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Factors Which Control π-Facial Selection in the Reduction of 5-Substituted Adamantanones

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Ab initio and semiempirical calculations of the transition states for reduction of 5-substituted adamantanones with AlH_3 show bond lengthening and molecular orbitals consistent with hyperconjugative stabilization. Electronic as well as torsional effects contribute to facial selection.

Introduction

Any explanation of facial selectivity in reactions of aldehydes and ketones[1] must account for (i) the high stereochemical preference for axial attack and substituent effects observed in the reduction of sterically unhindered cyclohexanones and (ii) the diastereoselection observed in reactions of acyclic aldehydes and ketones. Many theories have been proposed[2] to account for experimental observations but only a few have survived detailed scrutiny.

(i) Acyclic systems. Cram's proposal[3] for predicting the most favored diastereoisomeric transition state for nucleophilic attack at acyclic aldehydes and ketones was based on the size of the substituents α to the carbonyl. The preferred conformation from which reaction occurs has the largest adjacent group antiperiplanar to the carbonyl (Figure 1), and the nucleophile attacks from the side with the smaller (S) group.[4]

Karabatsos[5] similarly suggested that the incoming nucleophile approaches the carbonyl from the face with the smallest group but, in contrast to Cram, suggested that the preferred conformation from which reaction occurs has the medium sized substituent (M) eclipsed with the carbonyl (Figure 2).

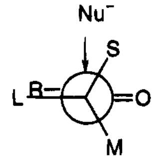

Figure 1. The Cram model for nucleophilic attack at acyclic carbonyl compounds.

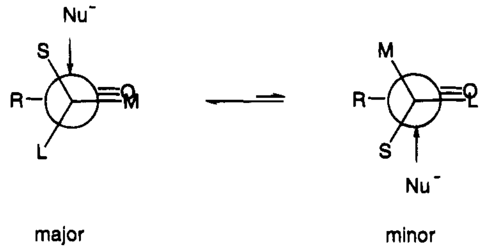

Figure 2. The Karabatsos model for nucleophilic attack at acyclic carbonyls.

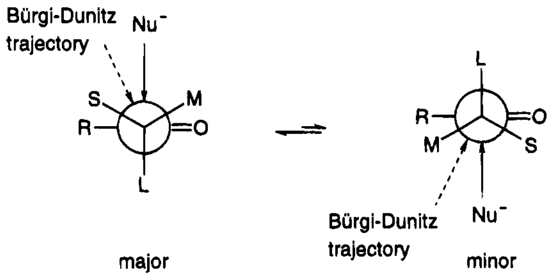

Figure 3. The Felkin model for nucleophilic attack at acyclic carbonyls.

Neither of these models could account for the effect of varying size of the carbonyl R group on the selectivity of reduction of acyclic ketones. Felkin[6] therefore proposed that nucleophilic attack would proceed so as to minimize torsional strain in the transition state such that the largest group, L, would be perpendicular to the carbonyl, and addition would occur trans to this group. By assuming that the interactions of the small and medium groups are greater with R than O (Figure 3), the most favored transition conformation was considered to have the medium group positioned near the carbonyl oxygen. Early *ab initio* calculations (STO-3G) by Anh and Eisen-

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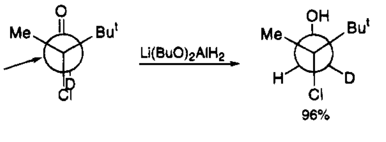
[®] Abstract published in *Advance ACS Abstracts,* December 15, 1994.

(1) Cieplak, A. S.; Tait, B. D.; Jonson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447–8462. (b) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540–4552. (c) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018–5027. (d) Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908–910. (e) Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916–1917. (f) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 1598–1605. *Ibid.* **1987**, *109*, 7239. (g) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836–3839. (h) Mikami, K.; Shimizu, M. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed; JAI Press: Greenwich, CT, 1994; Vol. 3, pp 45–77.

(2) (a) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas.* **1992**, *111*, 199–210. (b) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 8991–9004. (c) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449–462.

(3) Cram, D. J.; Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

(4) When one of the substituents is a highly polar group (e.g., halogen) Cornforth suggested that the polar group and oxygen atoms stay as far apart as possible in order to minimize dipolar interactions. Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. For example reduction of 1-chloro-1-deuterio-2,3,3-trimethylbutanal with lithium dibutoxyaluminium hydride; Blackett, B. N.; Coxon, J. M.; Hartshorn, M. P.; Richards, K. E. *Aust. J. Chem.* **1970**, *23*, 2077.



(5) Karabatsos, G. J. *J. Am. Chem. Soc.* **1976**, *89*, 1367.

(6) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199–2204.

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Figure 4. Interactions with adjacent σ-orbitals cause uneven orbital extension of the LUMO.

stein[7] supported Felkin's proposal that transition states are favored when nucleophilic attack occurs from an orientation antiperiplanar to an adjacent σ-bonded group. In this way the transition state is staggered and the large group is *anti* to the incoming nucleophile.

Anh made a second contribution by considering the importance of the Bürgi–Dunitz trajectory (a Nu–C–O angle of 105 ± 5°) for nucleophilic attack at a carbonyl.[8] For the two possible conformations having the large group perpendicular to the carbonyl the nucleophile will approach past the small group rather than the medium group (Figure 3).[9] Anh's theoretical study combined with Felkin's model has become known as the Felkin–Anh model.

The Felkin model and other models have been applied to explaining the preference for axial attack by nucleophiles on cyclohexanones and the effect of proximate substituents on facial selection.

(ii) Cyclohexanones. The first explanation for the preference for axial attack by hydride in conformationally rigid sterically unhindered cyclohexanones, became known as "product development control" and involved a "late" transition state.[10] Steric hindrance was considered to favor equatorial attack in hindered ketones and known as "steric approach control" caused by an "early" transition state. The antiperiplanar geometry that Anh regarded as important in nucleophilic attack of carbonyl compounds is compromised by torsional strain in the reactions of cyclohexanones from the equatorial face.[11]

Klein[12] was the first to consider that the LUMO of the carbonyl could be facially dissymmetric and could influence facial selectivity. For cyclohexanone it is now known that hyperconjugation of the π*-orbital of the carbonyl with the adjacent axial C–H bonds results in nonequivalent orbital extension of the LUMO[13] (Figure 4). This extension would favor axial addition of nucleophiles. *Ab initio* calculations[14] have also shown that orbital extension toward the axial side occurs not only for the LUMO but also for the HOMO.[13] This orbital extension could therefore be a factor in rationalizing the known preference for axial attack observed in electrophilic attack of methylenecyclohexane.[15]

