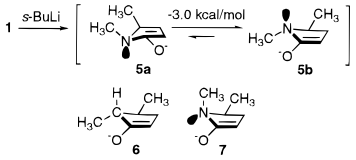
Torsional and Steric Effects Control the Stereoselectivities of Alkylations of Pyrrolidinone Enolates

Kaori Ando,[1a] Nora S. Green, Yi Li,[1b] and K. N. Houk*

Department of Chemistry and Biochemistry
University of California, Los Angeles, California 90095-1569

Received August 6, 1998
Revised Manuscript Received February 8, 1999

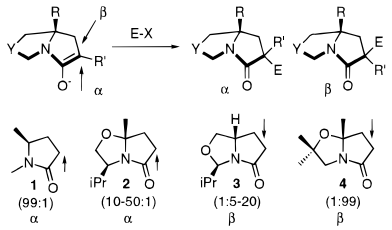
The origin of π-facial stereoselectivity remains a topic of intense scrutiny. An important, but perplexing, stereoselectivity has been observed by Meyers and others.[2−4] The enolates of bicyclic pyrrolidinones react with electrophiles to give products of α- or β-attack, depending on the nature of R and the second ring.[2,3] The source of this selectivity has remained an enigma. Recently, Meyers, Blake, and co-workers reported a computational prediction and experimental verification of α-stereoselectivity for the simple monocyclic pyrrolidinone **1**.[5] Ab initio calculations on transition states for reaction with methyl bromide showed that α-attack is favored by 1.0 kcal/mol over β-attack. Experimentally, the enolate derived from **1** gives 99% α-selectivity with benzyl bromide at −78 °C. The HOMO of the enolate **5b** from **1** is larger



on the α-face, which was attributed to the influence of the nitrogen lone pair. Since steric factors and chelation[6] are absent in the nearly planar enolate derived from **1**, Meyers et al. concluded that electrophiles attack anti to the nitrogen lone pair, because the amine lone-pair induces π-orbital distortion in enolates from **1**, **2**, and derivatives. In other cases, like **3** and **4**, steric factors can override this electronic preference.[5]

For other types of stereoselective reactions,[7−10] we have computational support for the Felkin model,[11] in which stereoselectivity is influenced by torsional strain and steric interactions. Experimental and crystallographic evidence for the importance of torsional effects in some electrophilic addition stereoselectivities has been provided by Seebach.[12] We also showed that the distortion of π-orbitals, noted by Fukui[13] and Anh,[14] also results from torsional effects.[9b] We report here how torsional, involving allylic CH bonds, and steric effects, but not orbital distortions, provide an explanation for the stereoselectivity of pyrrolidinone enolate alkylations. A prediction is made and verified experimentally.

We have computed the stereoselectivities of alkylations of the four enolates, **1**−**4**. Meyers et al. reported many similar calcula-



tions.[5b] The transition states for both α- and β-attack of methyl bromide on the enolate of **1** were located with RHF/6-31+G(d)[15] calculations; these compare well with Blake's calculations[5] (Figure 1). The α-attack was favored over β-attack by 1.7 kcal/mol (1.0 kcal/mol by MP3[5]) for **1**.

Newman projections (Figure 1 **A** and **B**) show that α-attack occurs with a staggered arrangement of all the vicinal bonds at the enolate carbon undergoing the hybridization change, while β-attack exhibits a nearly perfectly eclipsed arrangement. The 1−2 kcal/mol difference in energy can be compared to the 3 kcal/mol difference in energy between staggered and eclipsed ethane.[16]

If these torsional effects control the stereochemistry, then the amine lone pair should be an insignificant factor, except insofar as it influences the conformation of the enolate. Indeed, ab initio calculations for the reaction of methyl bromide with **6**, where the nitrogen of **5b** was replaced by CH, predict a similar endo preference. Both α- and β-attack transition structures are similar to those of **5b** (Figure 1). The α-attack is favored over β-attack by 1.0 kcal/mol, and this difference is in accord with torsional strain differences with allylic CH bonds (see **C** and **D**).

While *trans*-2,3-dimethylcyclopentanone proved to be difficult to handle because of the high volatility, the analogous *trans*-3-butyl-2-methylcyclopentanone, **11**, was synthesized using an analogous procedure.[17] Generation of the kinetic enolate with potassium hexamethyldisilazide in THF at −78°, followed by alkylation with benzyl iodide yielded the alkylated products, **12** and **13**.

The strong base, low temperature, and reactive electrophile were necessary in order to obtain the kinetic product mixture from the reaction. NOESY NMR was used to determine the relative

(1) (a) Permanent address: College of Education, University of the Ryukyus, Nishihara-cho, Okinawa 903-01, Japan. (b) Permanent address: Bristol-Myers Squibb, Wallingford, Connecticut.

(2) For reviews, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1−8.

