shown in the previous section that it was otherwise reliable. We therefore recalculated the energies of **11a–c** using the 3-21GP basis set defined previously. As expected, the result was that the preference for the inside position decreased (although it was still found to be the global minimum). **11a** and **11c** were calculated to be only 1.48 and 2.96 kcal/mol less stable than **11b**, respectively. The relative energies of **11a** and **11c** are very similar at the two levels of theory, thus confirming the reliability of the 3-21G basis set for the treatment of conformational processes that are not complicated by coordination to the metal. 3-21GP calculations on

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(50) See: Loushin, S. K.; Liu, S.-y.; Dykstra, C. E. *J. Chem. Phys.* **1986**, *84*, 2720. For a discussion of basis set superposition error and how to correct for it, see: Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

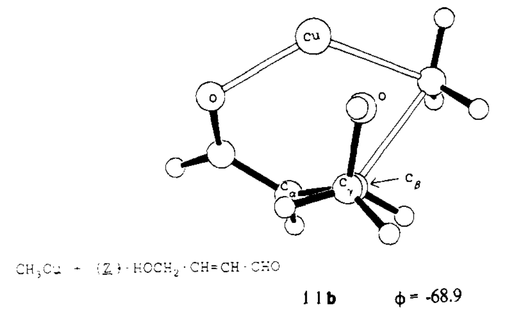

Figure 17. Local conformational minimum **11b′** (HF/3-21GP) for the transition structure for the addition of methylcopper to (*Z*)-4-hydroxy-2-butenal (inside conformation).

other rotamers in the region of **11b** showed that, at this level of theory, the minimum-energy structure is found for an even larger negative value of ϕ (**11b′**, Figure 17; $\phi = -68.9°$). The energy difference between **11b** and **11b′** is only 0.14 kcal/mol in favor of the latter.

Stereoselectivity of Conjugate Additions to α,β-Carbonyl Compounds. Having thus obtained a quantitative estimate of the effect of one substituent at the γ-carbon of both *E* and *Z* enal isomers, we are now in a position to assess the combined effect of two substituents. Although we have considered, for computational simplicity, only a methyl and a hydroxyl group in our calculations, the same conclusions that we shall derive in this section can be considered to apply to alkyl and alkoxy groups in general. In the synthetic application of this reaction, the γ-carbon is often a chiral center bearing either a hydrogen atom, an alkoxy group, and an alkyl group or a hydrogen atom and two groups of different steric bulk.

We shall assume, in our ensuing discussion, that the preference of any one substituent for a given position (outside, inside, or anti) is not affected by the presence of a second substituent. This is equivalent to stating that the energy of a disubstituted conformer (such as **12a**) as a function of ϕ can be expressed in terms of the energies of the monosubstituted conformers **12b** and **12c** and of the unsubstituted conformer **12d** for the same ϕ, as shown in Figure 18. Here we are assuming that any interaction that may be present between two substituents is independent of the conformation and cancels out when comparing the energies of two different conformers.[51]

As before, this approach can be used to obtain the energy of various rotamers of, say, **12a** as a function of ϕ. To obtain the minimum-energy value of ϕ more accurately, the points in the vicinity of the approximate local minimum were fitted to a parabola. In all cases, we have evaluated the energies of the favored transition-state conformation—which should lead to the major product—and of the most stable transition-state conformation among those that lead to the minor product. From the relative energies of the two conformers, a quantitative estimate of the stereoselectivity of the reaction can be calculated. The calculated and experimental stereoselectivities have then been compared. Here we give the results for *E* and *Z* isomers, in this order.