Calculations, by *ab initio* methods, of the reaction of cyclohexanone with LiH as a model for $LiAlH_4$ reduction have been carried out. Houk[14] concluded that orbital interactions resulting in differences in LUMO extension due to adjacent C–C, C–H, C–O, and C–S bonds are less important than torsional effects in rationalizing the axial preference of attack. The calculations of the transition states for axial and equatorial addition of LiH showed that for axial attack the transition state has an ideal staggered structure. The calculations also showed that in order to form an ideal staggered transition structure for equatorial addition, ring strain would have to be introduced. To minimize this ring strain the transition structure adopts a less than completely staggered conformation and is a higher energy transition structure than that calculated for axial addition. Comparable calculations for the reduction of cyclohexanone with AlH_3 show similar results.[16] In that study a four center transition state is calculated to be on the potential energy surface.[17] Similar calculations of the transition states for reactions of acyclic and cyclic systems which contain polar groups show[18] that relative transition state energies depend both on the electronic effects described by Anh and electrostatic interactions.[19] An alternative more recent and controversial hypothesis was proposed by Cieplak[1a,b] who has claimed that the controlling interaction in reactions "in cyclohexane-based systems" is "based on the concept of transition-state stabilization by electron donation into the vacant orbital $\sigma^{*\ddagger}$ associated with the incipient bond." Cieplak et al.[1a] state "the explanation of stereoselection in reactions of the cyclohexane-related systems based on the Cieplak proposition is as follows. During the axial attack of a reagent, the vacant orbital $\sigma^{*\ddagger}$ that develops along with the formation of the incipient bond interacts with the filled orbitals of the C(2)–H and C(6)–H bonds. During the equatorial attack, the $\sigma^{*\ddagger}$ orbital interacts with the filled orbitals of the ring bonds C(2)–C(3) and C(5)–C(6). The effect

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[7] Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70. (H^- attack on MeCHClCHO and EtCHMeCHO (STO-3G))

[8] Bürgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065–5067. Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956–1957. Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M. *Tetrahedron* **1974**, *30*, 1563.

[9] This explanation does not require greater interactions on the small and medium groups with R than O even when R = H, as implicit in Felkin's proposal.

[10] Dauben, W. G.; Fonken, G. S.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579.

[11] Felkin stated that "Whereas both torsional strain and steric strain can be simultaneously minimized in a reactant-like transition state when the substrate is acyclic....this is not possible in the cyclohexanone case. ...These reactions all proceed via reactantlike transition states, and that, in the absence of polar effects, their steric outcome is determined by the relative magnitude of torsional strain and steric strain" in the axial and equatorial transition states.[6]

[12] Klein, J. *Tetrahedron Lett.* **1973**, *44*, 4307–4310.

[13] Frenking, G.; Kohler, K. F.; Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1994**, *30*, 1146–1149.

[14] Wu, Y.-D.; Houk, K. N.; Paddon-Row, M. N. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1019–1021. The LUMO orbital of the carbonyl carbon interacts with the parallel allylic σ-bonds which are most aligned with the carbonyl orbitals, in an antibonding fashion. This leads to extension of the orbital in the direction trans to the allylic bonds. In cyclohexanone, the ring distortion causes the C–H bond to be more eclipsed with the π-orbitals (O–C–C–H dihedral angle 115°) than the C–C bond (O–C–C–C dihedral angle 127°), resulting in orbital distortion in the axial direction. This model is consistent with the axial nucleophilic attack preference of 1,3-dioxan-5-one derivatives (even higher than for cyclohexanones) and the equatorial attack for 1,3-dithian-5-one. In 1,3-dioxan-5-one the axial C–H bonds are in even better alignment with the carbonyl π* orbital than in cyclohexanone (O–C–C–H dihedral angle 80°). In 1,3-dithian-5-one ring distortions cause the C–S bonds to be more periplanar with the π orbital, causing equatorial orbital extension, and equatorial addition of hydride is favored.

[15] Dannenbery has attempted to provide a frontier orbital explanation for facial selectivity by a polarized π-frontier orbital method. The new (polarized) orbitals are schematically represented as the combination of a p-orbital with two s-functions and have different coefficients associated with each face of each π center. Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017–6024. Huang, X. L.; Dannenberg, J. J.; Duran, M.; and Bertrán. *J. Am. Chem. Soc.* **1993**, *115*, 4024–4030.

[16] Coxon, J. M.; Luibrand, R. T. *Tetrahedron Lett.* **1993**, *34*, 7097–7100.

[17] Coxon, J. M.; Luibrand, R. T. *Tetrahedron Lett.* **1993**, *34*, 7093–7096

[18] Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327–330. Wong, S. S; Paddon-Row, M. N. *Aust. J. Chem.* **1991**, *44*, 765–770. Frenking, G.; Köhler K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 9005–9018.

[19] Electrostatic interactions are considered to be the dominant controlling factor in the determination of stereoselection in the reduction of 3-fluorocyclohexanone and substituted 7-norbornanones. Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638–10639.

Table 1. Experimental and Calculated Ratio of *Anti/Syn* Alcohols for Reduction of 1–4

	anti/*syn* product ratio of alcohols,[1f] experimental conditions ($NaBH_4$)			calcd[a] (0 °C)		
reactant	MeOH, 0 °C	i-PrOH, 0 °C	i-PrOH, rt	AM1(PM3)	3-21G*	6-31G* [b]
1 X = CF_3		59/41		60/40		
CO_2Me	61/39			56/44		
F	59–62/39–41[c]	58/42	62/38	59/41		
Cl	62–67/33–38[c]	57/43	59/41	56/44		
Br	59/41			55/45		
OH	57/43			53/47		
H	50/50			50/50		
t-Bu	50/50[d]			46/54		
$Si(Me)_3$	49/51		45/55	45/55		
2		96/4[e]		58/42 (61/39)	91/9	97/3
3		62/38[e]		33/67		
4				60/40		

[a] Boltzmann weighted distribution from enthalpy differences. [b] This 6-31G* basis set has a set of diffuse s and p orbitals on the hydride ion (3-21G* geometry). [c] Reference 143–145. [d] $LiAlH_4$, rt.[1g] [e] Temperature not specified.

