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CONFORMATIONAL STEREOSPECIFICITY IN ELECTROPHILIC REACTIONS WITH CYCLIC ANIONS

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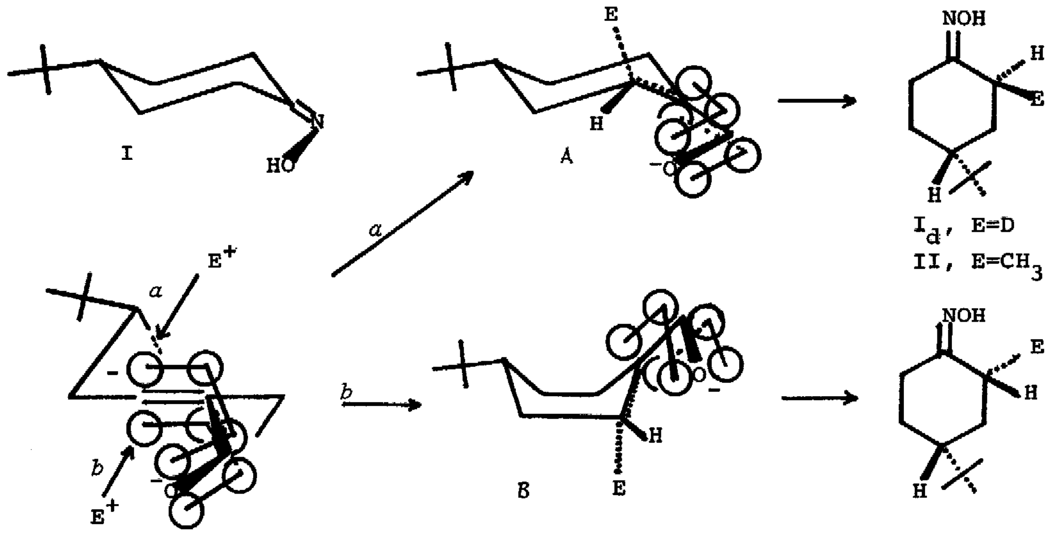
The reactions of the dianions of oximes have been shown to be highly regiospecific giving electrophilic substitution only at the α, Z carbon of the oximino system.[1] This observation suggested that the reaction should also be subject to stereoelectronic control if the system were a part of a six-membered ring. The electrophile would approach the α-carbon from a direction perpendicular to the plane of the oximino group. Such a system in a conformationally biased cyclohexane ring (such as 4-*t*-butylcyclohexanone oxime (I)) would give two possible transition states, one chair-like (A) and one boat-like (B). Obviously the former (A) would be more stable and should determine the conformation of the majority of the product.



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To test this hypothesis the dianion of 4-*t*-butylcyclohexanone oxime (I) was prepared and treated with deuterium oxide to give a monodeuterated I-$\underline{d}_1$. The nmr spectrum of I showed the Z-equatorial, α-hydrogen as a broad doublet at 4.20 ppm and the E-equatorial, α-hydrogen as a similarly shaped band at 3.05 ppm. The product of the deuterium reaction I-$\underline{d}_1$ showed no change in the signal at 3.05 ppm; however, the signal at 4.20 ppm appeared as a broad singlet at 4.20 ppm. The loss of the large coupling with the Z-equatorial hydrogen without decrease in the intensity of the signal showed that the axial substituent was now deuterium in I-$\underline{d}_1$ and confirmed the stereospecific, stereoelectronic control of the reaction.

The reaction of the dianion of I with methyl iodide gave a 2-methyl-4-*t*-butylcyclohexanone oxime (II) whose nmr spectrum showed the Z-equatorial α-hydrogen to be displaced to lower field (4.50 ppm) as an unresolved singlet. Again no change was noted in the signal for the E-equatorial, α-hydrogen. These results are consistent with a stereospecific, stereoelectronically controlled methylation to produce the Z-oxime of *trans*-2-methyl-4-*t*-butylcyclohexanone (II).

The direct steric interference of the oximino oxygen with its counter ion would prevent approach of the electrophile in the plane of the oximino function. Thus whether the alpha, ionic carbon is an inverting, pyrimidal, sp^3 hybrid or a planar, sp^2 hybrid, the electrophile would be expected to add to give the axially substituted product[2] (Id or II) for the reason described above.

