Transition Structure for the [2,3]-Wittig Rearrangement and Analysis of Stereoselectivities

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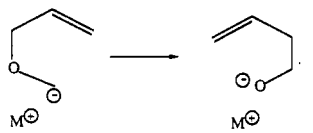
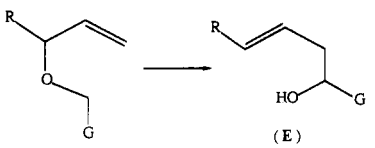
Summary: The transition structures for Wittig rearrangements of allyl lithiomethyl ether and substituted derivatives, located with ab initio molecular orbital calculations, provide a new hypothesis to account for the stereochemistries of these reactions.

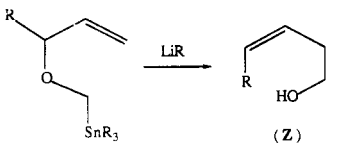
The [2,3]-Wittig rearrangement reaction (eq 1) has been widely used as a powerful strategy in organic synthesis.[1,2] There are two important types of stereoselectivities. First, (*E*)-homoallyl alcohols are usually the major products (eq 2). The *E* selectivity is very high when G



Eq. 1



Eq. 2

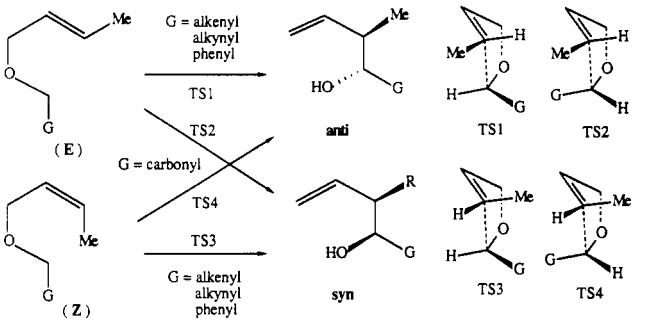


Eq. 3

is an alkenyl, alkynyl, or phenyl group.[3,4] An exception is that (*Z*)-homoallyl alcohols are the major products when G is a SnR_3 group (eq 3), but the tin group is lost in this process.[5] There is also diastereoselectivity with respect to the chiral centers formed at the termini of the new C–C bond. As shown in Scheme I, a *Z* substrate generally exhibits syn selection, while an *E* substrate leads to anti selectivity.[1,6] However, the opposite sense of selectivity is observed when G is a carbonyl group.[4,7]

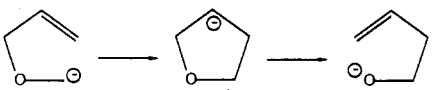
The reaction is considered to occur through a concerted five-membered transition state with an envelope conformation, and the stereoselectivity has been attributed to

Scheme I



steric interactions.[8,9] In this communication we report out initial study of the transition structure of the reaction and offer a new explanation for the stereoselectivities.

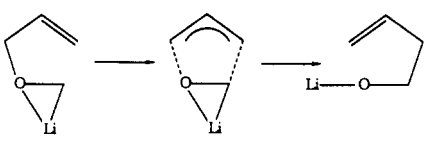
A concerted transition structure could not be located without inclusion of the lithium cation. As shown below, without a cation present, a five-membered intermediate forms, resulting from the addition of the carbanion to the double bond. As given in eq 4, the intermediate is con-



Eq. 4

3-21G	0.0	-27.5	-35.6
6-31+G/3-21G	0.0	-20.8	-49.0
MP2/6-31+G//3-21G	0.0	-26.3	-53.5

siderably more stable than the starting anion at all levels of calculations. Although the potential surface for the two steps was not explored, a concerted transition structure is unlikely to be located for the rearrangement. The transition structure for the reaction in eq 5, including the



Eq. 5

3-21G	0.0	41.8	-40.8
6-31+G	0.0	44.3	-48.7
MP2/6-31+G//6-31+G	0.0	16.2	-51.6

lithium cation, was located at both the 3-21G and 6-31+G basis set levels with Pople's GAUSSIAN 86 program.[10] A harmonic vibrational frequency calculation gives one imaginary frequency (726i cm^{-1}) for the 3-21G transition structure. The reaction is quite exothermic. At the best computational level employed, MP2/6-31+G, the product is more stable than the reactant by about 52 kcal/mol. The activation energy is high at the Hartree–Fock level, but drops to a more reasonable level with MP2 correlation energy corrections.