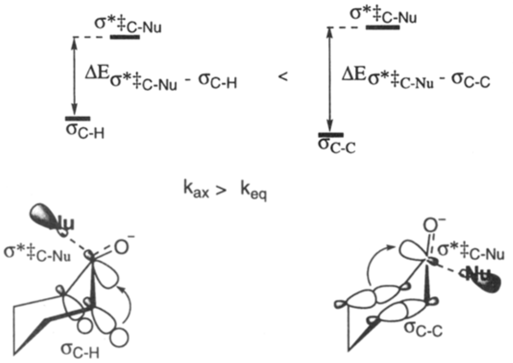
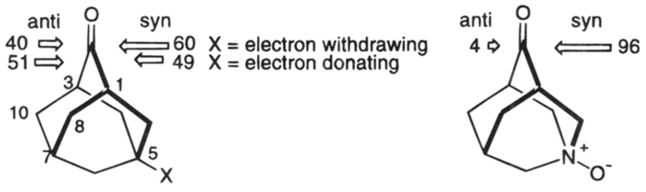


Figure 5. Cieplak model for axial and equatorial attack showing preference for axial addition.[20]

of steric hindrance favors, obviously, the equatorial attack. The effect of the hyperconjugative σ assistance, however favors the axial attack because the CH bonds are better donors than the CC bonds, and consequently the σ_{CH}, $\sigma^{*\ddagger}$ stabilization energy is greater than the σ_{CC}, $\sigma^{*\ddagger}$ stabilization." This is illustrated diagrammatically in Figure 5.

(iii) Adamantanone. It is now recognized that torsional and electrostatic effects are important in determining facial selectivity.[18,19] It is, however, of considerable interest to establish the magnitude of electronic effects on facial selectivity. The symmetry of 2-adamantanone makes this structure an ideal substrate[21] to investigate electronic effects on transition state energy since both faces of the carbonyl are little effected by steric effects of substitution at C5. In the presence of such C5 substituents the donor and acceptor ability of the four carbon–carbon bonds adjacent to the carbonyl can be varied without significantly altering the molecular structure.

The results of reduction experiments with $NaBH_4$ on 5-substituted adamantanones **1** with substituents at C5 that are electron withdrawing and 5-azaadamantan-2-one *N*-oxide (**2**) indicate preferential attack by the complex hydride *syn* to the substituent or nitrogen[1e,f] (Figure 6). In the case of **2**, the effect is striking, with a *syn/anti* attack ratio of 96/4 for the formation of the *anti/syn* alcohols, respectively[1e] (Table 1). Electron-donating substituents show a marginal preference for *anti* attack. Similarly *syn* facial selectivity is found in free radical reactions,[22] thermal and photocycloadditions,[23] sigmatropic rearrangements,[24] solvolytic reactions,[1f,25] and electrophilic additions[26] to methylene analogues of **1** which contain a C5 electron-withdrawing substituent.



1 **2**

Figure 6. Facial selection observed in the reduction of 2-adamantanones with $NaBH_4$.

Studies of adamantanone reduction have been interpreted by le Noble[2a] and Cieplak[1a] as consistent with the Cieplak hypothesis since the reaction occurs preferentially from the face opposite the more electron-rich σ-bond. Cieplak contends this is a result of the preferential donation from the more electron rich bond to the $\sigma^{*\ddagger}$-orbital shown schematically in Figure 7.[1e] However the effect of donation by the σ-bonds would be expected to be small since the donor σ-orbitals and the $\sigma^{*\ddagger}$ orbitals of the C–Nu forming bond are markedly different in energy and should not result in substantial stabilisation.

We now report the results of semiempirical and *ab initio* calculations of the transition states for the reduction of substituted adamantanones with AlH_3 as part of a continuing study of such reactions and provide a detailed orbital interaction analysis of the Felkin–Anh and Cieplak hypotheses which have been used to rationalize facial selectivity.

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[20] The energy level of the $\sigma^{*\ddagger}_{C-Nu}$ orbitals for axial and equatorial addition are unknown. The Cieplak hypothesis requires that ΔE_{axial} ($\sigma^{*\ddagger}_{C-Nu} - \sigma_{C-X}$) < $\Delta E_{equatorial}$ ($\sigma^{*\ddagger}_{C-Nu} - \sigma_{C-C}$).

[21] 2-Adamantanone is more rigid than cyclohexanone and less able to distort to achieve an optimal transition state geometry. The system avoids the problem present in studies of cyclohexanone of comparison of C–C and C–H.

[22] Bodepuri V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5874–5875.

[23] Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; Le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882–7883.

[24] Mukherjee, A.; Schulman, E. M.; le Noble, W. J. *J. Org. Chem.* **1992**, *57*, 3120, 3126. Lin, M. H.; Watson, W. H.; Kashyap, R. P.; le Noble W. J. *J. Org. Chem.* **1990**, *55*, 3597–3602. Lin, M. H.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 998–1000.

[25] Xie, M.; le Noble W. J. *J. Org. Chem.* **1989**, *54*, 3839–3841. le Noble, W. J.; Chiou, D.-M.; Okaya, Y. *Tetrahedron Lett.* **1978**, *22*, 1961–1962.

[26] Srivasta, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874–5875.

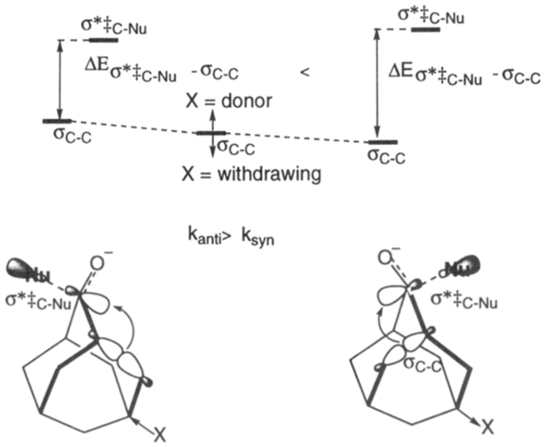

Figure 7. Cieplak preference for nucleophilic (reversion) addition *syn* to electron withdrawing and *anti* to electron-donating substituents.[27]

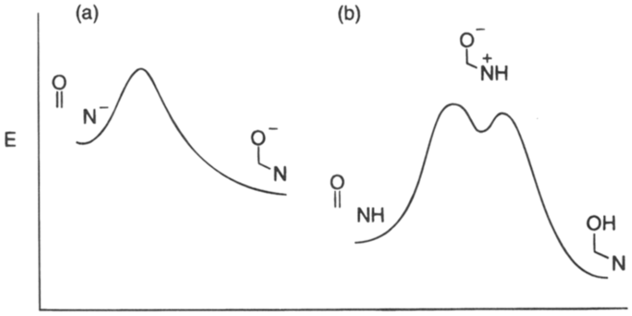

Figure 8. Reaction coordinate diagrams for reaction of an anion and a neutral nucleophile with a carbonyl.