This stereoelectronic control of the reaction of the oxime dianion is similar to that observed for an isoelectronic system 4-*t*-butyl-1-nitrosopiperidine (III). The nmr spectrum of III shows two broad doublets which are assigned as the signals for the *pro*-Z-equatorial, α-proton (5.35 ppm) and the *pro*-E-equatorial α-proton (5.10 ppm).* The signals for the axial hydrogens on the α,*pro*-Z and α,*pro*-E carbons appear further upfield at 2.50 and 3.70 ppm

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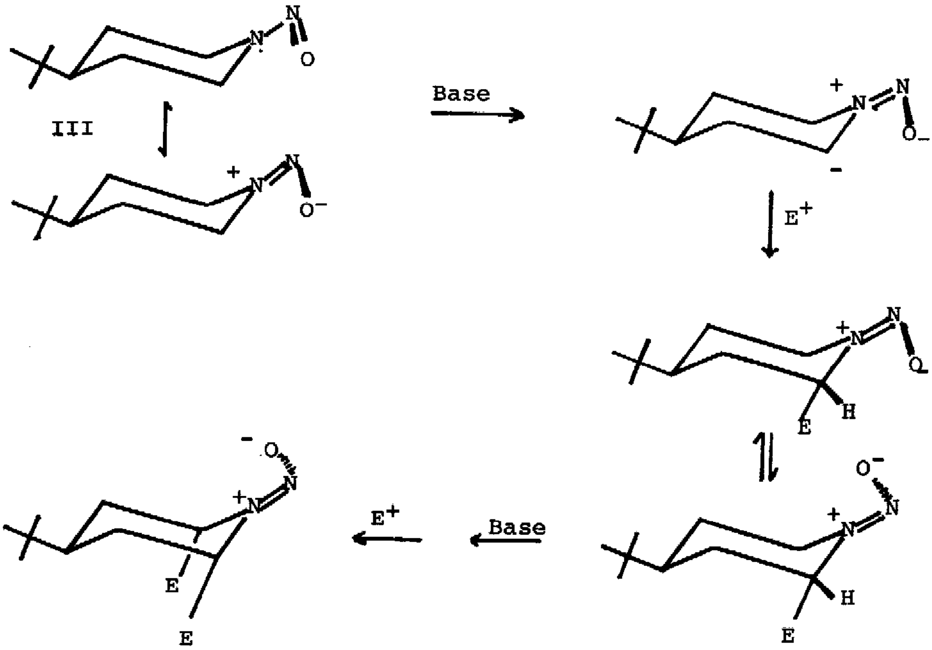
*The use of the term "*pro*" has been accepted for use with chiral compounds, and we propose the use of the terms "*pro*-Z" and "*pro*-E" to distinguish, otherwise identical, groups on the same or opposite side, respectively, as the higher priority group of a unsymmetrically substituted double bond.

respectively. In DMSO-d_6 with NaOD and D_2O at 100° the exchange of the axial hydrogens was complete within 30 minutes, for the signals at 2.50 and 3.70 ppm disappeared. Furthermore, the broad doublets at 5.35 and 5.10 ppm became broad singlets. There was no indication of a change in the intensity of the signals at 5.35 or 5.10 ppm showing that <u>no</u> exchange of the equatorial hydrogens occurred. This experiment demonstrated the stereoelectronic control of the deuterium exchange reaction with the 6π electron, 4-orbital nitrosamine system. Unfortunately, the low barrier to rotation about the N-N bond (∿25 kcal/mol) prevented demonstration of regiospecificity; however, such specificity was shown earlier on a related system.[3]



These results strongly suggest that the proposal of Jung and coworkers[1b] can be extended.[4] The stability of 6π-electron, 4-*p*-orbital systems represented by $\underset{ee}{W}-X=Y-\underset{ee}{Z}$ will be greatest with the atoms Z and W syn and reactions of these systems with electrophiles will show regiospecificity and, in appropriate systems, will show conformational stereospecificity.

This generalization was recently illustrated by the regiospecific and conformationally specific alkylations of dimethylhydrazones.[5] The high degree of stereoselectivity observed with these reactions suggests their importance in synthetic chemistry.

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