Tetrahedron Letters, Vol. 34, No. 32, pp. 5139-5142, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

# Significant Electrostatic Effects in π-Facial Stereoselection of Nucleophilic Addition Reactions to β,γ-Unsaturated Carbonyl Compounds

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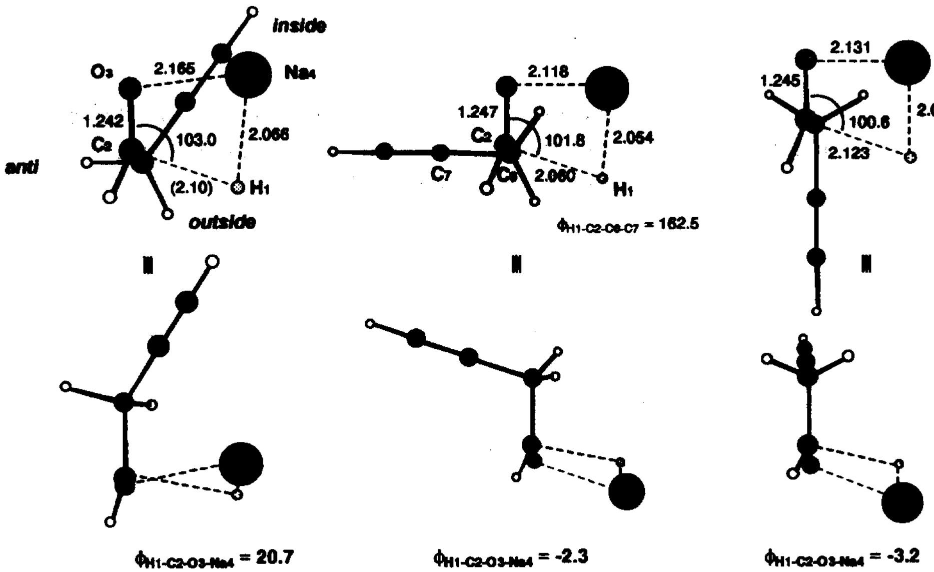
*Abstract:* The significance of electrostatic effects on the origin of π-facial stereoselectivity in nucleophilic additions to β,γ-unsaturated carbonyl systems was shown through theoretical studies (ab initio MO calculations of transition structures for NaH + $HCOCH_2C{\equiv}CH$) and experimental results ($M(BH_4)_n$ reduction of $PhCOCH(CH_3)R$ (M = Na, Zn, Cd; R = $C_2H_5$, $CH{=}CH_2$, $C{\equiv}CH$)).

The cause of π-facial stereoselectivity in nucleophilic additions to carbonyl compounds is still a matter of debate.[1] Recent ongoing discussion has emphasized the significance of electrostatic effects in nucleophilic additions to hetero-atom substituted ketones.[2] In this paper, electrostatic effects are demonstrated to be also dominant factors in nucleophilic additions to β,γ-unsaturated carbonyl systems where high stereoselectivities were previously reported.[3]

Transition structures for NaH addition to 3-butynal were computed (Figure 1).[4] The results include two significant findings. First, the most favored conformation **A** has an inside ethynyl group.[5] This structure is apparently stabilized by electrostatic attraction between $Na^+$ and the ethynyl group since the $Na^+$ is skewed towards the ethynyl group by 20.7° (the $Na^+\cdots C{\equiv}C$ distance: 2.9 Å). This accords with the Paddon-Row's results that deals with LiH additions to 2-fluoropropanal.[2a] Second, removal of $Na^+$ caused dramatic change in relative energy among the three conformations. Surprisingly, the conformation **A** is highest (HF/6-31G*) or second highest (MP2/6-31G*) in relative energy, and the most stable alternative is **B** having an anti ethynyl group. In the absence of $Na^+$, **A** is destabilized by electrostatic repulsion between π-electrons of the ethynyl group and the negative charge mainly lying on H1 and O3; the repulsion was most reduced in anti orientation of the ethynyl group (**B**).

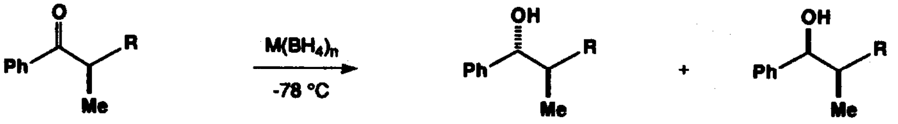


| | A | B | C |
|---|---|---|---|
| (a) | 0.00 | 3.24 | 4.01 |
| (b) | 0.00 | 2.11 | 2.96 |
| (c) | 0.00 | 4.00 | 5.57 |
| (d) | 3.72 | 0.00 | 3.54 |
| (e) | 3.24 | 0.00 | 4.26 |

**Figure 1.** HF/3-21G optimized transition structures for NaH attack on $HCOCH_2C{\equiv}CH$. Relative energy in kcal mol$^{-1}$: (a) 3-21G; (b) 6-31G*//3-21G; (c) MP2/6-31G*//3-21G; (d) 6-31G*//3-21G ($Na^+$ removed); (e) MP2/6-31G*//3-21G($Na^+$ removed). Bond lengths in Å and angles in degrees.

