Origin of Stereochemistry in Simple Pyrrolidinone Enolate Alkylations

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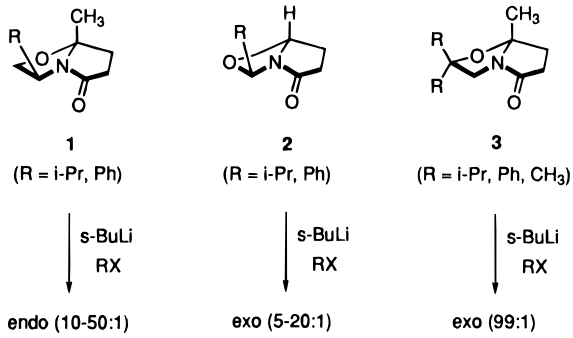
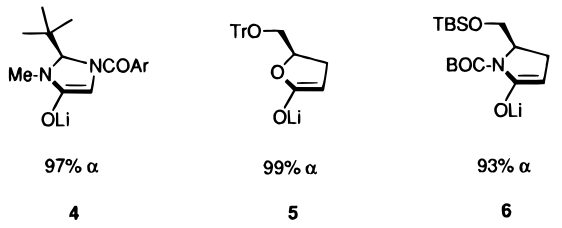
Over the past 10−15 years much effort has been expended in attempting to rationalize stereochemical results in enolate alkylations, particularly in lactones and lactams.[1] We recently described diastereofacial selective alkylations in bicyclic lactams **1**−**3** which led to either *endo* or *exo* products depending upon



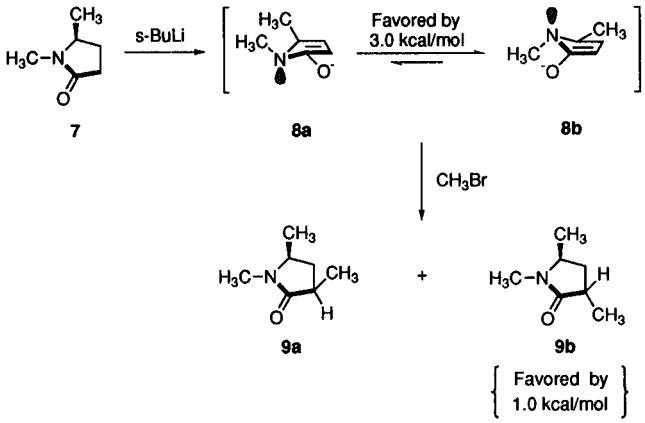
remote variations in substitution.[2] Although steric considerations could be invoked as the cause of these facial selectivities, it seemed that other factors were also playing a role. For example, the monocyclic enolates derived from imidazolidinones **4**,[3] butyrolactones **5**,[4] and 2-pyrrolidinones **6**[5] are devoid of any



polycyclic concave−convex faces, yet they still alkylate with very high degrees (>95%) of facial selectivity. In all these instances, alkylation takes place *anti* to a relatively large ring substituent, and even though they exhibit 1,3-relationships, the results could be based on steric factors. For the enolate **4**, Seebach[3] has suggested a stereoelectronic effect based on a slight pyramidalization of the enolate β-carbon. Recently, a study[6] was reported on lactam alkylations where the stereochemistry was said to be due to bulk created by chelation of the metal ion of the enolate to the ligands present in the lactam. Furthermore, the notion that the lone pair on nitrogen had some electronic effect on the facial alkylation of the π-C−C bond was advanced by several authors[3,6,7] but with no hard evidence to support this claim.

Due to our current interest in the *exo*−*endo* alkylation of bicyclic lactams **1**−**3**, we sought a simpler system which could provide some more direct insight into the factors governing selective facial alkylation. We, therefore, chose the pyrrolidinone **7** which appears to be devoid of rigid geometry (e.g., **1**−**3**), large steric groups (e.g., **4**−**6**), and chelating ligands. We also chose **7** since its enolate could be generated as a "pseudo-planar" five-membered ring. If we could alkylate **7** with high facial selectivity, then we would have isolated a fundamental electronic effect.

Initially, *ab initio* calculations were performed[8] on the enolate of **7** to establish its global minimum. Energies were computed with third-order Møller−Plesset theory[9] on the 6-31+G(d)[10] optimized structures MP3/6-31+G(d)//6-31+G(d). Calculation of the vibrational frequencies verified all structures as either minima or transition states and enabled computation of enthalpies at 298 K. It was determined that, of the two lowest energies of the enolates **8a**/**8b**, **8b** was favored by 2.95 kcal/mol.[11] This



is expected in view of the two methyls in **8a** exhibiting strong 1,2-interaction. Determination of the S_N2 transition states for alkylation of **8b** with methyl bromide (Figure 1a) revealed that α-entry to **8b** was favored over β-entry by 0.99 kcal/mol. Thus, **9b** was predicted to be the preferred product of alkylation over **9a** by a ratio of 5.3:1 (25 °C).[12] Furthermore, it is evident by inspection of the HOMO (Figure 1b) that the larger coefficient found in the π-face was *anti* to the nitrogen lone pair. This difference is more clearly seen by mapping the value of the HOMO onto the electron density isosurface (Figure 1b).

