9. SUMMARY

Diastereofacial selection in the reactions of carbonyl compounds and related heterotopic ligand is an area of intense research in physical organic chemistry. We have in our present work made an attempt to probe the effects of remote substituents in the benzylation of conformationally immobile cyclic β-keto ester enolates. For this purpose we have chosen trans decalone systems 81, 85 and 92 (Scheme 3.2-3.4), with strategically placed C-8a Substituents. The remote substituents on the substrate were electron-donating methyl, electron-withdrawing COOEt (ester) along with reference H. These substrates were benzylated with benzylbromide having different (CH₃, NO₂, Cl, Br) C-4' substituents (para substituents). Thus electronically fine tuned benzyl bromide was reacted with β-keto ester to get zu and en benzylated products. The diastereomers were isolated in most of the cases and characterized on the basis of intensive NMR spectral analysis and X-ray crystal structure study of the selected representative of each series.

Results obtained in this study, are summarized in the Table 6.1-6.3 and are concisely presented in the Scheme 9.1 along with results of methylation reactions performed by Rao and Reddy for comparison. Experimental results were analyzed by cost effective semi empirical method, using AM1 Hamiltonian with the help of MOPAC package. To explain the results of SN₂ type benzylation reaction, we have developed 'improvised proton model'. Analysis of the results shows that p substitution in the benzyl ring does not have marked influence on the stereoselectivity.

However the theoretical work on both methylation and benzylation reaction clearly delineated the following:

1. Methylation reactions using CH₃I follow SN2 pathway and for substrate 81 R = H zu attack is favored due to the absence of steric influence, on the other hand when the substrate is 85 R = CH₃, due to steric hindrance en attack is favored. In the case of substrate 92 R = COOEt zu attack is favored, may be due to electrostatic attractive forces between the methylene CH of the ester and developing negatively charged halide ion(iodide) in SN2 TS.

2. Theoretical study clearly indicates SN1 type mechanism for benzylation reactions. In the case of benzylation of 81 R = H zu attack is favored because of the torsional interaction of the C-2 axial hydrogen is more severe than the steric interaction with syn axial hydrogen. In the benzylation of 85 R = Me substrate, steric hindrance results in exclusive en attack. For the substrate 92 R = COOEt, since the electrostatic stabilizing interactions are not operative due to SN1 mechanism, steric hindrance from the C-8a
COOEt group forces predominant \textit{en} attack. Theoretical study also reveal the absence of Cieplak / Felkin-Anh hyperconjugative effects as determinant in stereoselection.

3. The experimental and theoretical work on the regioselectivity (C vs O) of alkylation showed interesting dependence of the result on rate of the reaction and charge on the alkylation agents 94-97.

\[ \text{X = CH}_3, \text{H, NO}_2, \text{Cl, Br}. \]

\textbf{Scheme 9.1} Summary of experimental results