Chemistry II (Organic): Introduction to Stereoelectronics

Nucleophilic Addition to Cyclohexanone: Cieplak's Model

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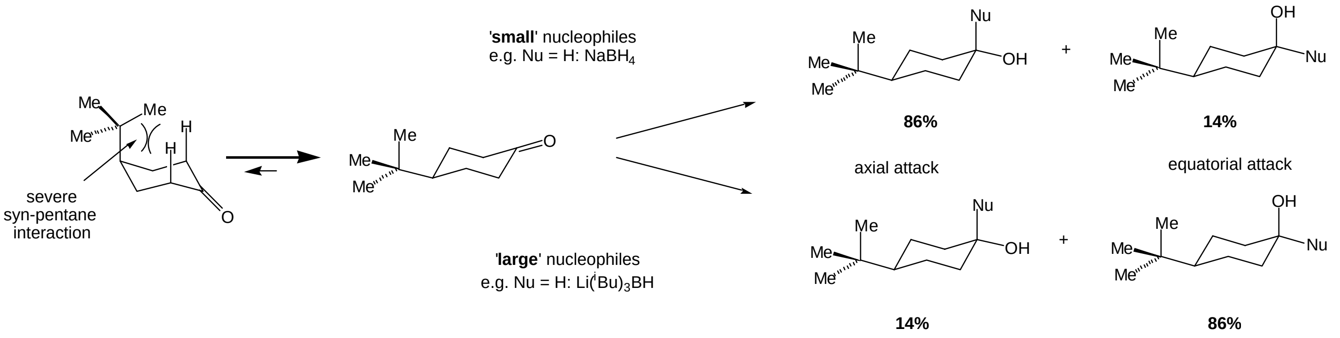
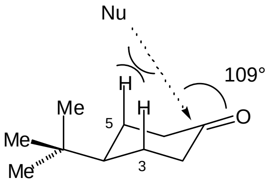
THE EXPERIMENTAL FINDINGS:

'Small' nucleophiles [e.g. $LiAlH_4$, $NaBH_4$] react with conformationally locked cyclohexanones predominantly to give products resulting from *axial* attack on the carbonyl function. 'Large' nucleophiles [e.g. $Li(^iBu)_3BH$, ^iPrMgBr, ^sBuMgCl] give products resulting from *equatorial* attack on the carbonyl function.



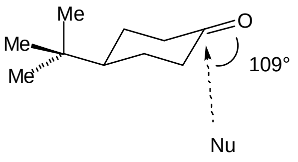
THE RATIONALE:

Steric control is certainly responsible for the equatorial preference of large nucleophiles. Thus if we consider that a nucleophile must approach the carbonyl function along a Burgi-Dunnitz trajectory (109°) then attack to give axial product encounters significant steric clashes with the axial hydrogen's at positions 3 and 5. In contrast approach to give equatorial product is relatively unhindered.



axial attack is sterically hindered

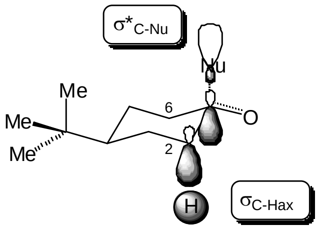
cf.



equatorial attach is relatively unhindered

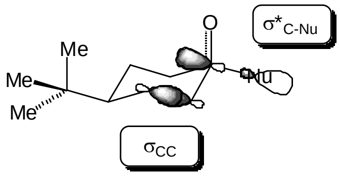
The question then is why do 'small' nucleophiles have a tendency to approach from the more hindered face? There have been a large number of theories aired to try to account for this seemingly anomalous trend (see: *Tetrahedron* **1979**, 35, 449). The theory which currently seems to offer the most satisfactory explanation is due to Cieplak (*J. Am. Chem. Soc.* **1981**, 103, 4540; *J. Am. Chem. Soc.* **1989**, 111, 8477).