(3) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A. *J. Org. Chem.* **1996**, *61*, 5712−5713. See also: Roth, G. P.; Leonard, S. F.; Tony, L. *J. Org. Chem.* **1996**, *61*, 5710−5711; Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140−3143.

(4) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748; Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094−4098; Hon, Y.-S.; Chang, Y.-C.; Gong M.-L. *Heterocycles* **1990**, *31*, 191−195.

(5) (a) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565−4566. (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7429−7438.

(6) On the basis of MNDO calculations, Durkin and Liotta proposed that the Li counterion and solvation were responsible for stereoselectivity: Durkin, K. A.; Liotta, D. *J. Am. Chem. Soc.* **1990**, *112*, 8182−8183. However, there is no experimental evidence for such effects.

(7) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908−910.

(8) Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656−3664; Ando, K.; Houk, K. N.; Busch, J.; Menassé, A.; Séquin, U. *J. Org. Chem.* **1998**, *63*, 1761−1766; Ando, K.; Condroski, K. R.; Houk, K. N.; Wu, Y.-D.; Ly, S. K.; Overman, L. E. *J. Org. Chem.* **1998**, *63*, 3196−3203; For a general review of this approach, see: Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439−2461.

(9) (a) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018−5027; Wu. Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 10992-10993. (b) Wu, Y.-D.; Houk, K. N.; Paddon-Row: M. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1019−1021.

(10) Lucero, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 826−827; Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchison, D. R.; Leanna, M. R.; Audia, J. E.; Droste, J. J.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 2204−2210.

(11) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204; Cherest, M.; Felkin, H. *Ibid.* **1968**, 2205−2208.

(12) Seebach, D.; Maetzke, T.; Petter, W.; Klötzer, B.; Plattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781−1786.

(13) Inagaki, S.; Fukui, K. *Chem. Lett.* **1974**, 509−514; Fujimoto, H.; Fukui, K. *Tetrahedron Lett.* **1966**, 5551−5554.

(14) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Dau, M.-E. T. H. *J. Am. Chem. Soc.* **1973**, *95*, 6146−6147.

(15) Ab initio calculations were performed with Gaussian 94 Revision D.3, Gaussian, Inc.; Pittsburgh, PA, 1995. HOMO plots were drawn with *SPARTAN* V.4.1.2.

(16) Torsional strain is different from the steric repulsion. Although the methyl group is considerably larger than hydrogen, the torsional energy (the rotation barrier) in propane is only a little higher than for ethane (3.3 kcal/mol vs 3.0 kcal/mol).

(17) Schow, S. R.; Bloom, J. D.: Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2662.

10.1021/ja982791z CCC: $18.00
Published on Web 05/20/1999

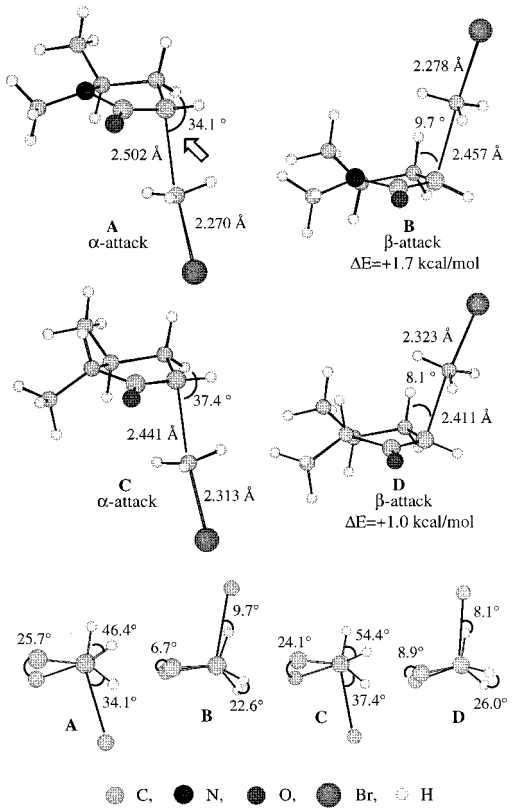
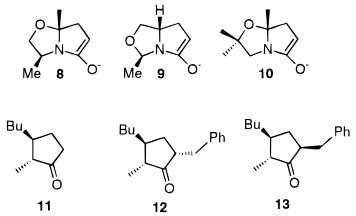


Figure 1. Transition structures for the α- and *β*-attack of methyl bromide on **5b** (**A** and **B**) and **6** (**C** and **D**) (RHF/6-31+G(d)). Newman projections are views from the direction indicated by the arrow in **A**.

stereochemistry of the major product **12**. A small NOESY cross-peak between the two α protons indicated that the methyl and benzyl substituents were on the same side of the ring. In addition, there were also characteristic cross-peaks between the proton at C-2 and the benzylic protons, as well as with the protons of the methyl substituent; this indicated that substituents at the 3 and 5 positions were in an anti orientation in the major product. From analysis of the ^{1}H NMR integration, the ratio of α attack to *β* attack (**12**:**13**) was about 85:15, in excellent agreement with the computational prediction. The product mixture of the alkylation reaction was then subjected to equilibrating conditions with sodium methoxide in methanol at room temperature. Equilibration resulted in a 1:2 ratio of **12** and **13**.



