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Different Transition Structures for [2,3]-Wittig Rearrangements of Stabilized and Unstabilized Allyloxy Methyl Anions: Rationale for the Dichotomous Sense of Stereoselection

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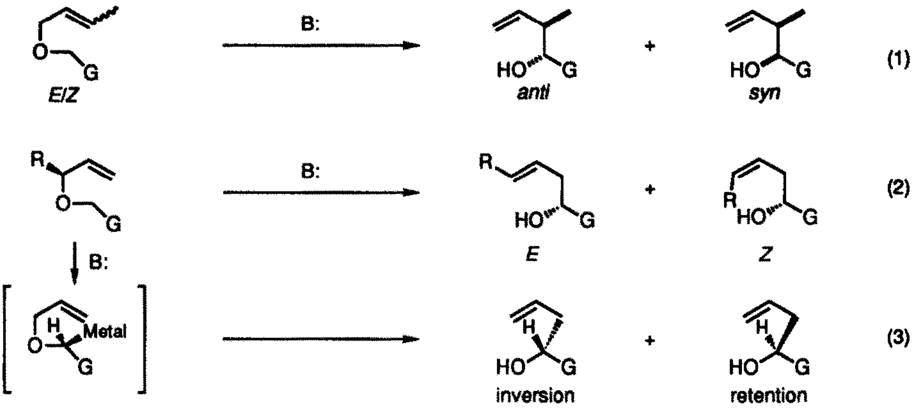
Abstract: *Transition structures of [2,3]-Wittig rearrangements of allyloxymethyl anion, allyloxypropargyl anion, allyloxyacetaldehyde anion, and their 1-methyl (crotyl) and 3-methyl analogs have been located. The transition structure of the rearrangement of allyloxymethyl anion is extremely early, with the C---C bond nearly unformed, and largely reflects inversion of the carbanion center and breaking of* C_3---O_4 *bond. The transition structure becomes much different when the anion is stabilized by an ethynyl substituent; now the C---C forming bond is 2.3 Å, and the C---O bond is only slightly broken. The ethynyl group is calculated to strongly prefer exo orientation. In agreement with experimental observations, formation of Z-alkene is calculated to be slightly favored for the rearrangment of 3-methyl-allyloxymethyl anion, while E-alkene is formed exclusively when the anion is stabilized by an ethynyl group. The ethynyl group also shows the exo preference in E- and Z-crotyl ether cases, while the formyl group prefers the endo position in the E-crotyl system. Thus, not only the general trend of E to anti and Z to syn diastereoselection but also the anomalous sense of E to syn selectivity for carbonyl substituents can be rationalized.*

Introduction

The [2,3]-Wittig sigmatropic rearrangement has emerged as a general, useful tool for organic synthesis, which involves at least three different types of stereochemistry (Scheme 1).[1] The first and most basic is the diastereoselection, namely internal 1,2-asymmetric induction with respect to the newly created vicinal chiral centers (eq. 1). *E*-substrates mainly exhibit *anti*-selectivity, while Z-substrates generally lead to *syn*-selection.[2] However, the opposite sense of *E* to *syn* selectivity is observed when G is a carbonyl derivative.[3] The second is the geometrical stereoselection over the newly created double bond (eq. 2). Usually, a high *E*-selectivity is observed.[1] A dichotomous sense of Z-selection is obtained in the Still rearrangement with the lithiomethyl ether terminus (G = SnR'_3 -> Li).[4] Still suggested a very early transition state in which steric repulsion disfavoring the Z-olefin formation was not advanced. Recently, Bruckner reported that the Z-preference is almost cation independent[5] in the rearrangement via reductive metalation of sulfide (G = SR').[6] The Z-preference has also been reported in the enolate [2,3]-Wittig rearrangements.[3a,b,f,g] The third is the stereoselection at the carbanion terminus, namely inversion or retention of the absolute oxycarbanion configuration (eq. 3).[7] In a combination of the three different types of stereochemistry, the high level of chirality transfer can be established from chiral allylic ethers to chiral homoallylic alcohols with control of absolute and relative stereochemistry.[3e,8]