Stereochemistry of Addition to (*E*)-γ-Alkoxy α,β-Unsaturated Carbonyl Compounds. Using the additivity relationship described in Figure 18 (see **12a–d** and **13a–d**), we estimated the energies of various conformers for different values of ϕ. The lowest energy conformer was found to be **14(i)** (Figure 19), in which the methyl group is anti and the hydroxyl group inside; ϕ is equal to −12.2°. The only conformer of comparable energy, **14(ii)** ($\phi = 6.2°$; Figure 19), has the methyl group anti and the hydroxyl group outside, and this leads to the other diastereomer. The calculated energy difference is 0.60 kcal/mol. At room temperature, the corresponding rate constant ratio can be calculated straightforwardly,

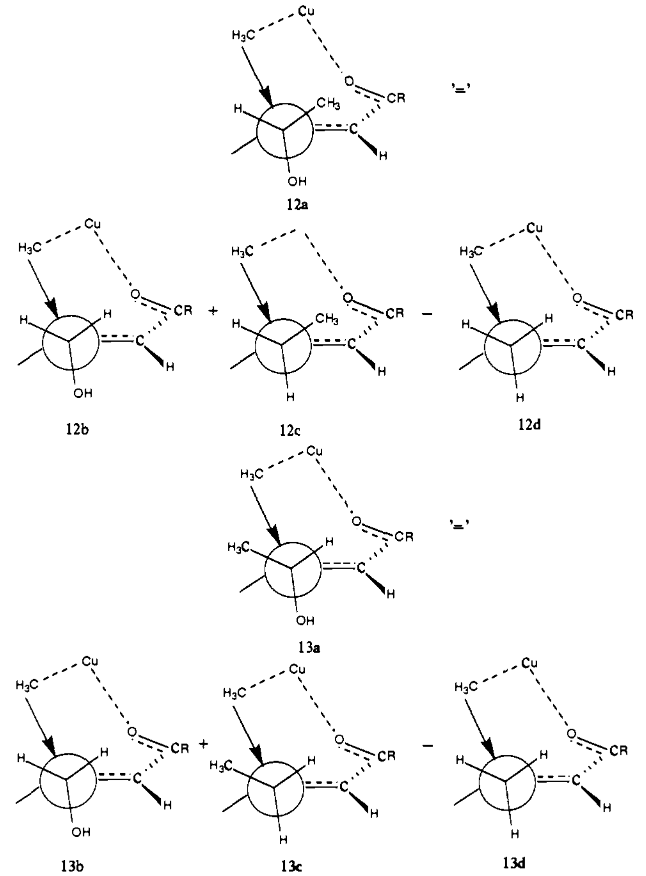

Figure 18. Schematic illustration of the evaluation of the energy of disubstituted conformers **12a** and **13a** in terms of the energies of monosubstituted (**12b**,**c**, **13b**,**c**) and nonsubstituted (**12d**, **13d**) conformers.

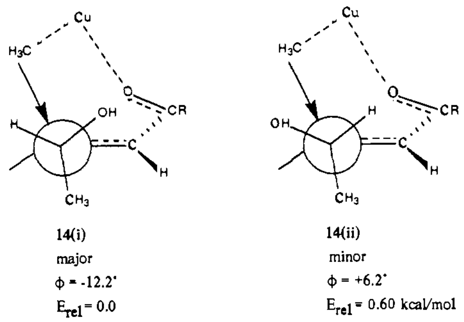

Figure 19. Transition structures **14(i)** and **14(ii)** leading to the major (anti) and minor (syn) diastereomer, respectively, in the addition of methylcopper to (*E*)-4-hydroxy-α,β-unsaturated carbonyl compounds.

if we assume the same entropies of activation for the addition reactions via **14(i)** and **14(ii)**. Since these reactions are kinetically controlled, this ratio can be equated to the yield ratio, and hence the predicted enantiomeric excess can be obtained. **14(i)** leads to the anti[52] product, while **14(ii)** leads to the syn isomer. We thus calculate a diastereomeric excess of 73:27, favoring the anti isomer. For the addition of methylcopper to an *E*-γ-alkoxy α,β-unsaturated ester, the reported experimental ratio[17] (69:31) agrees well with this calculated value.

It is noteworthy that the "best" transition structure, **14(i)**, has the methyl group anti and the hydroxyl group inside. We have argued at length as to why the methyl group should prefer the anti position. As for the hydroxyl group, our previously discussed calculations suggest a slight but significant (0.63 kcal/mol) preference for the outside position over the inside position (see structure **8a** and **8b** in Figure 12); yet **14(i)** (with an *inside*

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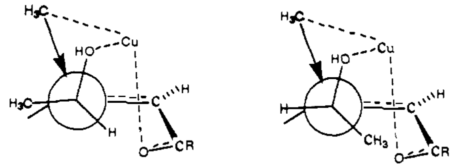
(51) Our assumption has been checked for all the conformational minima (for both *E* and *Z* isomers) estimated from this approximate procedure. The *relative* energies of the disubstituted local minima were calculated explicitly, and they were found to agree with the estimated values within 0.2 kcal/mol in all cases.

