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Transition State Hyperconjugation as a Cause of π-Facial Selection in Cyclohexanones.

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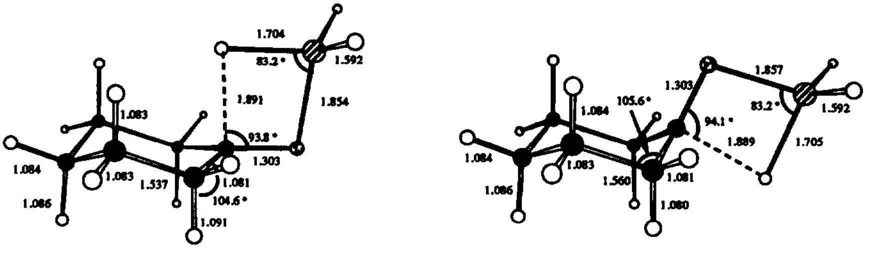
***Abstract:** Ab initio and semiempirical calculations of the transition states of cyclohexanone reduction by AlH_3 show bond length changes and molecular orbitals consistent with hyperconjugative stabilisation. Both electronic and torsional effects contribute to facial selection.*

Several explanations have been proposed for the preference of axial attack by sterically unhindered nucleophiles ($LiAlH_4$, $NaBH_4$, AlH_3) in cyclohexanones.[1] Recent ab initio studies have concluded[2] that torsional strain and uneven orbital extension of the $\pi^*_{C=O}$ LUMO are involved in stereoselection. Cieplak has proposed that transition state stabilisation by hyperconjugative delocalisation of an adjacent antiperiplanar σ-bond into the incipient σ*-orbital[3] can control stereochemistry with nucleophilic attack anti to the better electron donating σ-bond being favoured. le Noble has emphasised that an antiperiplanar alignment with the nucleophile may be more important than inherent electron donating ability in determining participation of C-H or C-C in cyclohexanone.[4]

We have examined the energy surface of the gas phase addition of AlH_3[5] to cyclohexanone. AlH_3 is effective in carbonyl reduction, and exhibits facial selection.[6] The reaction proceeds via initial complex formation, followed by intramolecular rate determining nucleophilic attack of aluminium hydride.[7] The four-centre ab initio 3-21G* transition states for axial and equatorial attack of hydride (Figure 1) show the incipient H_{Nu}--C bond distances, 1.891 and 1.889 Å respectively, to be somewhat shorter than for LiH reduction (2.057 and 2.028 Å)[2], indicative of a later transition state for AlH_3. Projections down the C_2-C_1 bond (Figure 2 a,b) show a O-C-C-H_{eq} dihedral angle in the axial and equatorial transition states of 34.4°

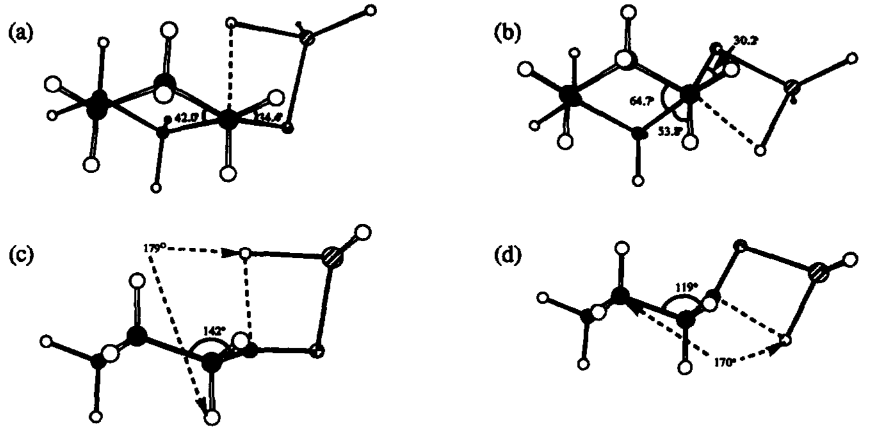


axial attack

equatorial attack

Figure 1. Transition states (3-21G*) for axial and equatorial AlH_3 addition to cyclohexanone.

and 30.2°, respectively, consistent with greater torsional strain in the latter, as first suggested by Felkin,[8] and confirmed by Houk.[9] Noteworthy is the distortion of the ring, as measured by the angle of the $C_1C_2C_6$-$C_2C_3C_5$ planes (Figure 2 c,d). The ring is flattened to 142° at the transition state for axial and puckered to 119° for equatorial attack, compared with a value of 130° in cyclohexanone. The ring $C_6C_1C_2C_3$ dihedral angles (Figure 2 a,b) distort from 54° in cyclohexanone to 42° for axial and 65° for equatorial attack.[10] The dihedral angles of the adjacent C-H and C-C bonds with the forming C--H_{Nu} bond are significant since they provide a measure of the ability of these bonds to participate in hyperconjugation. For axial attack an almost perfect antiperiplanar relationship[11] is calculated (H_{Nu}--C-C-H_{ax} dihedral 179°); the H_{Nu}--C-C-C dihedral for equatorial attack is 170° (Figure 2 c,d). Ring distortion provides a balance between minimising torsional strain, and maximising orbital interactions with the adjacent σ-bonds (C-H for axial and C-C for equatorial attack).