Results and Discussion

A ketone can be attacked by a nucleophile which can be an anion or a neutral molecule. In the latter case the nucleophile must bear an acidic hydrogen to allow for the formation of a thermodynamically favored neutral product.[28] Two of several possible reaction coordinate diagrams are shown in Figure 8. Since reduction is exothermic the transition state is closer in energy and structure to the reactants ($C{=}O + N^-$ or $C{=}O$ and NH) than the products ($O^-{-}C{-}N$ or $HO{-}C{-}N$). The Hammond postulate dictates that the transition state energy and structure, in such an exothermic reaction, would be best able to be predicted from the reactant orbitals rather than from the product orbitals.[29]

(i) The Felkin–Anh Proposal. A Frontier Orbital Analysis. The Felkin–Anh proposal can be stated as follows: (i) torsional strain is minimized in the transition state, (ii) the reaction occurs from a conformation with the large group orthogonal to the carbonyl,[30] and (iii) the trajectory of the nucleophile is *anti* to the large group and past the small group (Figure 3).

The second feature of this proposal can be rationalized by frontier orbital theory. Interaction of the carbonyl π^*-orbital with an adjacent periplanar σ^*-orbital lowers the energy of the LUMO. This reduces the energy difference with the nucleophile HOMO (Figure 9). The closer in energy that the π^*_{CO} is with an adjacent σ^*-orbital the greater the lowering ($\Delta E'$) of the LUMO and the more favored the reaction will be, i.e. the HOMO–LUMO separation becomes smaller.

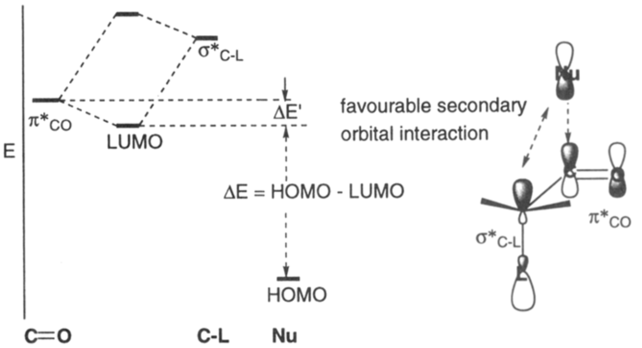

Figure 9. Interaction of the antibonding carbonyl orbital with an adjacent unoccupied σ-orbital.

Calculations have in fact shown that the energy of the LUMO is sensitive to the conformation about the Cα–C bond of an acyclic ketone.[2b] In the absence of overriding steric considerations the lowest energy transition state will have the bond with the lowest lying σ^*-orbital orientated perpendicular to the plane of the carbonyl. The diastereoisomer favored will result from attack from the opposite face of the carbonyl to the σ-bond with the lowest lying σ^* orbital and involves a staggered transition state. Acceptor substituents increase reactivity consistent with the transition state acquiring negative charge in a reaction where the rate determining step is addition of nucleophile.[31] Donor substituents on the carbonyl raise the energy of the π^*_{CO} orbital and reduce reactivity.

(ii) The Cieplak Hypothesis. The Cieplak hypothesis considers interactions of σ-bonds adjacent to the transition state with the $\sigma^{*\ddagger}$ orbital of the forming C–Nu bond. As such the hypothesis differs from the usual frontier molecular orbital analysis of reactions which treats interactions between reactant orbitals as a way of predicting transition state energy. For a facially dissymmetric carbonyl Cieplak focuses attention on the $\sigma^{*\ddagger}$ orbitals of the transition states which are a result of attack of a nucleophile at either face of the carbonyl. The interaction of adjacent donor σ orbitals with the $\sigma^{*\ddagger}$ of the forming C–Nu bond is considered to be responsible for the preferential stabilization of the transition state involving attack (removal) of the nucleophile *anti* to what

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[27] The energy level of the $\sigma^{*\ddagger}_{C-Nu}$ orbitals for anti and syn addition are unknown. The Cieplak hypothesis requires that ΔE_{anti} ($\sigma^{*\ddagger}_{C-Nu} - \sigma_{C-C}$) < ΔE_{syn} ($\sigma^{*\ddagger}_{C-Nu} - \sigma_{C-C}$).

[28] Coxon, J. M.; McDonald, D. Q. *Tetrahedron* **1992**, *48*, 3353–3364.

[29] It is less satisfactory to predict the energy of the transition state from a frontier orbital analysis of the products in an exothermic reaction.

[30] If L is an electronegative substituent (e.g. Cl) with a low lying σ^*-orbital, in the absence of overriding steric effects, the preferred face from which nucleophilic attack occurs is *anti* to the Cl which will be preferentially orthogonal to the carbonyl at the transition state; the transition state is staggered and there is a favorable secondary orbital interaction of the nucleophile and the adjacent antiperiplanar σ-bond. By contrast, attack syn to the σ^*-orbital will result in eclipsing torsional interactions and unfavorable secondary orbital interactions between the nucleophile and σ^*-orbital. An antibonding secondary orbital and eclipsing interaction disfavors synperiplanar attack. The most favorable transition state has the substituent with the lowest energy σ^*-orbital aligned antiperiplanar to the nucleophile and in the plane of the π^*-orbital. Application of the rule requires a knowledge of the energy of the σ^*-orbitals, often inversely related to the size of a group: large < medium < small. The σ^*-orbital is stabilized by proximate electron-withdrawing groups. For the reaction of a series of acyclic aldehydes with lithium enolates, Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353–3361, concluded that the preference for substituents to be anti to the incoming nucleophile is in the order: MeO > t-Bu > Ph > i-Pr > Et > Me > H, a sequence determined by a balance of the σ^*-orbital energies and steric effects.

[31] Norman, R. O. C.; Coxon, J. M. *Principles of Organic Synthesis*, 3rd ed., Blackie, Chapman and Hall: London, 1993; p 88.

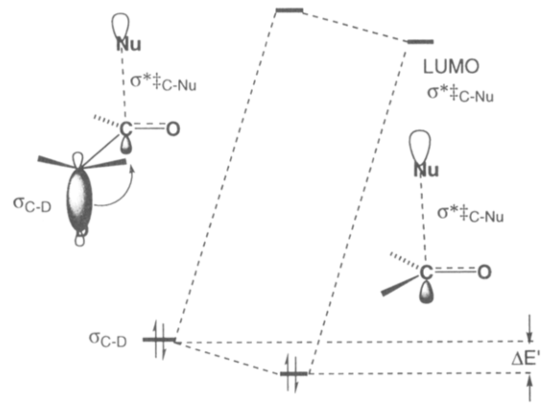

Figure 10. Donation by an adjacent antiperiplanar C–D into the $\sigma^{*\ddagger}{}_{C-Nu}$ lowers the energy of the transition state.