(52) Syn and anti are defined in the same way as in the published experimental studies.[14,17]



15(i)
major
$\phi = -65.4°$
$E_{rel} = 0.0$

15(ii)
minor
$\phi = -40.0°$
$E_{rel} = 4.07$ kcal/mol

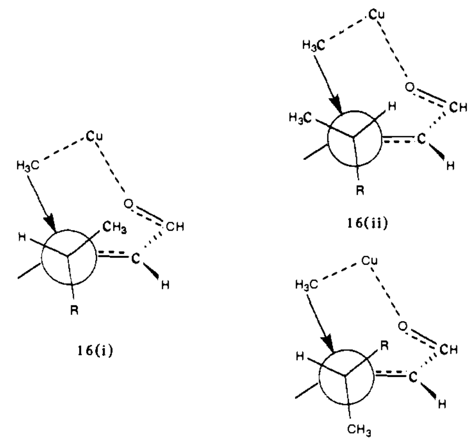
Figure 20. Transition structures **15(i)** and **15(ii)** leading to the major (syn) and minor (anti) diastereomer, respectively, in the addition of methylcopper to (*Z*)-4-hydroxy-α,β-unsaturated carbonyl compounds.

hydroxyl group) is preferred to **14(ii)** (*outside* hydroxyl group). The origin for this preference lies in the repulsion between the nucleophile and the *outside* hydroxyl group. This interaction can be relieved in **8a** since the OH group can swing away from the pathway of the incoming methyl group. In fact, **8a** corresponds to a fairly large (12.9°) value of ϕ. On the other hand, a similar motion of the *outside* OH group in **14(ii)** would lead to an inward rotation of the *anti* methyl group toward the hydrogen atom on C_α. The resulting destabilization roughly offsets the relief of the nucleophile-outside OH repulsion; the total energy of the system barely decreases for small values of ϕ ($\phi < 6.2°$) and rises considerably henceforth. On the contrary, rotation of the inside hydroxyl group away from the nucleophile in **14(ii)** is accompanied by rotation of the anti methyl group away from the formyl hydrogen. Both motions are favorable, and this leads to the preference for **14(ii)**.

Stereoselectivity of Addition to (*Z*)-γ-Alkoxy α,β-Unsaturated Carbonyl Compounds. We can use once again an additivity relationship analogous to that implied in Figure 18 for the *E* isomers so as to estimate the energies of various conformers as a function of ϕ. As we have shown in our earlier discussion, the hydroxyl group prefers the inside position over the outside, and the alkyl group prefers the anti position over the outside. There are thus three conceivable transition structure conformations to be considered. We might expect the most stable of these to have the alkyl group anti and the hydroxyl group inside. However, we have seen that the inside hydroxyl group has to swing by a considerable amount to coordinate with the metal center (ϕ in **11b′** is equal to −68.9°). This implies a motion of the anti substituent toward a very crowded region of the molecule—the formyl group. This factor may be expected to cause a destabilization of this kind of structure.

Indeed, the lowest energy conformer was found to be **15(i)** (Figure 20), in which the hydroxyl group is inside and the methyl group outside. The movement of the inside OH group toward the metal and that of the methyl group away from the nucleophile are both favorable, so that ϕ in **15(i)** is large (−65.4°). The lowest energy conformer that can lead to the other diastereomer is **15(ii)** ($\phi = -40.0°$), but this is higher in energy by 4.07 kcal/mol. This energy gap is so large that the experimental stereoselectivity of addition to (*Z*)-γ-alkoxy α,β-unsaturated carbonyl compounds should be complete, with only the syn[51] isomer being formed. In practice, the syn isomer is the major product, but the diastereomer ratio reported for the addition of methylcopper to an ester is only 78:22.[17] The numerical agreement between theory and experiment is poor. We believe that this may partly due to the difficulty in evaluating the O--Cu bond strength correctly in **11b** and **11b′**—and thus also in **15(i)** and **15(ii)**. However, we wish to point out that the stereoselectivity of addition to γ-alkoxy *di*esters occurs typically with the formation of a much larger diastereomer ratio (ca. 95:5).[17] Since a diester has one carbonyl group cis to the alkoxyalkyl group, one would expect the stereoselectivity to resemble that for the *Z* esters. While the origin of the difference in the experimental stereoselectivities is uncertain, the fact remains that very high diastereomeric excesses can indeed be observed in these reactions.