These computed results were consistent with the π-facial stereoselectivity in $NaBH_4$ reduction of ketones **1**. For **1a,b** (R = Et, $CH{=}CH_2$, respectively), predominant formation of R*,R* isomers (**2a,b**) is explained by the Felkin-Anh model[6] where the most bulky substituent (Et or vinyl) occupies the anti position. Interestingly, the ketone **1c** (R = $C{\equiv}CH$) gave R*,R* isomer **2c** with the highest diastereoselectivity (91 : 9).[7] This result means that the ethynyl group is oriented at the anti position in the Felkin-Anh transition state in spite of its little steric demand.[9] Thus, the observed diastereoselectivity is not ascribed to steric effects but most likely to electrostatic repulsion between the π-electrons and negative charge lying on the hydride and the carbonyl oxygen. This agrees with the selectivity order **1c** > **1b** since the π-electron density is **1c** > **1b**. Since the chelation control in $NaBH_4$ reduction in methanol is negligible,[10] the transition state is closely referred to the transition structure **B** that has the lowest relative energy in the absence of $Na^+$.

More significantly, the $Na^{+}\cdots C{=}C$ attraction in the conformation A suggests the possibility of chelation-controlled reduction of β,γ-unsaturated ketones. This was realized with softer counter ions ($Zn^{2+}$, $Cd^{2+}$) which have higher affinity with π-bases. Thus, the π-facial stereoselection in the reduction of **1b** was reversed when $Cd(BH_4)_2$[11] was employed; this unusual selectivity is attributable to the transition state in which $Cd^{2+}$ is chelated by both carbonyl oxygen and the π system.



1 2 (R*,R*) 3 (R*,S*)

| | | | | | |
|---|---|---|---|---|---|
| a: R = $CH_2CH_3$ | $NaBH_4$/MeOH | (76%) | 57 | : | 43 |
| b: R = $CH{=}CH_2$ | $NaBH_4$/MeOH | (71%) | 70 | : | 30 |
| | $Zn(BH_4)_2/Et_2O$ | (64%) | 53 | : | 47 |
| | $Cd(BH_4)_2/Et_2O$ | (46%) | 38 | : | 62 |
| c: R = $C{\equiv}CH$ | $NaBH_4$/MeOH | (81%) | 89 | : | 11 |

Previously, $(\sigma_{C\text{-}H})^{\ddagger}\text{-}\sigma_{C\text{-}C(anti)}{}^{*}$ interaction has been considered for the origin of high stereoselectivity in the nucleophilic additions to β,γ-unsaturated carbonyl compounds.[3c] However, this interaction does not seem significant since it must stabilize the anti conformers regardless of the presence of $Na^+$. In addition, the dihedral angle H1-C2-C6-C7 in conformation **B** is significantly deviated from 180°, most favored angle for the σ-σ* interaction, and is comparable to those observed for the NaH + $HCOCH_2CH_3$[13] where such interaction is not important.

An interpretation based on $\pi_{C=O}{}^{*}\text{-}\pi_{C=C}{}^{*}$ interactions has been also tentatively proposed.[3a,b] However, the transition structures for the reaction of NaH with 3-butenal showed that this interaction does not work effectively. Two conformers **D** and **E** were found for the transition structures with the anti ethenyl group (Figure 2). Although the $\pi_{C=O}{}^{*}$ orbital can effectively mix with the $\pi_{C=C}{}^{*}$ orbital in **D**, this conformation has higher energy than **E** in which the two π* orbitals hardly overlap each other.

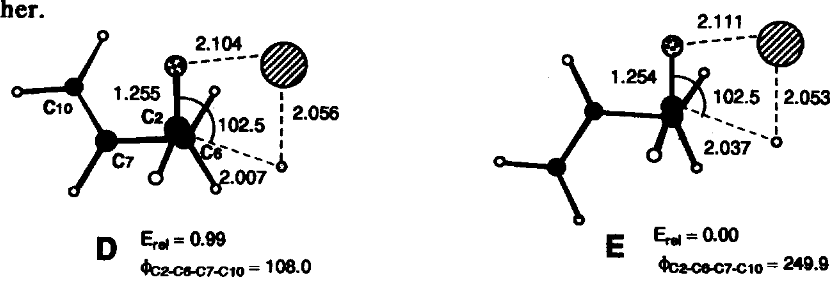


**Figure 2.** HF/3-21G optimized transition structures for NaH attack on $HCOCH_2CH{=}CH_2$. Bond lengths in Å, angles in degrees. HF/3-21G relative energies in kcal $mol^{-1}$.

The authors are grateful to Dr. Shoichi Saito of the University of Tokyo and Dr. Kota Sato of Chiba University for helpful discussions.

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(Received in Japan 6 May 1993; accepted 11 June 1993)