With the foregoing data predicting that there should be considerable bias toward electrophilic entry *anti* to the N-lone

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(1) For a recent, detailed summary of the alkylation of lactone and lactam enolates and their facial stereochemical outcome, see: (a) Stereoselective Synthesis. In *Houben-Weyl-Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, Germany, 1995; Vol. E21a, pp 762−881. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem.* **1996**, *35*, 2708.

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(4) Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094.

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(6) Micouin, L.; Jullian, V.; Quirion, J. C.; Husson, H. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2839.

(7) (a) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936. (b) Seebach, D.; Juaristi, E.; Miller, D. D.; Schikli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (c) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108. See also: *Isr. J. Chem.* **1989**, *29*, 321.

(8) All *ab initio* calculations were performed with Gaussian 94 Revision B.3, Gaussian, Inc., Pittsburgh, PA, 1995.

(9) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

(10) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294.

(11) All energetic values reported herein are given as enthalpies at 298 K computed from the MP3/6-31+G(d)//6-31+G(d) energies and 6-31+G(d) scaled (0.91) vibrational frequencies. The change in enthalpy relative to reactants was computed from $\Delta H_{298} = \Delta E^{elec}_0 + \Delta E^{vib}_0 + \Delta\Delta E^{vib}_{298} + \Delta E^{vib}_{298} + \Delta E^{rot}_{298} + \Delta E^{trans}_{298} + \Delta(PV)$. For a detailed discussion of this procedure, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(12) The issue of product control was considered in determining the selectivities. The ground state energies of **9a**,**b** were calculated and actually showed a slight preference for the *syn*-alkylated product (**9a**). On the other hand, the analogous system, **10a**, was allowed to equilibrate (*t*-BuONa, THF-*t*-BuOH, 25 °C, 72 h) and produced a 1:1 mixture of **10a**,**b**. See Supporting Information for NMR data. This reinforces the notion that transition states more accurately describe the facial selectivity than ground states.

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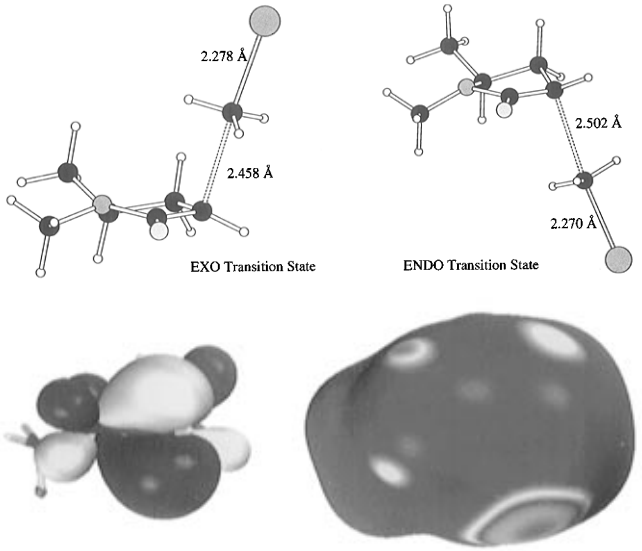
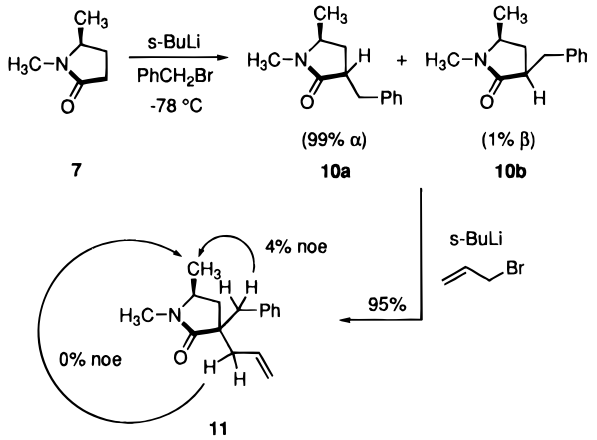


Figure 1. (top, a) 6-31+G(d) transition states for the β- and α-entry of methyl bromide to **8b**. (bottom, b) HOMO of **8b** calculated from the 6-31+G(d) wave function (left). Value of the HOMO mapped onto the electron density isosurface (right). The larger coefficient value is colored blue while the smaller values are colored red.

pair in the simple lactam enolates **8a**/**8b**, commercially available (±)-1,5-dimethylpyrrolidinone (**7**) was converted to its enolate (*s*-BuLi, THF, −78 °C). Treatment with benzyl bromide at −78 °C gave **10a**,**b** in 95% yield as a 99:1 ratio of α- to β-products.