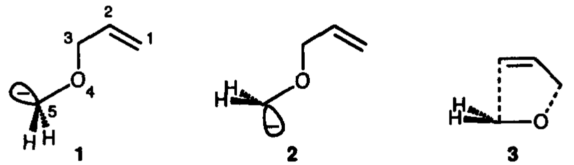
Scheme 1

The reaction is considered to proceed via a concerted five-membered transition state with an envelope conformation. Recently, Wu, Houk and Marshall reported ab initio calculations on the transition structure for the [2,3]-Wittig rearrangement of simplified allyl lithiomethyl ether and suggested the inversion process for the [2,3]-Wittig rearrangement.[9] Takahashi and Fukazawa also reported ab initio calculations,[10] however, for a different transition state conformation from that of Houk and Marshall and from the empirical model of Mikami and Nakai,[2b,11] and implied the retention process of the lithio carbanion involved. We report herein ab initio calculations for the [2,3]-Wittig inversion process to show that significantly different transition structures are located for the [2,3]-Wittig rearrangements of stabilized and unstabilized allyloxy methyl anions, which provide the theoretical rationale for the dichotomous sense of diastereoselection and olefinic stereoselection.

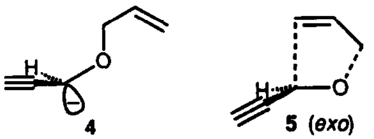
Results and Discussions

Calculations were performed with Gaussian 88 and 90,[12] and GAMESS[13] programs. Geometries were optimized with the STO-3G, 3-21G, MIDI4, 6-31G*, and 6-31+G basis sets. Energies were evaluated with the MP2 and MP3 correlation energy corrections and the 6-31+G* basis set.

The basic transition state conformation for the reaction of allyloxy methyl anion was first studied. Starting from conformation **1**, which has the anion lone pair *syn* to the C_3-O_4 bond, no Wittig rearrangement transition structure could be located. Upon attempted optimization, this species collapsed to the cyclic carbanion, due to addition of the carbanion to the double bond. However, a concerted transition structure for allyl lithiomethyl ether system **3** could be located starting from a less stable conformation with the anion lone-pair *anti* to the C_3-O_4 bond (**2**), with the 3-21G and 6-31+G basis sets. The transition structure at either level has a very long C_1-C_5 forming bond. Harmonic vibrational frequency calculations (3-21G: 711i cm^{-1}, 6-31+G: 713i cm^{-1}) indicated that the motion in the transition structure largely involves the *inversion* of carbanion, as exemplified in eq. 3, accompanied by breaking of the C3-O4 bond in **3**. The allyl group has anionic character: 0.26 unit of overall negative charge. The calculated activation energy is moderate at the Hartree-Fock levels.[14] When a metalated carbanion is formed as an intermediate, it is expected that the metal cation would be only loosely associated with the anion: a naked metal cation causes too much stabilization and results in a later transition state.[9] An alternative possibility would be a synchronous mechanism for the departure of the proton (or SnR_3 group) and the [2,3]migration, as addressed by Marshall.[15] Our calculations suggest that this is possible in the gas phase,[16] but the results are too marginal to call for the solution reactions. Although further studies are needed to distinguish the two mechanisms, an early transition structure like **3** is expected in both of the mechanisms.



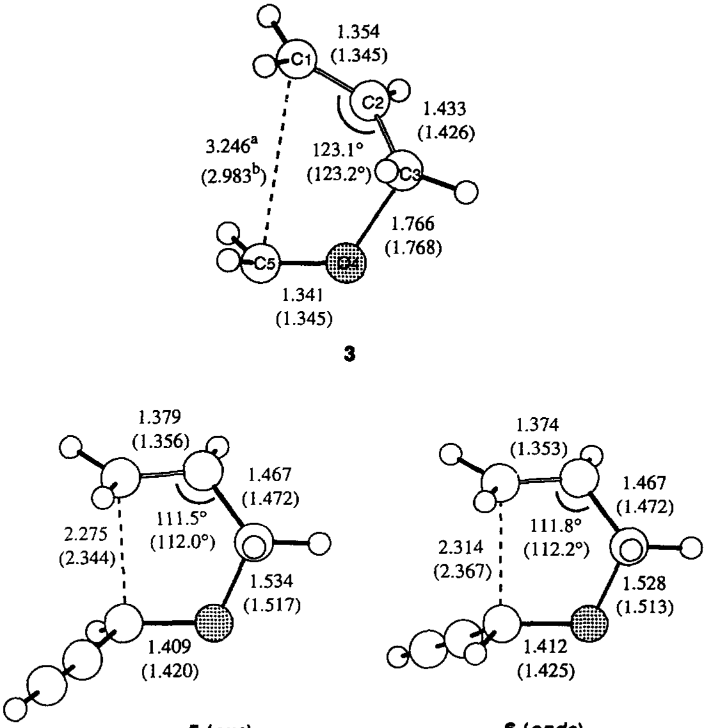
Basis set	1	2	3
3-21G//3-21G	-228.96243 (-1.2)^a	-228.96058 (0.0)	-228.92603 (21.7)
6-31+G//6-31+G	-230.18001 (-3.7)	-230.17410 (0.0)	-230.14647 (17.3)
6-31+G*//6-31+G	-230.26964 (-2.2)	-230.26607 (0.0)	-230.22701 (24.5)
MP2/6-31+G*//6-31+G	-230.98226 (-1.7)	-230.97956 (0.0)	-230.98561 (-3.8)
MP3/6-31+G*//6-31+G		-231.01057 (0.0)	-230.99978 (6.8)