Stereoselectivity of Nucleophilic Addition to α,β-Unsaturated Carbonyl Compounds Having an Alkyl and an Aryl Substituent on the γ-Carbon. The source of chirality at the γ position can be the presence of two groups of different size. Several studies of addition reactions to simple carbonyl compounds have been performed, in which the source of chirality was the presence of an alkyl and an aryl group at the α-carbon atom. The Felkin–Anh model provides an adequate rationale for the experimental results. The stereoselectivity in the analogous conjugate addition reaction is also of considerable interest, and detailed experimental investigations have been recently carried out by Kingsbury[15] and Yamamoto.[14] Typically, the two non-hydrogen substituents at C_γ are methyl and phenyl (or another aryl group); unfortunately, it is clear that the approximate computational procedure described above is not readily applicable to this case, since computational limitations render this kind of analysis impossible for the case of a phenyl substituent.[53-55]



16(i)
major
$\phi = -15.0°$
$E_{rel} = 0.0$

16(ii)

16(iii)
minor
$\phi = +24.5°$
$E_{rel} = 1.49$ kcal/mol

Figure 21. Transition structures **16(i)**–**(iii)** (R = CH_3 or aryl, see text). The first leads to the major diastereomer (anti) formed during the addition of methylcopper to (*E*)-4-R α,β-unsaturated carbonyl compounds; the other two both lead to the minor (syn) diastereomer. The value of E_{rel} of 1.49 refers to **16(ii)**.

We thus decided to base our approach on the evaluation of the preferred conformation in a system having two *methyl* groups at C_γ. For the addition to an *E* isomer, we have shown that a methyl group at C_γ prefers the anti position markedly over both outside and inside positions. A β-isopropyl group can thus have either of two conformations in the transition state (see Figure 21). The relative energies of the two conformers were evaluated by the same procedure described above for γ-hydroxy α,β-unsaturated carbonyls. It was found that the best conformation of the isopropyl group has the two methyl groups anti and inside (**16(i)**, R = CH_3; $\phi = -15.0°$), with the minor conformation having the methyl groups anti and outside (**16(ii)**, R = CH_3; $\phi = 24.5°$). **16(i)** is 1.49 kcal/mol more stable than **16(ii)**. Once again (cf. **14(ii)**), the outside position is destabilized by the interaction with the nucleophilic methyl group, and this repulsion cannot be relieved if the anti position is also occupied.

If we assume that a large group, such as phenyl, favors the sterically least hindered anti position over the inside or outside positions, the best conformation is obtained by replacing the anti

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(53) Other, more economical alternatives would include the use of semiempirical techniques[54] or force-field calculations with the introduction of suitable parameters (derived from quantum chemical calculations) for the description of transition structures.[55] The latter approach has been used successfully,[55] but in our systems the number of force constans, dipoles, etc., that must be defined is large, so that a considerable computational expenditure is required to derive them. Such an effort is now under way in our laboratories.

(54) See, for example: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902, and references therein.

(55) A detailed description of this approach is given in: Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. See also ref 1 and 6.

