Some Observations on the Validity and Generality of the "Cieplak Stereoelectronic Effect"

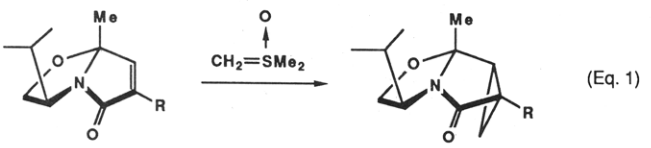
A. I. Meyers* and Richard H. Wallace

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received March 28, 1989

Summary: Diastereofacial addition to substrates capable of stabilizing developing antibonding orbitals in the transition state from a specific position do not follow the predicted stereochemical course.

Sir: In recent years, the interesting notion set forth by Cieplak[1] concerning stereochemical predictions in facial selectivity has been corroborated by several authors.[2–4] Generally, the "Cieplak Effect" may be described as the stabilization of transition states by hyperconjugative interaction of electron-rich bonds and adjacent antibonding orbitals. In other words, any stabilization afforded the developing antibonding ($\sigma^*_{\ddagger}$) orbital should enhance the formation of the bonding orbitals from the opposite side. In the stereochemical Cieplak model, convincingly demonstrated by le Noble,[2] the newly formed bond, either via nucleophilic or electrophilic attack, will be preferred on the face of a diastereotopic substrate when the most electron-rich bond is in the antiperiplanar position. In our own studies,[5] we recently applied the Cieplak rules in order to explain the stereochemical course of the reaction described in eq 1.



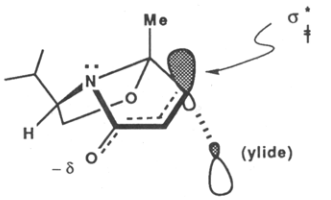
(Eq. 1)

1 (R = H, CO_2Me, Ph) **2** (*endo* 96-99%)

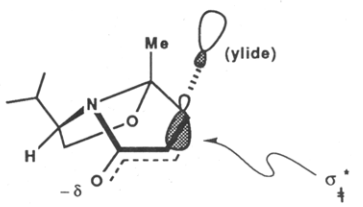
The cyclopropanation of the unsaturated lactams **1** proceeded with very high selectivity (96–99%) from the endo face, furnishing the adducts **2** in good yield. These results were explained by comparison of A and B, which clearly showed the essence of the Cieplak effect; namely, the stabilization of $\sigma^*_{\ddagger}$ by the adjacent electron-donating methyl (A) or the destabilization by the adjacent electronegative C–O bond (B). Thus, the preferred entry mode would be predicted to be A, which was, indeed, observed.[5] This potentially valuable and intriguing effect has since become a key component of our synthetic efforts, and we envision many interesting applications for future studies.

We subsequently felt it necessary to ask the question: Would the stereochemical outcome of the process in eq 1 change if the electronic nature of the group adjacent to the developing $\sigma^*_{\ddagger}$ was altered?

In this regard we prepared the strongly electronegative pentafluoroethyl derivatives **3** and **4** from procedures recently developed in our laboratory.[6] We hoped that the

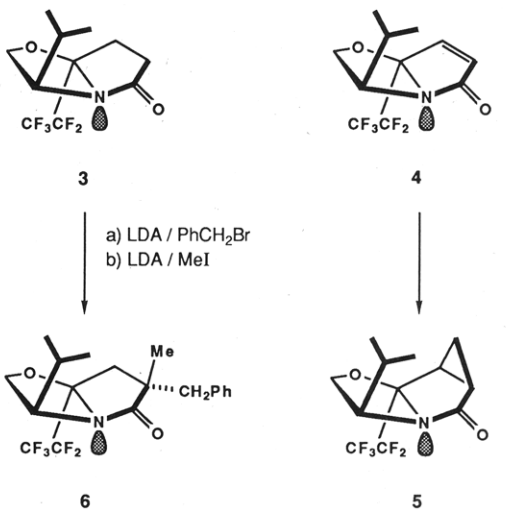


A (favored by Cieplak)



B (unfavored by Cieplak)

nucleophilic conjugate addition to **4**, to produce the cyclopropane **5**, in analogy to that shown in eq 1 above, would provide us with the answer to our question. Similarly, deprotonation of **3** with base, followed by alkylation, would also divulge any Cieplak-type stereoelectronic effect by furnishing alkylated material **6** whose endo–exo ratios would reflect the importance of stabilizing σ^* orbitals in the transition state. When addition of the dimethylsulfoxonium ylide to **4** was performed with trimethylsulfoxonium iodide (NaH, DMSO) at 25 °C there was obtained the cyclopropyl product **5** in 62% yield with the endo diastereomer predominating by almost 20:1. Confirmation of the stereochemistry was obtained from a single-crystal X-ray study of **5** (Figure 1). This was indeed surprising to us since it represented the "anti Cieplak" product; that is, the product derived from the crucial σ^* orbital forming on the same face as the strongly electron-withdrawing pentfluoroethyl group. This is counter to what would have been predicted from the earlier work by others on the directive effects of this theory.