	4	5 (*exo*)
STO-3G//STO-3G	-301.99533 (0.0)	-301.97439 (13.1)
6-31+G*//6-31+G	-305.98967 (0.0)	-305.94556 (27.7)
MP2/6-31+G*//6-31+G	-306.94587 (0.0)	-306.93626 (6.0)

Figure 1. Relative energies of allyloxy methyl anions and transition structures. ^{a}, relative energy in kcal/mol.

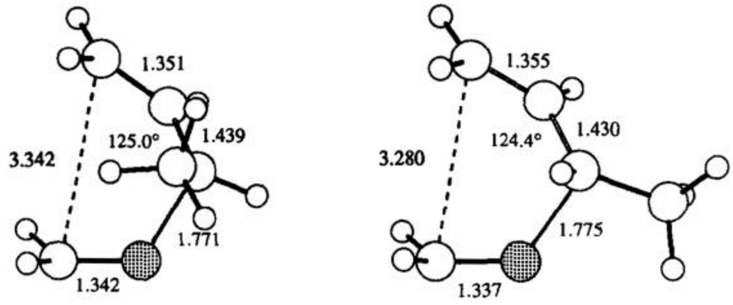
With an ethynyl group attached to the anionic center, two transition structures **5** and **6** were located. These structures are remarkably different from **3**, the C1-C5 bond is formed to a large extent and the C3-O4 bond is only slightly broken. This is quite different from the situation in the transition structures of [2,3]-sigmatropic rearrangements of sulfur ylides where an anion-stabilizing substituent (formyl group) has a much less significant effect on the transition structure.[17] The allyl moieties are only slightly negatively charged. The C1-C2-C3 angle is 112°, 11° smaller than that in **3**. The bond length of C≡C is in the range of 1.214~1.216 Å, indicating the propargyl anion character rather than the allenyl anion.



	5 (*exo*)		**6** (*endo*)	
3-21G//3-21G	-304.23028	(0.0)	-304.22724	(1.9)
6-31+G//6-31+G	-305.83228	(0.0)	-305.82994	(1.5)
6-31+G*//6-31+G	-305.94556	(0.0)	-306.94341	(1.3)
MP2/6-31+G*//6-31+G	-306.93626	(0.0)	-306.93286	(2.1)

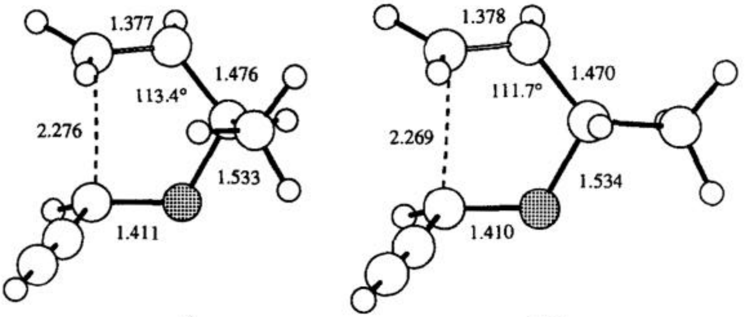
Fig. 2. Transition structures of [2,3]-Wittig rearrangements of allyloxy methyl anion (**3**) and allyloxy propargyl anion (**5** and **6**). [a], 6-31+G parameters; [b], 3-21G parameters.