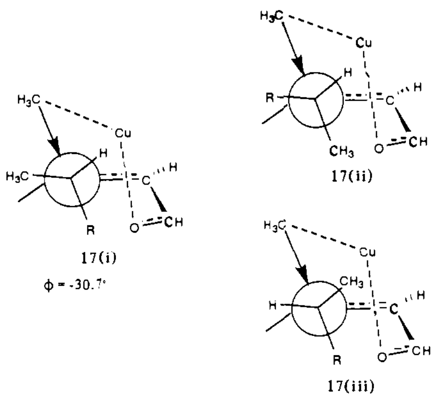

Figure 22. Transition structures **17**(i)–(iii) (R = CH_3 or aryl, see text) in the addition of methylcopper to (*Z*)-4-R-2-pentenal. **17**(i) leads to the syn stereoisomer, while **17**(ii) and **17**(iii) lead to the anti addition product.

methyl group of **16**(i) with a phenyl group. The minor product can arise either from replacement of the anti methyl group of **16(ii)** with phenyl or from replacement of the inside methyl group of **16**(i) with a phenyl group (see **16**(iii) (R = C_6H_5) in Figure 21). A rough estimate of the predicted stereoselectivity can be obtained if we assume that the energy difference between **16**(i) and **16**(ii) is the same (1.49 kcal/mol) regardless of whether the anti substituent R is methyl or phenyl. The corresponding diastereomer ratio is equal to 92:8 in favor of the anti isomer. The experimental[15] diastereomer ratio for the addition to (*E*)-γ-aryl α,β-unsaturated esters is equal to 88:12.

The quantitative agreement between theory and experiment is surprisingly good. In practice, owing to the drastic simplifications in the above argument, we think that our method cannot be used to predict the diastereomeric excess with quantitative accuracy. Nonetheless, it is important to point out that the most stable predicted transition-state conformation (**16**(i)) for conjugate addition to *E* isomers is the same as that calculated for the nucleophilic addition to the carbonyl group of ketones.[6] We feel we can confidently state that **16**(i) is the transition structure leading to the major product, as has been also postulated by Yamamoto.[14] As for the minor product, this could arise either from **16**(ii) or from **16**(iii), in which the phenyl and methyl group of **16**(i) trade places. Our present calculations do not allow us to distinguish between these two possibilities.

A similar approach was attempted to rationalize the observed stereoselectivity of addition to *Z* isomers. We have already seen how a methyl group cannot occupy the *inside* position in this case (see **10b**). Thus, an isopropyl group can *only* assume a conformation with the methyl groups anti and outside. The minimum-energy conformation was calculated to be **17**(i) (Figure 22, R = CH_3), where $\phi = -30.7°$. For this value of ϕ, the energy difference between anti and outside conformers of an ethyl group is equal to 0.93 kcal/mol in favor of the anti conformation. Therefore, when C_γ bears a phenyl group, the lowest energy transition structure should be **17**(i) (R = C_6H_5); this structure leads to the syn product. The transition structure obtained by replacement of the outside methyl group with phenyl (see **17**(ii), R = C_6H_5) should lead to the minor (anti) diastereomer.

On the contrary, anti addition was found[14] to be predominant in the addition of alkylcopper reagents to *Z* esters and diesters. The authors suggested[14b] that the major product should arise from a transition structure having the methyl group inside and the phenyl group anti (see **17**(iii) in Figure 22), which is analogous to the preferred conformation in the *E* isomers (**16**(i)). Our results, however, indicate that no alkyl group can occupy the inside position. The only hypothesis that can fulfill this requirement and account for the observed data is that **17**(ii) be more stable than **17**(i). This forced conclusion, however, seems not only counterintuitive, but it is also in contrast with our previous assumption of a preference for the anti position for the phenyl group in **16**(i).

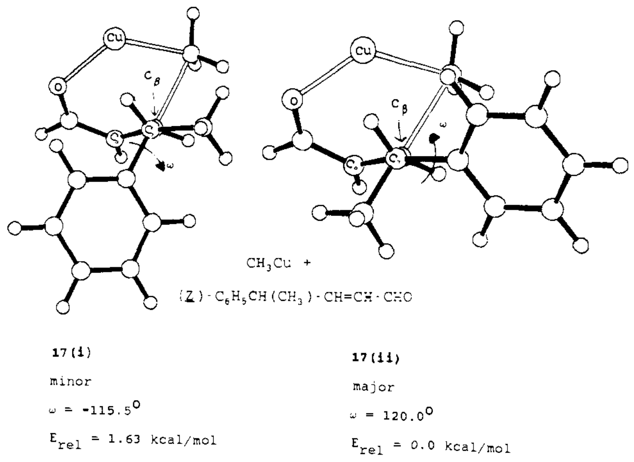

Figure 23. Calculated (see text) relative energies of structures **17**(i) and **17**(ii) and optimal ω values. ϕ was fixed to −30.7° (see text, Figure 22) in both cases.