11		[Allyl-Br] / [7]	11
-78 °C	(99% α)	< 0.01:1	(99% α)
0 °C	(96% α)	1:1	(99% α)
25 °C	(92% α)	10:1	(99% α)

Thus, the alkylation proceeded *anti* to the 5-methyl group with extremely high selectivity, as predicted by theory. This level of selectivity is unusual when one considers how sterically unencumbered enolate **8b** presents itself, and as mentioned above, there was little difference in the *syn/anti* ratios after equilibration.[12] As a further check on the alkylation stereochemistry, the monoalkylated lactams **10a**/**10b** were again transformed into their enolates (*s*-BuLi, THF, −78 °C) and treated with allyl bromide. The 2,2-dialkyl derivative **11** was formed in 95% yield with the α-allyl product **11** predominating over the epimeric β-product by >99:1.[13] Once again the topographically simple enolate **8b** gave exceedingly high entry *anti* to the 5-methyl group. Surprisingly, when this alkylation was repeated to give **11** at 0 and 25 °C, the ratio of *anti*-alkylation was still heavily favored at 25:1 and 11:1, respectively. The stereochemistry of **11** was readily supported by NOE experiments which showed peak enhancements of the 5-methyl group by the *syn*-benzyl hydrogens in **11**.[14]

To eliminate the possibility that the major product **10a** or **11** arose *via* interconversion of the two plausible enolates **8a**/**8b** (a Curtin−Hammett−Winstein−Holness situation),[15] we examined the effect of variable concentrations of the electrophile on the product ratios of **11** and its epimer. When the concentration of allyl bromide reacting with the lithium enolates of **10a/10b** was varied from 0.01 to 10 mmol (in 20 mL of THF), there was less than a 1.0% variation in the product ratio of **11** (NMR).[13] Due to the large ratio of products observed and the potential inability to observe significant changes in product ratios, we sought additional confirmation that the equilibrium between enolates **8a**,**b** was inoperative under these conditions. The enolate of **10a** was generated at 0 °C (30 min) and allowed to reach 25 °C (over 1 h). The solution was rapidly cooled to −78 °C and after 15 min treated with 5 equiv of allyl bromide. The ratio of products obtained for **11** was ∼10:1 (α/β alkylation) and not 99:1 as observed in the earlier alkylation at −78 °C. This seems to confirm that the enolates **8a**,**b** were unable to equilibrate under these reaction conditions and led to products reflective of the previous alkylation at 25 °C. This may be considered as a further and related example of the diastereomeric dynamic thermodynamic resolution[16a] recently described by Beak[16b] and Hoffmann.[16c]

Finally, the role of aggregates in enolate alkylations have been frequently addressed[1b] and we also briefly considered their impact on the results presented above. In this regard we found that there was no significant change in product ratios for **10a**/**10b** or **11** when enolate solutions were prepared in either 0.02 or 0.2 M solutions. Thus, a change in enolate concentration over 1 order of magnitude, usually affecting aggregate concentrations, produced no change.

It now appears that we have been successful in isolating a heretofore unappreciated electronic effect involving facial (*syn* or *anti*) alkylation of a nitrogen-containing enolate. The nitrogen lone pair has been shown by both experiment and calculation to facially bias the electronic character of the π-system in enolates **8**, a phenomenon earlier considered by Eschenmoser.[7a] The lack of any other factors (steric, chelation) present in "pseudo-planar" **8b** leads one to the conclusion that the stereochemical result presented here appears to be based only on the electronic nature of the enolate. Of course, the predominance of **8b** from lactam **7** is due to steric repulsion in the other enolate (**8a**) so one should still consider this a true stereoelectronic effect.[17] Other examples of the electronic importance to facial alkylation are being studied and will be reported in due course.

Acknowledgment. This manuscript is dedicated fondly to Professor Dieter Seebach on the occasion of his 60th birthday. The authors are grateful to the National Institutes of Health and the National Science Foundation for support of this program. The authors thank Professors J. Norton and P. Beak for helpful discussions.

Supporting Information Available: Experimental procedures for **10a**,**b** and **11** and their spectral properties (28 pages). See any current masthead page for ordering and Internet access instructions.

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(13) The ratios were determined by repeated integrations of the NMR data and are accurate to ±1.0%.

(14) Complete spectral data are given in the Supporting Information.

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(17) The drop in diastereofacial alkylation in **11** from 99:1 at −78 °C to 11:1 at 25 °C is considered due to the increased population of enolate **8a** at higher temperatures. Alkylation of **8a** would be expected to favor the β-face since its HOMO is more electron rich *anti* to the α-face nitrogen lone pair.