E_{rel} = 0.0
0.0 (cyclohexanone fragment)
0.0 (AlH_3 fragment)
0.0 (electron interaction energy
0.0 (-H^-)
0.0 (-H^-, add -0.4 charge)

E_{rel} = 1.1
0.5 (cyclohexanone fragment)
-0.2 (AlH_3 fragment)
0.8 (electron interaction energy)
-1.2 (-H^-)
0.5 (-H^-, add -0.4 charge)

Figure 2. Dihedral angles in the transition states (3-21G*) for axial and equatorial AlH_3 addition to cyclohexanone. Relative energies are in kcal/mole calculated at the 3-21G*//3-21G* level.

Both semiempirical and ab initio calculations parallel experimental values[12] for reduction of 4-*t*-butylcyclohexanone (Table I). The transition state for axial attack is favoured over equatorial by 1.1 kcal/mole (3-21G* and AM1).[13] This enthalpy difference can be separated into three components; the cyclohexanone fragment, the AlH_3 fragment, and an interaction enthalpy between these fragments. Their relative contributions can be estimated by calculating the enthalpy of each fragment fixed at the transition state geometry. The axial cyclohexanone fragment is more stable by 0.5 kcal/mole.[14] The AlH_3 fragment shows a small enthalpy difference favouring equatorial attack (0.2 kcal/mole). The difference in energy between the transition states and the energies of the components at the transition state geometries, but at infinite separation, is a measure of the electronic interaction at the transition state: 0.8 kcal/mole favouring axial attack. This demonstrates that electronic effects[15] as well as torsional effects are significant in determining facial selection in cyclohexanone reduction.

Hyperconjugative stabilisation, reported earlier for cyclohexanone as uneven orbital distribution[2b, 16] exists in the transition states for AlH_3 reduction. Inspection of the molecular orbitals of the H_{Nu}--C bond in the axial transition state shows a significant interaction with the antiperiplanar C-H bonds. The corresponding molecular orbitals for the equatorial transition state show a contribution from the antiperiplanar C-C bond. This is further evidence that hyperconjugative stabilisation is a significant component of the electronic interaction enthalpy. The role of the attacking hydride in stabilisation of the transition state is shown by its removal: the enthalpy of the resulting frozen fragments results in favouring equatorial approach by 1.2 kcal/mole. A natural bond order analysis shows that the hydride bears a -0.4 a.u. charge in each transition state. When a point charge of -0.4 is added back at the location of the removed hydride, the axial approach is favoured by 0.5 kcal/mole consistent with the importance of the charge.

Table I
Reduction of 4-*t*-butylcyclohexanone (eq/ax alcohols)

Experimental		Ref	Theoretical[17] (25°)[a]	
$LiAlH_4$	90/10	6d	LiH (3-21G//3-21G)[2b]	84/16
			LiH (6-31G*//3-21G)[2b]	95/5
			LiH (MP2/6-31G*//3-21G)[2a]	91/9
AlH_3	85/15	6d	AlH_3 (AM1)	86/14
$NaBH_4$	86/14	1	AlH_3 (3-21G*//3-21G*)	87/13

a. Boltzmann weighted distribution from the enthalpy difference.

In each transition state, the bonds which are antiperiplanar to the forming H_{Nu}--C bond are elongated, axial C-H's for axial attack, and C-C bonds for equatorial (Figure 1). This effect has been noted in calculations of the Diels-Alder transition states.[18] Using the calculated length of the adjacent axial C-H bond of cyclohexanone (3-21G*)(1.087 Å) as a reference, there is a further lengthening[19] to 1.091 Å (0.37%) in the axial transition state, with no extension of the C_α-C_β bond. The equatorial transition state shows a C_α-C_β bond extension to 1.560 Å (0.84%) compared with the calculated bond length of cyclohexanone (1.547 Å), with no extension of the C_α-H_{ax} bond. Similarly, the C_α-$C_{C=O}$ bond length shortened in both axial (1.509 Å, 0.4%) and equatorial structures (1.499 Å, 1.1%) compared to the corresponding calculated bond length in cyclohexanone (1.515 Å).

The better antiperiplanar orientation of the nucleophile with the adjacent C-H bond in axial attack compared with the C-C bond for equatorial attack supports the suggestion that orbital alignment is important. The calculated structural changes of the transition states and their molecular orbitals are consistent with hyperconjugative delocalisation of the C_α-H_{ax} bond for axial and the C_α-C_β bond for equatorial attack.