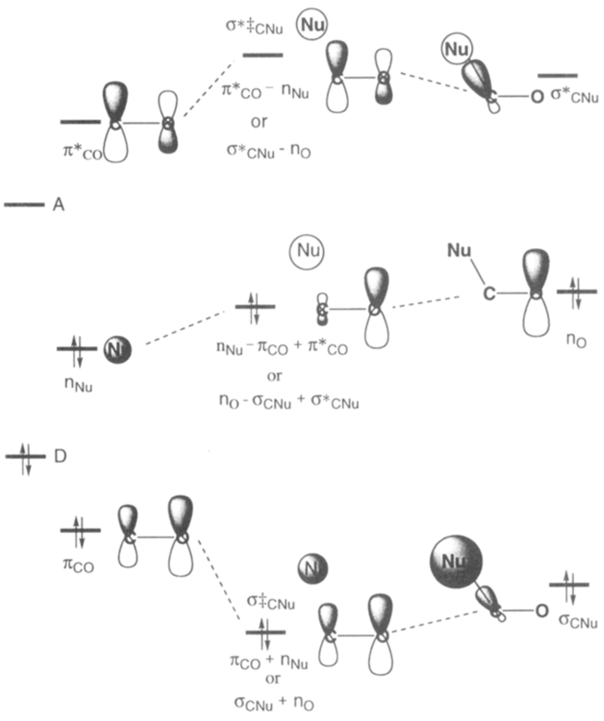

Figure 11. Molecular orbitals associated with nucleophilic addition to a carbonyl.

he considered to be the best α-donor.[32] Figure 10 shows that the mixing of the adjacent antiperiplanar C–D (D = donor) with the $\sigma^{*\ddagger}{}_{C-Nu}$ of the transition state lowers the energy of the transition state. Houk[1c] has shown from *ab initio* calculations that electron donor substituents are disfavored electronically from being orthogonal to the carbonyl.

Since the adjacent donor σ-orbitals differ greatly in energy from the $\sigma^{*\ddagger}$ orbitals, the mixing of these particular orbitals would not give rise to significant stabilization of the transition states.

The effect of substituents at C5 in adamantanones on facial selectivity offers the potential to measure the magnitude of an electronic effect, provided that steric, torsional, and electrostatic effects can be assumed to be invariant.

Let us examine the molecular orbitals of the transition state for nucleophilic attack on a carbonyl in more detail. Figure 11 shows on the left the frontier MO's of a nucleophile (Nu) and a carbonyl group. The orbitals of the transition state for nucleophilic addition may be constructed by mixing the reactant orbitals. The three orbitals in the center of the diagram can be correlated with reactant orbitals as follows: (1) the lowest orbital is the π orbital into which some of the Nu lone pair orbital has been mixed in a bonding fashion. The highest energy orbital is the antibonding admixture of the π* orbital and the lower energy lone pair orbital. The central orbital is the Nu lone pair which has mixed with the π in an antibonding fashion and, simultaneously, with the π* orbital in a bonding fashion.

Alternatively, the transition state orbitals can be correlated with the product orbitals shown on the right of the diagram. The σ and σ* of the bond formed between nucleophile and the carbon of the carbonyl group and the lone pair on oxygen are the appropriate product orbitals which can be mixed to form the transition state FMOs.

We have previously reported the study[17] of the potential energy surface of the reaction of AlH_3 with formaldehyde. The saddle transition structure for this reaction is computed to be a four-center transition state. By removing the AlH_2^+ fragment from this structure and performing a single point calculation of the organic fragment (and separately AlH_2^+) we obtain molecular orbitals that might reflect the molecular orbitals for reaction H^- with formaldehyde at such a point in a gas phase reaction. It is not possible by normal methods to obtain such a structure as a stationary point since reaction of a neutral molecule with a charged species results in a spontaneous reaction without a transition barrier. The orbitals corresponding to the transition state orbitals of Figure 11 are shown in Figure 12. The node in the HOMO is between the carbon and oxygen.

The facility for interaction with the σ*C–Nu and the $\sigma^{*\ddagger}$C–Nu orbitals will be dependent on the relative orientation of the donor and will be at a maximum when these orbitals are aligned *syn* or *anti* periplanar. Referring to Figure 13, a donor substituent attached to the carbon α to the carbonyl will interact with the $\sigma^{\ddagger}{}_{CNu}$ orbital to some extent, causing destabilization, and with the $\sigma^{*\ddagger}{}_{CNu}$ orbital to give stabilization (see also Figure 11). However, a donor will interact more strongly with the $\pi^*{}_{CO}$ of the reactant carbonyl, so that the transition state will be stabilized less than the reactants by a donor. This is the origin of the deactivation of carbonyl groups by electron-donating substituents. The deactivation will be minimized when the σ_{CD} orbital is antiperiplanar to the $\sigma^{*\ddagger}{}_{CNu}$ orbital. This results in a staggered transition state, and one which has the nucleophile *anti* to the best donor. Looking from the adduct side, a donor substituent will interact strongly with the $\sigma^*{}_{CNu}$ orbital of the adduct, so in the reverse reaction, the ability of the donor to accelerate the reaction will depend upon the relative energies of the $\sigma^*{}_{CNu}$ and the $\sigma^{*\ddagger}{}_{CNu}$ orbitals.

Figure 13 shows the orbitals in question, the donor orbital of a bond to the α carbon, and the transition state $\sigma^{\ddagger}$ and $\sigma^{*\ddagger}$ orbitals. Why does a nucleophile like to attack *anti* to the D? The preferred *anti* arrangement of geminal doubly occupied σ orbital of the donor and vacant σ* or $\sigma^{*\ddagger}$ orbitals arises because the overlap is larger than that for the *syn* arrangement.

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[32] A Cieplak analysis of substituent effects on $\sigma^{*\ddagger}$-orbital might therefore be expected to predict better reactivity for fragmentation of the zwitterion in path b since reaction from the zwitterion is exothermic. This requires a description of the molecular orbitals of the zwitterion which would be expected to be somewhat similar to the transition state orbitals.