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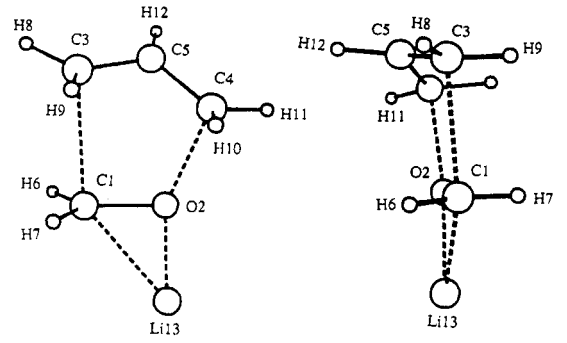

r(Å)	3-21G	6-31+G	< (°)	3-21G	6-31+G
1 - 2	1.436	1.374	1 - 2 - 4	115.3	114.8
1 - 3	2.198	2.393	2 - 1 - 3	91.9	92.5
2 - 4	1.615	1.884	1 - 3 - 5	93.9	89.3
3 - 5	1.368	1.374	2 - 4 - 5	104.0	98.5
4 - 5	1.438	1.400	3 - 5 - 4	111.5	117.4
1 - 13	2.195	2.215	1 - 2 - 13	89.0	90.9
2 - 13	1.686	1.716	2 - 1 - 13	50.2	50.8
6 - 8	2.690	2.782	3 - 1 - 2 - 4	2.9	1.5
6 - 5	2.986	2.989	3 - 5 - 4 - 12	144.1	155.1
6 - 12	3.225	3.235	2 - 1 - 3 - 5	24.0	25.0
7 - 8	3.104	3.144	1 - 2 - 4 - 5	28.8	27.8
7 - 9	2.384	2.378	E (a.u.)	-236.41114	-237.63420

Figure 1. Two views of the 6-31+G transition structure and selected geometrical parameters of the 3-21G and 6-31+G transition structures of [2,3]-Wittig rearrangement of allyl lithiomethyl ether.

Both the transition structures have the envelope conformation. The structure shown in Figure 1 is from the 6-31+G calculation. The partially formed C_1---C_3 and O_2---C_4 bonds are almost eclipsed with each other. This conformation has been most frequently assumed in analyzing the stereoselectivity and is somewhat different from the one proposed recently by Mikami and Nakai.[11] The envelope flap carbon (C_5) is considerably pyramidal and H_{12} is out of the C_6–C_5–C_4 plant by 25°. This geometry facilitates the overlap between the central p orbital and the partially formed bonds. The lithium cation coordinates nearly antiperiplanar to the C_1–C_3 and O_2–C_4 partial bonds. This is similar to the situation in the reactant, except that the lithium is shifted closer to the oxygen atom in the transition structure.

The transition structure is very unsymmetrical. The partially formed C_1–C_3 bond length is 2.38 Å, which is longer than the forming C–C bond lengths (~2.2 Å) found in other pericyclic transition structures.[12] The partially broken O_2–C_4 bond, however, is only 1.89 Å, which is longer than a normal C–O bond by about 0.45 Å. This "early" transition structure is partially the result of the large exothermicity of the reaction. The C_3–C_5–C_4 fragment is geometrically similar to the allyl anion, but the C_3–C_5–C_4 angle is only 117° while the allyl anion has an angle of about 130°.[13] This small angle is probably caused by the constraint of a five-membered ring transition structure and the partial negative charge.

Based on the calculated transition structure, it is clear why (*E*)-alkenes are the favored products. H_9 and H_{10} are at axial positions, and the H_9–H_{10} distance is only 2.53 Å. This distance is smaller than the 1,3-diaxial hydrogen distance in cyclohexane, which is ~2.6 Å. Replacement of H_{10} by an alkyl group is expected to introduce significant steric destabilization, while replacement of H_{11} by an alkyl group should not introduce steric hindrance.

The preference here is different from that of the free crotyl anion (where the methyl group favors the syn position).[14] The syn preference in the crotyl ion is believed to be the result of electrostatic interactions. Since the methyl group is an electron-donor, the methyl hydrogens are partially positive A syn methyl is stabilized by the negative charge on the allyl fragment. In the present case, the C_3–C_5–C_4 fragment is only partially negative, and the electrostatic effect is not important in determining the relative stability of syn and anti substitutions.

The general trend in diastereoselectivity at the forming bond indicates that the substituent, G, at C_1 generally perfers the exo position (H_7 in Figure 1). According to the calculated transition structure, this exo position is more sterically crowded compared to the endo position. H_7, the exo hydrogen, is 3.1 and 2.4 Å from H_8 and H_9, respectively. H_6, the endo hydrogen, is 2.8 and 3.0 Å away from H_8 and C_5, respectively. Thus, the H_7–H_9 interaction should be quite large. It was proposed previously that an endo G group has severe steric interactions with H_{12}.[1a] However, the H_6–H_{12} distance in the transition is 3.2 Å, and steric interactions involving groups at these positions seem not to be important.

In Diels–Alder reactions, substituents often prefer the endo position. Many explanations have been invoked, including that the endo position is favored by steric effects,[15,16] "secondary orbital interactions", or electrostatic interactions.[17] In the present case, a negative charge develops at C_3 in the transition structure, and the electrostatic effects should be much greater than in the neutral Diels–Alder reactions. An endo π-acceptor, or positively charged substituent, should stabilize the transition structure. On the other hand, an endo π-donor, or negative charged substituent, should destabilize the transition structure.