These results prompted further analysis of the stereoselectivity in this system. We therefore performed calculations at the HF/3-21G level on the two conformers **17**(i) and **17**(ii) (in each case ϕ is equal to −30.7°). The large size of these systems forced us to perform single-point energy calculations at set values of the torsional angle about the C_γ–$C_{1(\text{phenyl})}$ bond, so that the orientation of the phenyl group was fixed in each case. The dihedral angle C_β–C_γ–$C_{1(\text{phenyl})}$–$C_{2(\text{phenyl})}$ (ω) was assigned a value that would minimize the repulsion between the phenyl group and the nearby atoms, namely, the two methyl groups and the carbonyl group. In both conformers this corresponds to having one C=C ring bond approximately eclipsed to the C_γ–H bond, with both C_γ–C bonds out of the plane of the phenyl ring;[56,57] however, there is still some arbitrariness involved in the choice of the precise value of ω. We therefore performed three energy calculations at different values of ω, and we obtained the value of the energy minimum from a parabolic fit for both conformers.

Our calculation confirmed our hypothesis that **17**(ii) is indeed the more stable of the two. The energy difference was found to be 1.63 kcal/mol, with ω being equal to −115.5° and 120.0° (Figure 23) in **17**(i) and **17**(ii), respectively. Before analyzing the origin of this difference, it is important to point out two experimental data that support our conclusion. The first is the finding that addition of methylcopper–boron trifluoride to di*cyano*olefins[14b] yields stereochemistry opposite to that observed for α,β-unsaturated di*esters*.[14] This can be rationalized in terms of a transition structure similar to **17**(i) being favored for the former—in which the *anti* substituent does not suffer from severe nonbonding repulsive interactions with the cyano group—and a structure analogous to **17**(ii) being favored for the latter. The second is the fact that bulky Grignard reagents[15] react with the diesters giving stereoselectivity opposite to that observed with methylcopper–boron trifluoride. Again, this is readily explained in terms of a transition state similar to **17**(ii) being favored for small nucleophiles (methyl or primary alkyl groups) and disfavored when the outside position is sterically encumbered by the presence of a bulky nucleophile. We wish to stress that neither finding can be rationalized by assuming a transition structure similar to **17(iii)** for the reaction with diesters or *Z* esters. Indeed, the interpretation offered by Yamamoto and co-workers[14b] was that electron transfer was involved. Evidence both in favor[18] and against[58] this interpretation of the mechanism of action of dialkylcuprates is plentiful

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(56) It is known from both theory[57a] and experiment[57b] that an alkyl group attached to a benzylic carbon prefers to be perpendicular to the plane of the ring. In ethylbenzene, the perpendicular conformation is favored over the planar one by 2.2 kcal/mol[57a] (1.3 kcal/mol[57b]).

(57) (a) Hehre, W. J.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1972,** *92*, 1496. (b) Bruckwedde, F. G.; Moskow, M.; Scott, R. B. *J. Chem. Phys.* **1945,** *13*, 547.

(58) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984,** *12*, 3063.

in the literature, but there are no unambiguous examples supporting the electron-transfer mechanism for the reaction of alkylcopper–Lewis acid systems.

Finally, a possible theoretical rationale for our findings is as follows. The phenyl group, although larger than the methyl group, is a weak –I group. It therefore has an electronic preference for the outside position over the anti position, which contributes to stabilize **17**(ii) over **17**(i). This somewhat compensates for the repulsion between the phenyl group and the nucleophile. The latter steric effect is presumably still dominant; however, the preference for the anti position is reduced by the destabilizing electronic effect. The methyl group prefers the anti position to the outside position for both steric and electronic reasons and thus occupies the anti position in preference to the phenyl group.

