# Diastereofacial Selectivity in Intramolecular 1,4-Conjugate Additions: Conclusive Evidence for the Importance of Ground-State Conformations and the σ* Orbital Effect

Benjamin W. Gung* and Matthew B. Francis

*Department of Chemistry, Miami University, Oxford, Ohio 45056*

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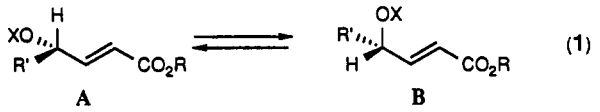
*Summary:* The effects of the ground-state conformations and σ* orbital energies are both important to the diastereofacial selectivity of intramolecular 1,4 conjugate additions.

Recently, we reported studies of the conformational preferences of C1-oxygenated chiral alkenes.[1] It was further established by the VT NMR method that the protective group (X) on the hydroxy function dictates the preference of the conformational equilibrium, eq 1.[2] The




(1)

CO eclipsed form (**B**) is favored by ~700 cal/mol when X is a TBDMS group, while the CH eclipsed form (**A**) becomes the preferred ground-state (GS) conformation by ~300 cal/mol when X = $CH_3$.[2]

Since control of π-facial selection is a topic of current interests,[3-7] we have chosen to study the intramolecular 1,4-conjugate addition reaction based on the above knowledge. The transition states of these intramolecular cyclizations resemble conformers **A** and **B** and also correspond to the Felkin–Anh[8,9] and the Cieplak[5] models, respectively, Scheme I. With regard to the difference between the two models, the Anh–Eisenstein[8] theory aligns the more electron-withdrawing ligand (in this case the C–O bond) with the $\pi_{C=C}$ orbital, while the Cieplak model assigns the electron-donor ligand (the C–H bond) anti to the attacking agent.[5] In the intramolecular 1,4-conjugate additions, one model is opposed by the other; i.e., either the nucleophile attack trajectory is anti to the acceptor bond (C–O) in **A** or anti to the donor bond (C–H) in **B**, Scheme I.[10,11] Therefore, there should be no ambiguity as to which effect is more important in nucleophilic additions.

The substrates **1a,b** were treated with various bases in THF, toluene, or DMSO, yielding a mixture of cis (**2a,b**) and trans (**3a,b**) disubstituted tetrahydropyrans (THP) in greater than 95% (GC) yield for all reactions listed in Table I.[12] These cyclizations were found to be kinetically controlled and irreversible.[13] By proper choice of the reaction conditions, the TBDMS-protected substrate **1a** and the methyl-protected ether **1b** have produced asymmetric inductions ranging from 7:1 to 1:20, respectively (entries 3 and 17, Table I).

In order to unambiguously determine the product stereochemistry, the TBDMS group on compounds **2a** and **3a** was removed via treatment with n-$Bu_4NF$. The cis product, **2a**, proceeded to cyclize in situ yielding the lactone **4**, which shows a small coupling constant ($^3J$ = 2.6 Hz) between H2 and H3. However, the trans product, **3a**, did not lactonize under various conditions. Instead, after deprotection **3a** was converted to the acetate, **5**, using acetyl chloride and $Et_3N$. The resulting $^1H$ NMR spectrum showed clearly separated signals for H3 and H2. The large coupling constant ($^3J$ = 10.6 Hz) indicated a trans relationship.

The ratio of **2**:**3** varies with a number of factors, including the protecting group, counter ion, solvent, and temperature, Table I. For compound **1a**, high cis selectivity (more of the Cieplak product) was obtained by using polar solvents (such as THF or DMSO), larger cations (such as $K^+$), and catalytic amounts of base (see entries 1–4). However, by using less polar solvents (toluene), smaller, more tightly coordinating cations ($Na^+$), or larger amounts of base this selectivity disappears (entries 5–8), or even reverses (entry 9). The results are consistent with the GS conformational preference of **1a**, at least in polar solvents with large cations. But why do nonpolar solvents and small cations reverse the π-facial selectivity?