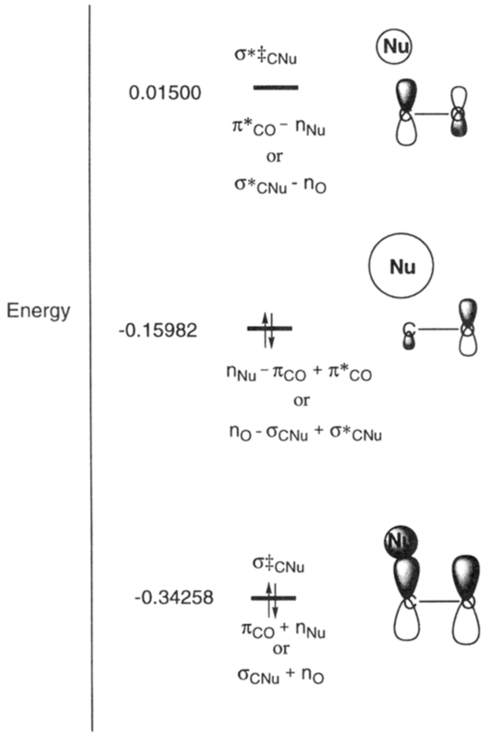

Figure 12. Molecular orbitals at the four-center transition state geometry for AlH$_3$ addition to formaldehyde but after removal of AlH$_2^+$ (3-21G*).

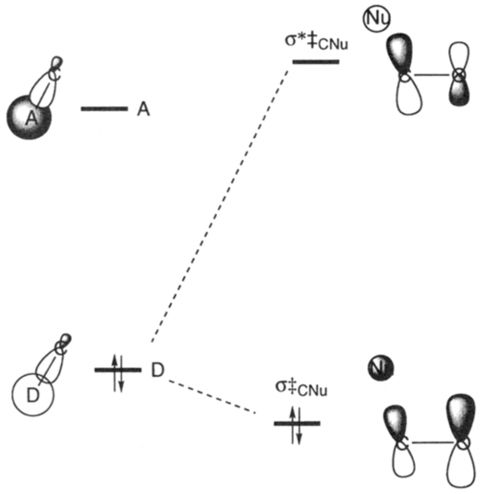

Figure 13. Interaction of a donor ligand on transition state orbitals.

At the same time, but not pointed out by Cieplak, there is less closed shell repulsion between the donor orbital and the σ orbital in the *anti* arrangement than in the *syn*. In fact, these are two of the interactions which cause the transition state, or indeed, any vicinal bonds to prefer to be *anti* rather than *syn*. When all vicinal bonds on a substituted ethane are *syn*, an energy maximum, the eclipsed conformation, occurs. When all vicinal bonds on a substituted ethane are *anti*, an energy minimum is obtained. By aligning the α-donor group *anti* to the $\sigma^{*\ddagger}$, Cieplak also aligns the two filled orbitals *anti*. Both of these operate simultaneously and in the same direction.

The usual alignment of an α-donor *anti* to the forming bond can also be understood in this diagram. This maximizes the overlap of the σ^* orbital with the $\sigma^\ddagger$ orbital. An α bond, no matter whether it is to a donor or to an acceptor, always prefers to be *anti* to the forming bond to maximize stabilizing filled–vacant orbital interactions and to minimize filled–filled orbital interactions.

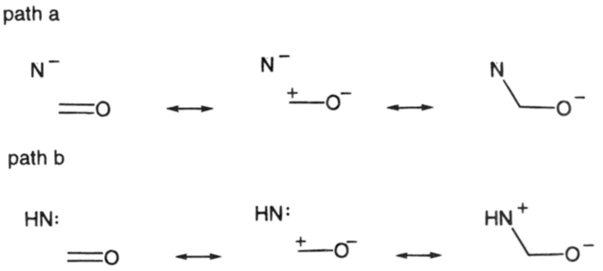

Figure 14. Valence bond representation of nucleophilic addition (N$^-$ *path a* or HN: *path b*) to a carbonyl.

These considerations show that the orbital interactions cited by Cieplak cannot be the controlling orbital interactions in nucleophilic additions. Why, then, is the Cieplak hypothesis nevertheless successful in so many cases? It is important first of all to acknowledge that there are a number of effects operating in nucleophilic additions, and no one of them controls stereoselectivity in every case.[18c] The question is to determine the relative magnitudes of these and to have some useful generalizations about which effects operate in different types of molecules.

Either the molecular orbital or the valence bond method may now be used to analyze the interaction of substituents on the reactant, products, and transition states. Substituents which stabilize the transition state more than reactants will accelerate the reaction, while those which stabilize the reactant more than transition state will slow down the reaction. In valence bond theory, the reactants are represented by a nucleophile lone pair as an anion (path a) and a neutral nucleophile (Figure 14, path b), and the carbonyl by the covalent and ionic resonance structures.[33]

The reactant may be considered as a polarized carbonyl bond, reflected in approximately equal contributions of covalent and ionic resonance structures. As the reaction proceeds, the contribution of both of these is replaced by the structure at the right of the diagram. Because of the greater concentration of positive charge on carbon in the reactant, donor substituents stabilize reactants more than transition state. In summary donors' substituents deactivate carbonyls.

Cieplak acknowledged that the reactivity effect of a donor might be different from its stereochemical effect. What about the case where a donor orbital is present and the only question is which face of the carbon group is attacked more readily?

(iii) Calculations on the Reduction of 5-Substituted Adamantanones. Nucleophilic attack at adamantanone is necessarily axial to one ring containing the carbonyl and equatorial to the other. The geometry of the transition structure at the reaction site is therefore between that associated with axial and equatorial addition to cyclohexanone. Furthermore torsional effects in the carbonyl containing rings at the transition state of nucleophilic addition to adamantanone are compromised by the symmetry of the system allowing electronic effects to dominate in determining facial selectivity.

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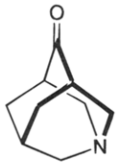
[33] le Noble has pointed out a similarity between Cieplak transition state stabilization and Winstein's proposal of σ assistance in the formation of carbocations.[1f,2a] In the Cieplak model, neighboring σ-electrons delocalize into the $\sigma^{*\ddagger}$-orbital which forms with the nucleophile; in Winstein's carbocation model, the σ-electrons delocalize into a vacant p orbital.

Table 2. Comparison of Semiempirical and *ab Initio* Results

	AM1 (kcal/mol)	3-21G* (au)	6-31G*sp (au)
1	−67.321	−451.17009	
1−AlH_3 complex	−72.107	−701.57380	
1−AlH_3 transition state	−49.233	−701.54344	
2	−18.535	−549.41770	
2−AlH_3 complex	−20.321	−791.81599	
2−AlH_3 *syn* transition state	1.224	−791.78833	−796.09302
2−AlH_3 *anti* transition state	1.408	−791.78638	−796.08990

We now report semiempirical and *ab initio* calculations of the transition structures of a series of 5-substituted adamantanones **1** and 5-azaadamantanone *N*-oxide (**2**) resulting from addition of aluminum hydride (AlH_3).[34] Calculations were carried out using the SPARTAN (AM1) and GAUSSIAN 92 programs.[35] Transition state geometries were located with full optimization with a 3-21G* or 6-31G* basis set and in each case were characterized by having only one imaginary vibrational frequency.