According to this interpretation, there is a favourable stereoelectronic interaction between the incipient Nu-carbonyl carbon anti-bonding sigma orbital and the two antiperiplanar axial C-H sigma orbitals at positions 2 and 6 (i.e. $\sigma_{CHax} \rightarrow \sigma^*_{C\text{-}Nu}$). The corresponding interaction in the case of equatorial attack would be between the incipient Nu-carbonyl carbon anti-bonding sigma orbital and the two antiperiplanar axial C-C sigma orbitals (i.e. $\sigma_{CC} \rightarrow \sigma^*_{C\text{-}Nu}$) and this is less favourable.



axial attack

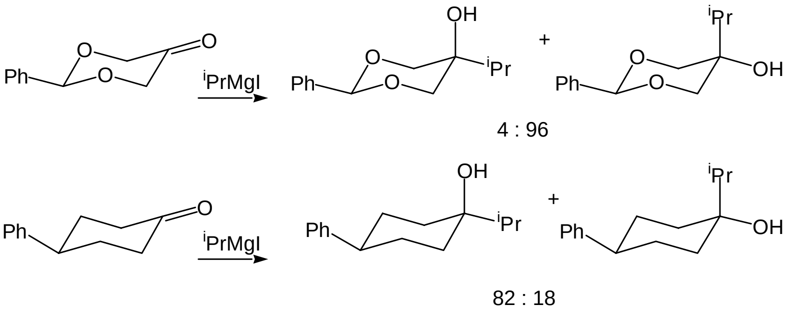
cf.



equatorial attack

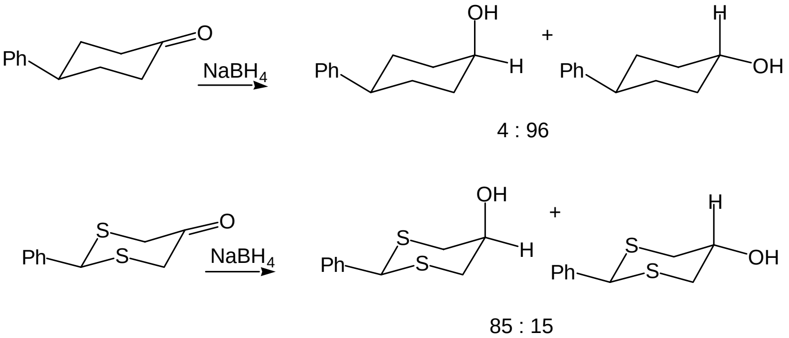
The theory rests on the σ_{CHax} bonds being better donors than the σ_{CC} bonds. This is a contentious matter. For a summary of evidence supporting this assertion see: A.S. Cieplak *J. Am. Chem. Soc.* **1981**, 103, 4540. For a summary of evidence disputing it see: K.N. Houk *et al. J. Am. Chem. Soc.* **1982**, 104, 1189.

However, the following results appear to lend support to the Cieplak model. If the reactivity of cyclohexanone is contrasted with a 1,3-dioxo analogue it is apparent that the latter has a significantly more marked tendency to yield products of axial attack:



This can be interpreted as reflecting the fact that σ_{CO} bonds are significantly worse donor bonds than σ_{CC} bonds (see ‘A highly qualitative organic chemists guide to orbital interactions and stereoelectronic phenomena’ handout) and hence ‘compete’ even less effectively with the σ_{CHax} donation. It should be noted however that the steric hindrance to axial attack in the 1,3-dioxo compound has also been reduced (lone pairs on oxygen *vs.* axial hydrogen’s).

If the reactivity of cyclohexanone is contrasted with a 1,3-dithio analogue it is apparent that the selectivity is substantially reversed: i.e. there is a marked tendency, in the dithio case, to yield products of equatorial attack, even for small nucleophiles:



This can be interpreted as reflecting the fact that σ_{CS} bonds are significantly better donor bonds than both σ_{CC} and σ_{CHax} bonds and hence a Cieplak type stereoelectronic interactions now favour equatorial attack.

EXTRAPOLATION TO OTHER SYSTEMS:

Stereoelectronic interactions of the type described above for nucleophilic attack on cyclohexanone are not confined to this system. Interactions of this type are generally referred to as ‘Cieplak effects’ and have been invoked to explain a disparate range otherwise difficult to rationalise stereoselective phenomena. e.g.

V.K. Aggarwal, J.G. Ford, S. Fonquerna, H. Adams, R.V.H. Jones, and R. Fieldhouse, ‘Reaction outcomes of Catalytic asymmetric epoxidation of aldehydes. Optimization, mechanism, and discovery of stereoelectronic control involving a combination of anomeric and Cieplak effects in sulfur ylide epoxidations with chiral 1,3- oxathianes’, *J. Am. Chem. Soc.* **1998**, 120, 8328.

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