With this question in mind we have studied the methyl protected substrate (**1b**) because it has an opposite GS

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(10) The silyl ether **1a** was prepared by (1) treatment of 5-(tetrahydropyranyloxy)pentanal with *p*-chlorosulfenyl methyl acetate,[11] (2) protection of the resulting secondary hydroxy group with a *tert*-butyldimethylsilyl (TBDMS) ether, and (3) hydrolysis of the tetrahydropyranyl ether. The γ-methoxy-α,β-unsaturated ester **1b** was obtained through the ozonolysis of 4-methoxy-7-(tetrahydropyranyloxy)-2-heptene followed by an in situ Wittig reaction of the resulting aldehyde with $Ph_3P{=}CHCO_2Et$.

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(12) A typical cyclization procedure: 1.5 mL of a 0.05 M solution of **1a** in distilled THF was cooled to −23 °C in a dry ice/$CCl_4$ bath. 0.5 mL of a 0.015 M NaHMDS solution in THF was added (0.1 equiv), and the solution was stirred at −23 °C for 30 min. The reaction product was diluted with ether and washed with 10% HCl, a saturated $NaHCO_3$ solution, and a saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The product ratios were determined by GC/MS without further purification.

(13) A sample of **2a**/**3a** (75.8%:24.2%) was dissolved in 2 mL of distilled toluene. 1.0 equiv of NaHMDS was added, and the solution was stirred for 15 h. The product ratio was then redetermined by GC/MS (**2a**, 75.6%, **3a**, 24.4%).

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**Scheme I**

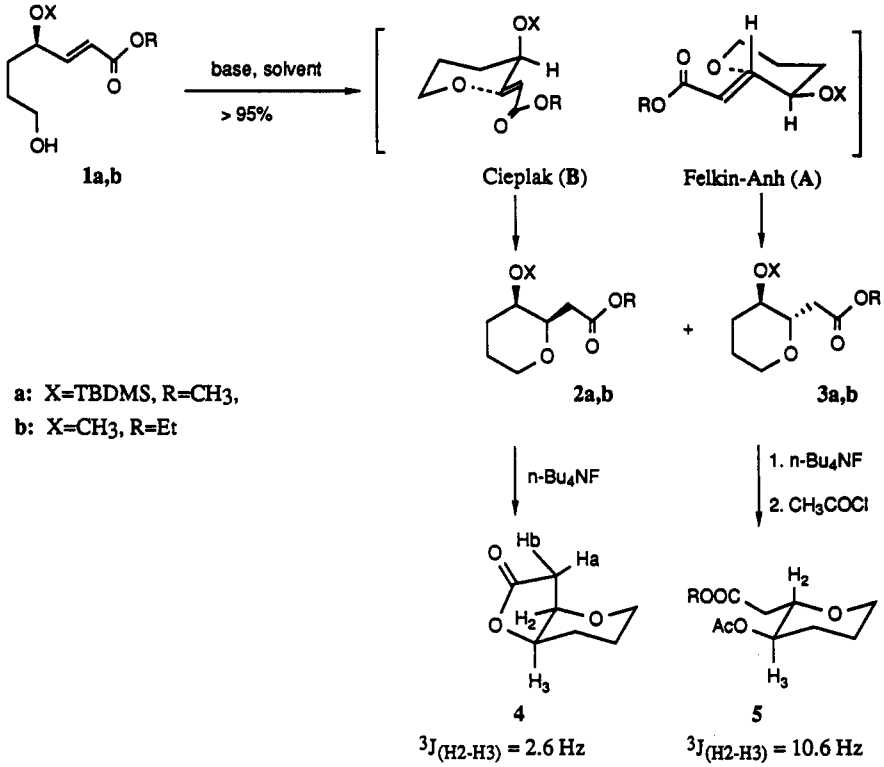


**Table I. Results from Intramolecular 1,4-Conjugate Additions of Compounds 1a,b (Ratios Are Determined by Capillary GC Equipped with a Mass Selective Detection System)**