In order to study the effect of transition structure on olefinic stereoselection, the [2,3]-Wittig rearrangement of 3-methyl substituted allyloxymethyl anion and allyloxypropargyl anion are examined as shown in Fig. 3. The methyl substituent has very little effect on the transition state geometry. Structure **7**, which has the methyl group pseudo-axial, is calculated to be slightly more stable than structure **8**. This is in agreement with experimentally observed *Z*-preference shown in eq. 2. This *Z*-preference is mainly caused by the anionic character of the allyl moiety, as pointed out by Hoffmann;[1f] the *syn* methyl group has an attractive electrostatic interaction with the anion.[18] A large C_1-C_2-C_3 angle also reduces steric interaction between the methyl and C_1 terminal. In sharp contrast, the propargyl structure **10** is considerably more stable than structure **9**, and leads to the formation of the *E*-alkene product. This is in agreement with the observed *E*-stereoselectivity of the normal [2,3]-Wittig rearrangement. This *E*-preference is primarily caused by the steric interaction in structure **9**, as indicated by short 1,3-diaxial (H, C) distance of 2.7 Å.



7 **8**

	7		8	
6-31+G	-269.17010	(0.0)	-269.16952	(0.3)
6-31+G*//6-31+G	-269.26557	(0.0)	-269.26528	(0.2)
MP2/6-31+G*//6-31+G	-270.16098	(0.0)	-270.16085	(0.1)

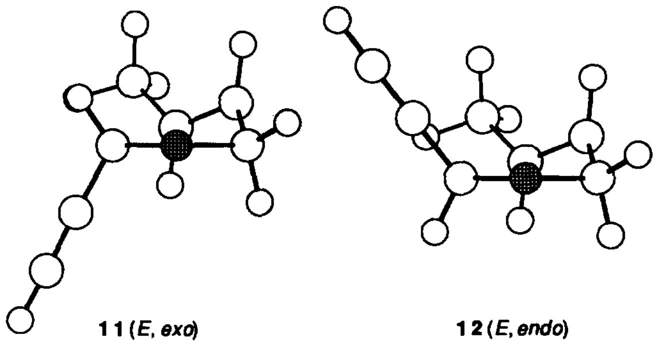


9 **10**

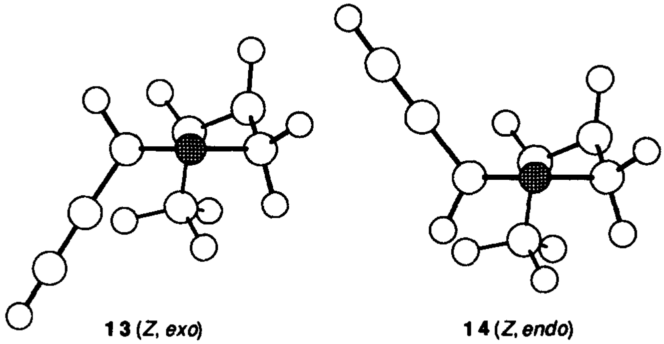
	9		10	
3-21G//3-21G	-343.05267	(1.9)	-343.05574	(0.0)
6-31+G//6-31+G	-344.85337	(2.4)	-344.85722	(0.0)
6-31+G*//6-31+G	-344.98204	(2.4)	-345.98592	(0.0)
MP2/6-31+G*//6-31+G	-346.10755	(2.3)	-346.11117	(0.0)

Fig. 3. The 6-31+G transition structures of [2,3]-Wittig rearrangements of 3-methylallyloxy methyl anion and 3-methylallyloxy propargyl anion.

Transition structures for the [2,3]-Wittig rearrangements of *E*- and *Z*-crotyl ether systems were then examined to study the substituent effect on the sense of diastereoselection. The results for propargyl ether systems are shown in Fig. 4. The *exo* structures **11** (*E*, *exo*) and **13** (*Z*, *exo*) are more stable than the corresponding *endo* structures **12** (*E*, *endo*) and **14** (*Z*, *endo*), respectively. Thus, the ethynyl group is calculated to prefer the *exo* position. These results are in agreement with experimentally observed *E* to *anti* and *Z* to *syn* preference.