References and Notes

1. For a historical review: Wigfield, D.C. *Tetrahedron.* **1979**, *35*, 449-462. Equatorial attack is favoured for sterically hindered cyclohexanones or reducing agents.

2. (a) Wu, Y.-D.; Houk, K.N.; Paddon-Row, M.N. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1019-1021. (b) Frenking, G.; Köhler, K.F.; Reetz, M.T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1146-1149. (c) Wu, Y.-D.; Tucker, J.A.; Houk, K.N. *J. Am. Chem. Soc.* **1991**, *113*, 5018-5027.

3. Cieplak, A.S. *J. Am. Chem. Soc.* **1981**, *103*, 4540-4552. Cieplak, A.S.; Tait, B.D.; Johnson, C.R. *J. Am. Chem. Soc.* **1989**, *111*, 8447-8462.

4. Li, H.; le Noble, W.J. *Recl. Trav. Chim. Pays-Bas.* **1992**, *111*, 199-210. Fundamental to the Cieplak hypothesis is the question of which adjacent σ-bond will better participate, C-H or C-C. Houk has concluded that C-C bonds are more electron donating than C-H. The Cieplak effect is controversial and not considered important from ab initio LiH/cyclohexanone studies.[2c]

5. Many theoretical investigations have used addition of LiH (Kaufmann, E.; Schleyer, P. von R.; Houk, K.N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560-5562) as a model for aldehyde and ketone reduction, although this reagent rarely reduces carbonyl groups. Klusener, P.A.A.; Brandsma, L.; Verkruijsse, H.D.; Schleyer, P. von R.; Friedl, T.; Pi, R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 465-466 and references therein. Enolate formation is faster than addition to the carbonyl with activated LiH prepared by hydrogenating butyl lithium in the presence of tetramethylenediamine.

6. (a) Norman, R.O.C.; Coxon, J.M. *Principles of Organic Synthesis*, 3rd Ed., Blackie, Chapman and Hall, London, **1993**, p. 651-652. (b) March, J. *Advanced Organic Chemistry*, 4th Ed., Wiley, 1992, p 911. (c) House, H.O. *Modern Synthetic Reactions*, 2nd Ed., Benjamin, Menlo Park, CA, 1972, p 45. (d) Guyon, R.; Villa, P. *Bull. Soc. Chim. France.* **1977**, 145-151. (e) Ashby, E.C.; Boone, J.R. *J. Org. Chem.* **1976**, *41*, 2890-2903. (f) Ayres, D.C; Kirk, D.N.; Sawdaye R. *J. Chem. Soc. (B)* **1970**, 505-510.

7. Luibrand, R.T.; Coxon, J.M. *Tetrahedron Lett.* **1993**, submitted for publication.

8. Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2205-2208.

9. In LiH addition, torsional strain differences in the transition states is considered[2a] to be the factor which most controls stereoselection.

10. Values for LiH reduction[2c] are 43° and 63°, respectively.

11. The importance of ring flattening to achieve an antiperiplanar approach for axial attack in cyclohexanones was first noted by Anh. Anh, N.T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61-70. Anh, N.T. *Top. Curr. Chem.* **1980**, *88*, 145-162.

12. The reaction may serve as a model for $NaBH_4$ reduction whose enthalpy surface is complicated.

13.	AM1 (kcal/mole)	3-21G*(a.u.)
cyclohexanone	-63.334	-306.19162
cyclohexanone complex	-68.560	-548.59300
transition state, axial attack	-46.216	-548.56404
transition state, equatorial attack	-45.122	-548.56222

14. Enthalpies calculated for the cyclohexanone fragments are consistent with greater torsional strain in the equatorial transition state. The difference in strain of the cyclohexanone fragments is greater for AlH_3 than for LiH addition (3-21G*).[2a,b]

15. SPARTAN (version 2.1. Wavefunction, Inc., Irvine, CA 92715), GAUSSIAN 92 (Gaussian, Inc., Pittsburgh, PA) and MOPAC programs were used. Geometries were fully optimised at the 3-21G(*) and AM1 levels and transition states characterised as having only one imaginary vibrational frequency.

16. Houk[2a] has explained this in terms of secondary orbital interactions of the most eclipsed allylic σ-bonds with the $\pi^*_{C=O}$ LUMO.

17. This is consistent with a significant electronic interaction contribution to the transition state enthalpy difference.

18. Coxon, J.M.; McDonald, D.Q. *Tetrahedron Lett.* **1992**, *33*, 651-654.

19. In cyclohexanone C_α-H_{ax} bonds are already somewhat extended due to their interaction with the carbonyl. These calculated values parallel experimental data of pyramidalised cyclohexanone Lewis acid complexes. Laube, T.; Hollenstein, S. *J. Am. Chem. Soc.* **1992**, *114*, 8812-8817.

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