It is natural to ask whether a similar argument might then apply to the reaction of the *E* isomers discussed earlier. Specifically, it could be argued that structure **16**(i) (Figure 21, R = C_6H_5)) is less stable than structure **16**(iii) (R = C_6H_5), having the phenyl group inside and the methyl group anti. Indeed, the latter conformation is probably more favorable electronically. The steric preference for the anti position over the inside position, however, is very large, as can be seen in Table I. In **16**(i), the value of ϕ is equal to $-15°$ (see above, and Figure 21); for this value, the methyl group favors the anti position over the inside by about 3.9 kcal/mol. This preference for the less hindered position is most probably too large to be overcome by the electronic effect which should favor **16**(iii).

Summary and Conclusion

Ab initio calculations have been carried out to study the conjugate addition of alkylcopper reagents to chiral α,β-unsaturated carbonyl compounds. We have shown that there are certain similarities to the related nucleophilic additions to carbonyl groups, particularly with regard to the steric requirements of the addition to *E* isomers. On the other hand, the electronic characteristics are quite different; the substituent effects calculated in our study are more in line with the behavior expected for *electrophilic* reactions than with the findings of calculations on other nucleophilic additions.[6,37]

Significant differences have been found between the modes of addition to *E* and *Z* isomers. In particular, the latter do not usually exhibit staggering of the C_γ substituents with respect to the forming nucleophile–C_β bond, as the Felkin–Anh model would predict. This is a consequence of the steric encumbrance of the inside position as well as the possibility of coordination of the metal center by a suitable inside substituent.

Model transition states have been deduced from our calculations, and qualitative (and in some cases quantitative) agreement has been found between the calculated and observed stereoselectivity of the addition reactions to chiral 4-alkoxy and 4-phenyl α,β-unsaturated carbonyl compounds. The transition structures for addition to the *E* isomers prefer a conformation in which the two substituents prefer the anti and inside positions, respectively. In both cases, the hydrogen atom occupies the hindered outside position. When C_γ bears an alkyl and an alkoxy group, the former takes the anti position and the latter the inside. When an alkyl and an aryl group are present, the former occupies the inside position and the latter the anti. In (*Z*)-4-alkoxy, α,β-unsaturated carbonyl compounds, the favored conformation in the transition structure has the alkyl group *outside* and the alkoxy group *inside*, since this permits coordination of the oxygen to the copper center. Finally, in (*Z*)-4-aryl α,β-unsaturated carbonyl compounds, the preferred transition structure has the aryl group outside and the methyl group anti. We believe that these models provide a realistic description of the mode of addition of alkylcopper reagents as well as other alkylmetals (including Grignard reagents) that undergo nucleophilic additions to the C=C bond of conjugated systems.

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Chiral Discrimination and Phase Transitions in Langmuir Monolayers

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Abstract: Chiral discrimination is investigated theoretically for chiral molecules that form an insoluble Langmuir monolayer at the water/air interface. For particular tripodal shaped molecules, we calculate the chiral discrimination for various types of intermolecular interactions: van der Waals, dipoles, charges, etc. The calculation, based on Boltzmann-weighted averaging of molecular orientations, predicts a preferred heterochiral behavior for van der Waals interactions and homochiral behavior for electrostatic ones. Other interactions are also discussed. To understand monolayer phase diagrams, we draw the analogy with sublimation experiments in bulk systems and propose a three-component thermodynamic model. The variable area per molecule and also the chiral discrimination parameter enter as important parameters in the model. Phase diagrams for conglomerates and racemic compounds are calculated in qualitative agreement with experiments. Possible connections and interpretation of existing experimental data are discussed, and some new experiments for chiral monolayers are proposed.

I. Introduction

Molecules with one or more chiral centers have been studied since the nineteenth century because of their tremendous importance in many biological and organic chemical processes as well as their applications as optically active materials. Although a vast amount of knowledge has been accumulated about chiral interactions,[1] it is quite difficult to give an explanation to the origin of *chiral discrimination* and consequently predict whether a given chiral molecule interacts more favorably with its stereomeric twin

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(1) *Optical Activity and Chiral Discrimination*; Mason, S. F., Ed.; Reidel: Dordrecht, 1979.

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