AM1 calculations of the *syn* and *anti* transition states for the addition of AlH_3 to 5-substituted adamantanones **1** closely parallel experimental results with $NaBH_4$ (Tables 1 and 2). Electron-withdrawing groups at C-5 favor attack *syn* to the substituent and result in excess *anti* alcohol. With the electron-donating trimethylsilyl group a marginal preference for *anti* attack is observed for $NaBH_4$. Our calculations predict results in this direction. The reduction of the free amine **3** is an exception to the pattern that electron-donating groups favor *anti* attack (*syn*/*anti* attack 62/38). Semiempirical AM1 calculations predict a 33/67 ratio; however, if complexation occurs to give **4** the predicted ratio (60/40) is virtually identical to experiment ($NaBH_4$: 62/38).



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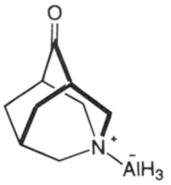

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AM1 and PM3 calculations predict a modest *syn*/*anti* preference (58/42, 61/39) for reduction of **2** and do not reproduce experiment. However, the *ab initio* results predict the high selectivity (3-21G* *syn*/*anti* 91/9; 6-31G* 97/3) observed by experiment ($NaBH_4$ reduction is 96/4).

The 2-adamantanone structure calculated at the 3-21G* level of theory shows no evidence of unsymmetrical ring distortion. Inspection of the 3-21G* calculated transition state for AlH_3 addition to unsubstituted adamantanone reveals that flattening occurs on the ring undergoing axial attack, i.e., the $C_{C=O}$ bends away from the direction of the approaching nucleophile from its initial position between the two bridgehead hydrogens in adamantanone. Flattening can be determined by the angle defined by the $C_\alpha C_{C=O}C_{\alpha'}$−$C_\beta C_\alpha C_{\alpha'}$ planes, which is 135° in the ring undergoing axial attack (Figure 15). The more flexible cyclohexanone AlH_3 transition state flattens to a corresponding angle of 142° in axial attack.[16] The internal C_α−$C_{C=O}$−$C_{\alpha'}$−$C_{\beta'}$ dihedral angle is also effected by the flattening and is 50° in the axial ring, compared to 42° in the axial cyclohexanone transition state. In adamantanone, the bending of the $C_{C=O}$ away from the nucleophile causes the ring undergoing equatorial attack to pucker, which also occurs in the equatorial attack transition state of cyclohexanone. However, ring puckering is greater in the adamantanone transition state, as measured by the 115° angle defined by the planes $C_\alpha C_{C=O}C_{\alpha'}$−$CC_\alpha C_{\alpha'}$ with an internal C_α−$C_{C=O}$−$C_{\alpha'}$−$C_{\beta'}$ dihedral angle of 69° compared to the corresponding measurements of 119° and 65° in the cyclohexanone equatorial transition state. The O−$C_{C=O}$−C_α−H dihedral angle is 32°, compared to 34 and 30° in axial and equatorial cyclohexanone transition states,[16] indicative of a degree of torsional strain which is between the latter two structures.

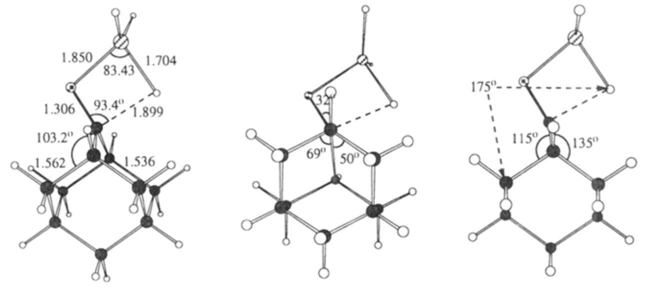

Figure 15. 3-21G* transitions state geometry for reduction of adamantanone (**1**, X = H) with AlH_3.

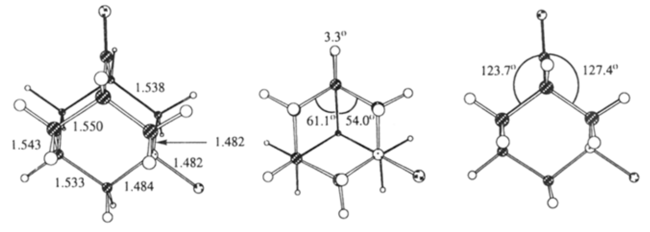

Figure 16. 3-21G* geometry of **2**.

A measure of the ability of the adjacent σ-bonds to participate in a hyperconjugative interaction with the transition state orbitals is given by the H_{Nu}−$C_{C=O}$−C_α−C_β dihedral angle of 175° which is midway between the corresponding value for the axial (179°) and equatorial (170°) transition states for cyclohexanone reduction.

(iv) Calculations on the Reduction of 5-Azaadamantanone *N*-Oxide. The *N*-oxide group in **2** causes a flattening of the ring which contains the N and bending of the carbonyl group away from the nitrogen (3-21G*) (Figure 16). Since the positively charged N withdraws electrons from the proximate *syn* C_α−C_β bonds, the C_α−C_β bonds in the ring *anti* to the N have more electron density and better interact with the carbonyl. The ring flattening increases the ability for preferential hyperconjugation of the carbonyl with the electron-rich *anti* C_α−C_β bond by improving the antiperiplanar relationship. The increased donor ability and better orbital alignment with the carbonyl orbitals results in uneven orbital extension and pyramidalization of the carbonyl.[1c] The π-orbital extension is predicted to occur by interac-

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[34] The reductions of **1** and **2** with $NaBH_4$ are known (Table 1).[1f] Since product ratios for reduction of 4-*tert*-butylcyclohexanone with AlH_3 and $NaBH_4$ closely parallel experimental results, the reactions of adamantanones with $NaBH_4$ are considered a suitable model for the reaction with AlH_3.

[35] SPARTAN (Version 2.1, Wavefunction, Inc., 18401 Von Karman, Irvine, CA 92715) and GAUSSIAN and MOPAC programs were used: AM1: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. Gaussian 92: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, M. A.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1992.

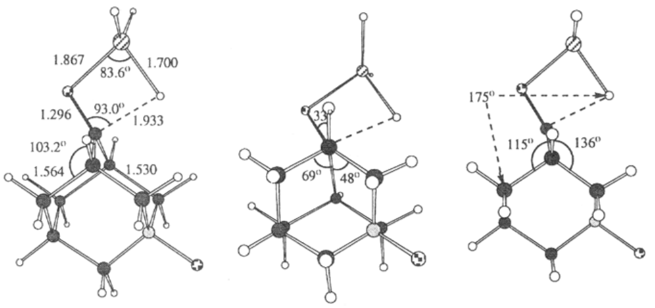

Figure 17. 3-21G* transitions state geometry for *syn* reduction of **2** with AlH_3.