| entry | subs | prot. group | solvent | temp (°C) | base[a] (equiv) | cis (2) | trans (3) |
|---|---|---|---|---|---|---|---|
| 1 | 1a | TBDMS | THF | 23 | KHMDS (0.1) | 75.8 | 24.2 |
| 2 | 1a | TBDMS | THF | 0 | KHMDS (0.1) | 83.6 | 16.4 |
| 3 | 1a | TBDMS | THF | -23 | KHMDS (0.1) | 87.5 | 12.5 |
| 4 | 1a | TBDMS | DMSO | 22 | KHMDS (0.1) | 80[b] | 20 |
| 5 | 1a | TBDMS | DMSO | 22 | KHMDS (5.0) | 58[b] | 42 |
| 6 | 1a | TBDMS | DMSO | 22 | NaHMDS (0.5) | 56.9 | 43.1 |
| 7 | 1a | TBDMS | Toluene | 22 | NaHMDS (1.0) | 42.5 | 57.5 |
| 8 | 1a | TBDMS | Toluene | -78 | NaHMDS (1.0) | 38.9 | 61.1 |
| 9 | 1a | TBDMS | THF | 22 | KHMDS (3.0) | 21[b] | 79 |
| 10 | 1b | $CH_3$ | THF | 22 | KHMDS (0.1) | 51.6 | 48.4 |
| 11 | 1b | $CH_3$ | THF | -23 | KHMDS (0.5) | 28[b] | 72 |
| 12 | 1b | $CH_3$ | THF | 0 | NaHMDS (0.5) | 12 | 88 |
| 13 | 1b | $CH_3$ | THF | 22 | LiHMDS (0.5) | 24[b] | 76 |
| 14 | 1b | $CH_3$ | Toluene | 22 | KHMDS (0.9) | 18[b] | 82 |
| 15 | 1b | $CH_3$ | Toluene | 22 | NaHMDS (1.0) | 12.0 | 88.0 |
| 16 | 1b | $CH_3$ | Toluene | 0 | NaHMDS (1.0) | 10.4 | 89.6 |
| 17 | 1b | $CH_3$ | Toluene | -78 | NaHMDS (1.0) | 4.6 | 95.4 |

[a] MHMDS = $MN(SiMe_3)_2$ (M = Li, Na, K). [b] Ratio was determined by integration of $^1H$ NMR spectrum.

conformational preference. This time, the trans isomer (the Anh product) is always predominant, even under the polar solvent/large cation conditions. When smaller cations and less polar solvents are used with this compound, extremely high trans selectivity can be obtained (entries 14–17). There is a clear trend for both compounds (**1a** and **1b**) to give more of the trans product under the conditions of nonpolar solvents and small cations.

Simple steric effects are not consistent with the observed differences. Although a TBDMS group is larger than a methyl group **1a** gives the cis product, opposite to what is expected from the consideration of steric interactions, Scheme I. Electrostatic (chelation) effects are also inconsistent with the observed selectivity. A higher concentration of cations gives more of the trans-isomer (compare entries 1 and 9, Table I), opposite to chelation considerations. On the other hand, under polar solvent/large cation conditions the product ratios consistently resemble the populations of the respective GS conformers (**A** and **B**).[2] This suggests that the GS conformational preferences are reflected in the transition state under these conditions.

Currently, we prefer the Anh–Eisenstein theory for the rationalization of the enhanced trans selectivity in the presence of small cations/nonpolar solvent.[8] The ligand with the lowest lying $\sigma^*$ orbital should be perpendicular to the double bond plane in the transition state (**A**, Scheme I). This arrangement permits the mixing of the $\sigma^*$ and the $\pi^*$ orbitals leading to a lower energy LUMO. Under conditions of nonpolar solvents/small cations, the oxygen anion is stabilized by cation coordination and the HOMO of the nucleophile is substantially lowered in energy, which leads to higher activation energy for the cyclization. This larger activation energy renders the GS conformational preferences insignificant. Therefore, the stereoelectronic (Anh–Eisenstein) effect influences the stereochemistry only when the activation energy is higher than the interconversion barrier between the rotamers. This $\sigma^*$

orbital effect was also previously found to be important by other investigators.[14]

In summary, the $\pi$-facial selectivity of 1,4-conjugate nucleophilic additions can be controlled by choice of the protective groups and the reaction conditions. Kinetic quenching can be obtained by employing polar solvents and large cations.[15] Under such conditions, the diastereomeric product ratio resembles the GS conformational distribution. Further experimental efforts in our laboratories are being directed toward quantitizing the reaction rates and activation energies and toward exploring the scope and limitations of using protective groups to direct $\pi$-facial selections.

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**Supplementary Material Available:** Physical data ($^1$H NMR, $^{13}$C NMR, IR, and HRMS) and NMR spectra for compounds 1–5 (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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