HOMOs of **5b** and **6** were calculated. Although the extent of HOMO distortion is small, the larger coefficients were found on the α-side of the enolates in both cases. We also computed the HOMO of **7**, in which the direction of the nitrogen lone pair of **5b** is inverted. The shape of the HOMO in **7** is almost same as in **5b**, except in the region of the nitrogen. At the *β*-side, the alkene HOMO overlaps the most eclipsed allylic CH bonding orbital in an antibonding fashion. This leads to an extension of the HOMO in the direction anti to the overlapping allylic CH bond.[9] In **5b** and **6**, the *β*-C−H is pseudoaxial and contributes more to the HOMO than the α-side C−H. This *β*-C−H *σ* orbital mixes in an antibonding way with the *π* orbital, causing the *π* orbital to have a larger extension on the α-face than the *β*-face.

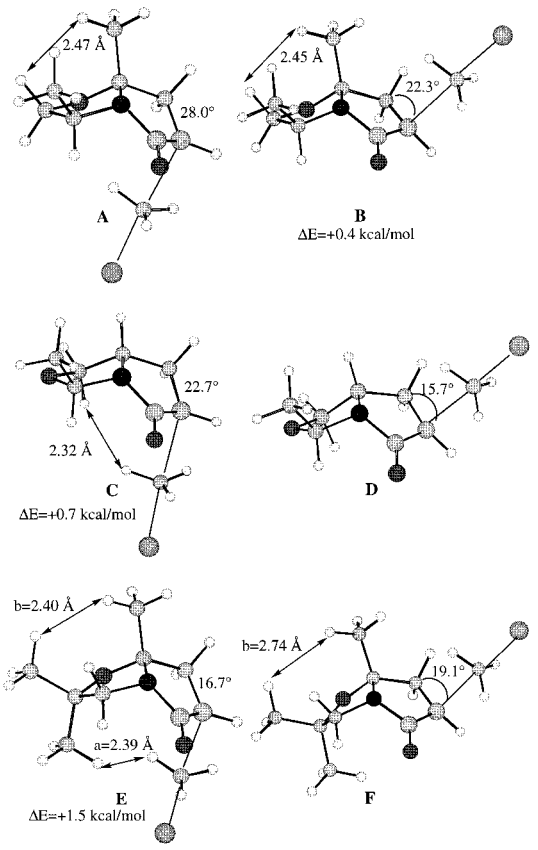


Figure 2. Transition structures for the α- and *β*-attack of methyl chloride on **8** (**A** and **B**), **9** (**C** and **D**), and **10** (**E** and **F**) (RHF/6-31+G(d)).

It is not this orbital extension per se, but the eclipsing with this bond which controls stereoselective attack on the opposite face of the alkene.

Torsional effects can be overcome by steric effects in crowded cases, as noted by Meyers et al.[5b] We computationally explored the analogues of **2** and **3**, in which the *i*-Pr group was replaced by a Me group (**8** and **9**), and MeCl was the attacking electrophile.

Transition states for the reactions of **8**−**10** with methyl chloride were located (Figure 2). For the reaction of **8**, *β*-attack (**B**) occurs with an eclipsed arrangement. Since there is no steric interaction in either transition state, α-attack (**A**) is favored over *β*-attack by 0.4 kcal/mol. For the α-transition state of **9** (**C**), there is a repulsive interaction between the hydrogens which are separated by only 2.32 Å, which is less than the sum of their van der Waals radii (2.4 Å). The *β*-attack **D** has slightly larger torsional strain, and the total energy difference is 0.7 kcal/mol, favoring *β*-attack. The α-transition state for **10** (**E**) also suffers from a significant steric repulsion (a = 2.39 Å) which causes some conformational distortion in the vicinity of the dimethyl part of the molecule as can be seen by the lengths *b* in structures **E** and **F**. *β*-attack (**F**) is now favored over α-attack (**E**) by 1.5 kcal/mol.

The calculated activation energy differences described here correspond to product ratios of 75:25 for **8**, 15:85 for **9**, and 2:98 for **10** at −78 °C (calculated by $k_1/k_2 = e^{-\Delta E/RT}$), and are in good agreement with experimental results.[5]

The stereochemistry of pyrrolidinone enolate alkylation can be explained by a combination of torsional and steric effects in the transition states.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health, and the NCSA for financial support. K. A. is grateful for the 1995 Toray Award in Synthetic Organic Chemistry. We thank A. I. Meyers and James F. Blake for helpful discussions. This paper is dedicated to the memory of Kenichi Fukui.

JA982791Z