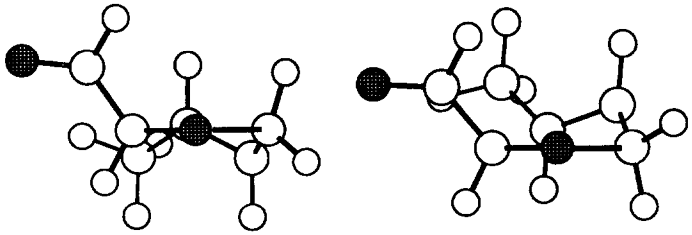
	1 1 (*E*, *exo*)	**1 2** (*E*, *endo*)
STO-3G//STO-3G	-340.56051 (0.00)	-340.56003 (0.30)
MIDI4//MIDI4	-344.43781 (0.00)	-344.43623 (0.99)
6-31G*//MIDI4	-344.95563 (0.00)	-344.95400 (1.02)
MP2/6-31G*//MIDI4	-346.05921 (0.00)	-346.05783 (0.87)



	1 3 (*Z*, *exo*)	**1 4** (*Z*, *endo*)
STO-3G//STO-3G	-340.55344 (0.00)	-340.55321 (0.14)
MIDI4//MIDI4	-344.43122 (0.00)	-344.43109 (0.08)
6-31G*//MIDI4	-344.94947 (0.00)	-344.94850 (0.61)
MP2/6-31G*//MIDI4	-346.05429 (0.00)	-346.05271 (0.99)

Fig. 4. Transition structures of [2,3]-Wittig rearrangemants of crotyloxy propargyl anion.

In sharp contrast, formyl group shows an anomalous *endo* preference with respect to the central carbon (C_2) of the *E*-crotyl moiety (Fig. 5). The *s-trans* formyl conformations (**15** and **16**) are located in the enolate [2,3]-Wittig rearrangement. Significantly, the *endo* conformation (**16**) is favored over the *exo* conformation (**15**) even in the non-lithiated transition structures. In Diels-Alder reactions, substituents often prefer the *endo* orientation, because of "secondary orbital interactions" or electrostatic interactions. In the [2,3]Wittig rearrangements, a negative charge develops at C_2 in the transition structure, and the electrostatic interactions would be greater than in the neutral Diels-Alder reactions. The *endo* preference is in good agreement with the anomalous sense of *E* to *syn* diastereoselection in the enolate [2,3]-Wittig rearrangement.[3,9]

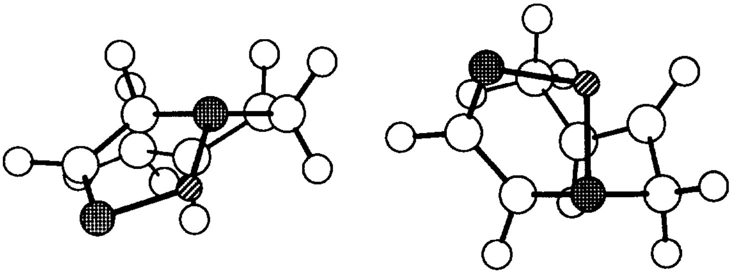


	15 (*s-trans-exo*)	**16** (*s-trans-endo*)
MP2/6-31G*//MIDI4	-344.02182 (0.93)	-344.02331 (0.00)

Fig. 5. Transition structures of [2,3]-Wittig rearrangements of enolate of crotyloxy acetaldehyde.

With Li cation (Fig. 6), the *s-cis* formyl conformation, namely chelation of the carbonyl oxygen to the Li cation is attributable to the *endo* preference as previously suggested,[3] because the Li-O distance was shorter (1.681 Å) in the *s-cis-endo* structure. Since the Li-C_2 distance (2.320 Å) in the *endo* structure was much shorter than that (3.853 Å) in the *exo* structure, an interaction of the anionic olefin moiety (C_2) to the Li cation, might additionally contribute to the *endo* preference.

By applying these features, we can rationalized not only the general trend of *E* to *anti* and *Z* to *syn* diastereoselectivities but also the anomalous sense of diastereoselection that carbonyl substituents lead to the opposite sense of *E* to *syn* stereoselectivity.



	17 (*s-cis-exo*)	**18** (*s-cis-endo*)
STO-3G//STO-3G	-384.63110 (12.84)	-384.65156 (0.00)
6-31G*//STO-3G	-389.53281 (6.10)	-389.54253 (0.00)
MP2/6-31G*//STO-3G	-390.70082 (6.22)	-390.71074 (0.00)

Fig. 6. Transition structures of [2,3]-Wittig rearrangements of lithium enolate of crotyloxy acetaldehyde.

In summary, we have disclosed that significantly different transition structures are located for the [2,3]-Wittig inversion processes of stabilized and unstabilized allyloxymethyl anions, and hence reasonably interpreted not only the general sense of olefinic and diastereoselectivities but also the anomalous sense of stereoselectivities.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research.

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