For qualitative evaluation of the orientational preferences of G, 3-21G single point calculations were carried out by replacing H_6 or H_7 with a standard substituent. The results are given in Table I. When G is CCH, little steric interaction is expected for either endo or exo positions. Nevertheless, the exo position is favored by about 0.9 kcal/mol. This can be attributed to the electron-rich character of the group. Cyano is a weak electron-deficient π-acceptor, but the calculations still gave a 0.5 kcal/mol preference for the exo position. This result could be somewhat problematical since previous calculations on the reactions of butadiene and cyclopentadiene with substituted ethylenes give a systematic incorrect exo preference for cyano group compared to experiments.[18] The formyl group, a good π-acceptor, was arranged in the syn conformation with respect to the C_1–O_2 bond. The calculations gave a 2.8 kcal/mol preference for the endo position. This is similar to the endo preference calculated for the Diels–Alder reaction of butadiene with acrolein, where the formyl group favors the endo position by 0.3–0.4 kcal/

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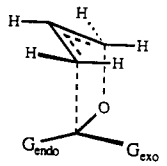
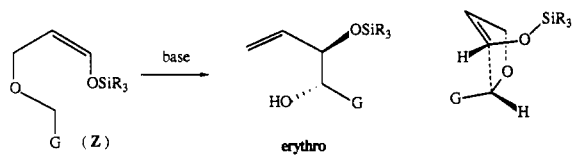
Table I. Relative Energies (kcal/mol) of Endo and Exo Substitutions Estimated by Single Point Calculations on the 3-21G Transition Structure with a Standard Substituent Replacing H_6 or H_7



G	E_{rel}(endo)	E_{rel}(exo)
C≡CH	0.9	0.0
C≡N	0.5	0.0
CHO	0.0	2.8
SiH_3	0.0	0.0
CH_3	1.5	0.0

Scheme II



mol.[19] The electronic interactions between the Li cation and the carbonyl oxygen of the formyl group could contribute somewhat to this endo preference, since the Li–O distance is 2.91 Å in the endo structure while it is 3.1 Å in the exo structure. However, the inherent endo preference of the group is clear.

When the substituents SiH_3 and CH_3 were calculated, they were arranged in the staggered conformation with respect to the C_1–C_3 bond. While SiH_3 gives no preference, CH_3 gives an exo preference of 1.5 kcal/mol. While there is no obvious steric reason for this, we can rationalize it by electrostatic arguments. Overall, methyl is negatively charged and SiH_3 is positively charged, according to Mulliken population analyses. Therefore, electronically SiH_3 should be favorable for the endo position.

Although optimizations and higher level basis sets are necessary to give a more accurate account of the steric and electronic effects, these initial simple calculations do suggest that while there is a general exo preference for G, good π-acceptors like the carbonyl group and electropositive groups like SiR_3 tend to favor the endo position. By applying these qualitative features, we can explain not only the general trends of the stereoselectivities but also the exception that carbonyl substituents lead to opposite sense of stereoselectivity. We also explain the exceptional anti selectivity for *Z*-siloxy allylic system observed by Nakai et al.[2f] (Scheme II) by the electrostatic argument. Namely, G tends to avoid a syn orientation to $OSiR_3$ because the lone pairs on O cause a significant destabilizing interaction with G.

Further studies on quantitative aspects of the steric and electronic effects of various substituents and molecular modeling of stereoselectivities have been undertaken[20] and will be reported in the near future.

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Methodology for the Enantioselective Synthesis of Aldols and Other 1,3-Dioxygenated Systems[1]

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Summary: The enantioselective synthesis of the spiroenones **3**, **4** from (*S*)-glycidol-*O*-benzyl ether and lithiated furan derivatives is described. After conjugate addition of lithium dimethyl cuprate or lithium divinyl cuprate and conversion of the resulting saturated ketones to their respective iodides **7** and **8**, fragmentation of these halides leads to the formation of acyclic aldol-containing carbon skeletons.

The plethora of natural products that arise from the polyacetate biosynthetic pathways has in recent years stimulated many elegant and efficient synthetic methods[2] for the construction of complex 1,3-dioxygenated carbon frameworks. While 1,3-diols can be used directly or after suitable blocking in further synthetic work, aldol systems are seldom used as intermediates in extended synthetic plans due to their susceptibility to dehydration and/or reverse reaction. In addition to the aldol unit's intrinsic value for the synthesis of molecules like erythromycin and FK-506, recent work[3] on directed reduction procedures that form 1,3-diols of predetermined stereochemistry make an aldol unit an attractive intermediate for the synthesis of complex polyoxygenated compounds. For this to be feasible it is necessary that the aldol unit be masked during the intermediate synthetic operations.

One such masked system is the Δ^2-isoxazoline grouping[4] which has been used in many successful syntheses[5] but in

(1) No reprints of this paper are available.

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