Origin of Stereochemistry in Simple Pyrrolidinone Enolate Alkylation

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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. We recently described diastereofacial selective alkylations in bicyclic lactams, particularly in lactones and lactams.1 We recently attempted to rationalize stereochemical results in enolate alkylations.

Example, the monocyclic enolates derived from imidazolidinones could be invoked as the cause of these facial selectivities.


Enolate Alkylations

compounds could be based on steric factors. For the enolate substituent, and even though they exhibit 1,3-relationships, the results could be based on steric factors. For the enolate 4, Seebach3 has suggested a stereoelectronic effect based on a slight pyramidalization of the enolate α-carbon. Recently, a study6 was reported on lactam alkylations where the stereochemistry of bicyclic systems with large size and 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 performed6 on the enolate of 7 to establish its global minimum. Energies were computed with third-order Möller–Plesset theory9 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 S2 transition states for alkylation of 8b with methyl bromide (Figure 1a) revealed that α-entry to 9b 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).

The foregoing data predicting that there should be considerable bias toward electrophilic entry anti to the N-lone pair 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 authors3,6,7 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.

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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 extensive simple enolate 

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was transformed into their enolates (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.

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 recently described by Beak and Hoffmann.

Finally, the role of aggregates in enolate alkylations have been frequently addressed 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. 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. Other examples of the electronic importance to facial alkylation are being studied and will be reported in due course.

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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.

References

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


(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.