(1) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(2) Cheung, C. K.; Tseng, L. T.; Lin, M. H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874. Lin, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 997.
(3) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875.
(4) Laube, T.; Stilz, H.-U. *J. Am. Chem. Soc.* **1987**, *109*, 5876.
(5) Meyers, A. I.; Romine, J. L.; Fleming, S. A. *J. Am. Chem. Soc.* **1988**, *110*, 7245.
(6) Meyers, A. I.; Sowin, T. A.; Lefker, B. A.; Westrum, L. *J. Org. Chem.*, submitted. These compounds were prepared by addition of CF_3CF_2Li (ref 7) to the *N*-valinol imide as described.
(7) Gassman, P.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481.

0022-3263/89/1954-2509$01.50/0

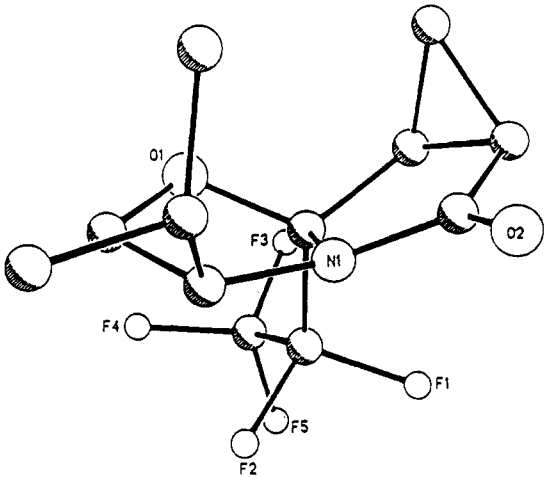


Figure 1. X-ray structure of **5**.

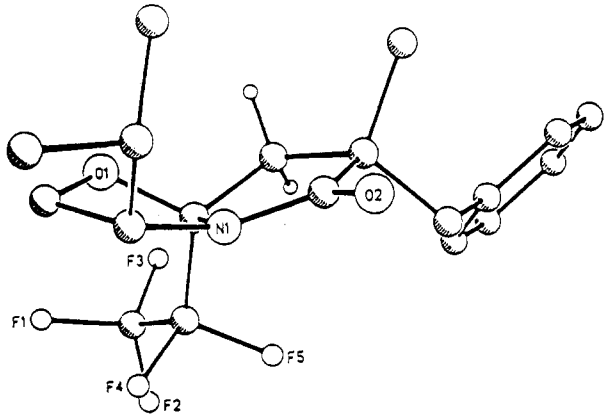


Figure 2. X-ray structure of **6**.

We then examined the electrophilic addition; namely, that which involved deprotonation–alkylation of **3** to determine if the pentafluoroethyl group would have any effect on the facial selectivity. Sequential metalation–alkylation with benzyl bromide and methyl iodide gave the quaternary bicyclic lactam **6** with a diastereoisomeric ratio of 10:1. The major isomer, determined by X-ray analysis (Figure 2), is that which allowed the methyl group to enter from the face of the ring system anti to the strongly electron-withdrawing pentafluoroethyl group. This is, once again, counter to what would have been predicted from the Cieplak model.

From these results, it may be stated at this time that the stabilization of the σ^* orbital in the transition state, in order to direct stereochemical events, is not a major player in the system discussed herein. Had the "Cieplak rule" held, as it did in earlier systems,[2-5] we would have seen opposite, or at least less selective, stereochemical behavior in the reactions for **3** and **4**.

If the σ^* stabilization is not a major factor, then what is responsible for the stereochemical results observed with these bicyclic lactams? The steric environment in these systems is such that the nucleophiles (sulfur ylides) or electrophiles (alkyl halides) approach from the most encumbered endo face, so this eliminates from consideration simple steric arguments. We feel that the reasons behind this endo entry lies not with Cieplak-type arguments (at least not completely as others have suggested), but with electronic perturbation of the π-system in the enolate of **3** or the C=C bond in **4** by the unshared lone pair on the lactam nitrogen.[8] Furthermore, the ring oxygen atom may also play a key role, as yet unknown, in this process. Additional experiments are in progress as well as computational studies in an effort to sort out this subtle effect on the stereochemistry, and as a result the major component in this riddle will hopefully be uncovered.

Acknowledgment. We are grateful to Bristol-Myers and the National Institutes of Health for financial support of this work.

(8) The electronic interaction of the N-lone pair with an adjacent π-bond has also been commented upon by a number of authors. See: Oppolzer, W.; Poli, G.; Starkemann, C.; Bernadinelli, G. *Tetrahedron Lett.* **1988**, *29*, 3529 and references cited therein for a list of others who have addressed this problem.