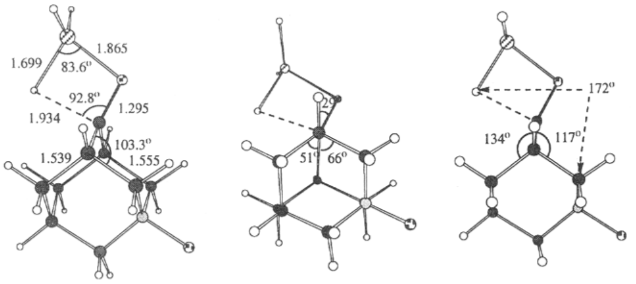

Figure 18. 3-21G* transitions state geometry for *anti* reduction of **2** with AlH_3.

tion with the better aligned $C_\alpha-C_\beta$ bond which is *anti* to the nitrogen and also corresponds to the more electron-rich bond. The interaction is antibonding and extension toward the *syn* face results, consistent with our calculations.[36] Relief of torsional strain may also play a role in the bending, since the bridgehead $H-C_\alpha$ bond no longer eclipses the carbonyl.

The calculated transition states for both *syn* and *anti* attack at **2** (Figures 17 and 18) are earlier along the reaction coordinate than the adamantanone transition state, as measured by the longer $H_{Nu}-C_{C=O}$ distances (*syn* 1.933, *anti* 1.934, unsubstituted, 1.899 Å) and shorter $Al-H_{Nu}$ lengths (*syn* 1.700, *anti* 1.699, unsubstituted 1.704 Å). For *syn* addition the transition state exhibits minor additional flattening (but the same puckering), and an increase of the $O-C_{C=O}-C-H$ dihedral angle from 32 to 33°, indicative of slightly less torsional strain. By contrast, the transition structure for *anti* attack undergoes less ring flattening and less puckering than its unsubstituted counterpart and has a $O-C_{C=O}-C-H$ dihedral angle of 29°, consistent with an increase in torsional strain. The transition state for *syn* attack of **2** is undiminished in its ability to achieve the antiperiplanar relationship ($H_{Nu}-C-C-C$ dihedral angle 175°), but the *anti* isomer has a dihedral angle of 172°.

The enthalpy difference between the *syn* and *anti* transition states favors the *syn* by 1.2 kcal/mol(3-21G*). This enthalpy difference can be factored into three components: distortion of the 5-azaadamantanone *N*-oxide skeleton to the transition state geometry, AlH_3 distorted to the transition state geometry, and an interaction enthalpy between these distorted fragments (electronic and steric). The relative contributions of these factors can be calculated by removing one component and calculating the enthalpy with a fixed geometry of the other (Table 3). The removal of AlH_3 shows the *syn* ketone fragment to be more stable than the *anti* by 0.9 kcal/mol. Distortions of the AlH_3 fragment, obtained after removal of the ketone component, show a small enthalpy difference, (0.2 kcal/mol favoring *anti* attack). The residual enthalpy contribution is due to interaction of the fragments. Assuming a negligible steric interaction, its origin is considered electronic, 0.6 kcal/mol, favoring *syn* attack.

Table 3. Difference in Energy of Reaction Fragments for *Syn* and *Anti* Addition to 2

	ΔE (*anti* − *syn*) (kcal/mol)
syn favored by	1.23
distorted adamantanone	0.87
distorted AlH_3	−0.21
(interaction energy)	0.57

Each of the calculated transition states showed an elongation of the C−C bonds which are antiperiplanar to the incoming nucleophile. Using the calculated (3-21G*) $C_\alpha-C_\beta$ bond length of adamantanone (1.546 Å) as a reference, the transition states of adamantanone and the amine oxide **2** (*syn*) with AlH_3 show an extension of the antiperiplanar bonds to 1.562 (1.0%) and 1.564 (1.16%), respectively, with no lengthening (in fact a shortening) of the $C_\alpha-C_\beta$ bonds on the opposite face of the carbonyl (Figures 15 and 17). The *anti* transition state of **2** shows a corresponding $C_\alpha-C_\beta$ bond lengthening to 1.555 Å (0.58%) (Figure 18). The $C_{C=O}-C_\alpha$ bond shortens from 1.514 to 1.500 Å (0.93%) and 1.502 Å (0.80%) for the parent and *syn* transition states, respectively. The *anti* amine oxide transition state shortens to 1.504 Å (0.66%). Smaller bond angles were calculated for the $C_{C=O}-C_\alpha-C_\beta$ angles on the side away from the nucleophile, diminished from 108.8° in adamantanone to 103.2° (0.54%) in the adamantanone and *syn* transition states, and to 103.3° (0.54%) in the *anti* transition state (Figures 15, 17, 18).

The calculated transition states for *syn* and *anti* addition of AlH_3 to **2** show a greater degree of carbonyl bending than is found for adamantanone. The degree of hyperconjugation will be controlled by orbital overlap and electron availability. The $H_{Nu}-C_{C=O}-C_\alpha-C_\beta$ dihedral angles calculated for the *syn* and *anti* transition states is indicative of the ability of the $C_\alpha-C_\beta$ bonds to participate. In the *syn* and *anti* transition states of the *N*-oxide the calculated angles are 175° and 172°, respectively, indicating a preferred geometry for the former. A measure of hyperconjugation at the transition state is the degree of extension of the $C_\alpha-C_\beta$ bond length which is antiperiplanar to the approaching nucleophile. These are calculated to be unequal for the *syn* and *anti* transition states, with the *syn* transition state showing greater bond length extension (to 1.564 Å, 1.16%) than the anti (to 1.555 Å, 0.58%). The greater hyperconjugation in the *syn* transition state reflects the greater electron density in its antiperiplanar $C_\alpha-C_\beta$ bonds. The *anti* transition state has both a poorer orbital alignment with the adjacent antiperiplanar $C_\alpha-C_\beta$ bonds which are poorer electron donors and exhibits more torsional strain than the *syn* transition state as determined by the O−C−C−H dihedral angles calculated at 29° and 33°, respectively. These conclusions are supported by the significant difference in enthalpy found in the azaadamantanone *N*-oxide, and AlH_3 components of the transition state and the interaction enthalpy. The enthalpy difference of the ketone fragments compares both the better hyperconjugative interactions in the *syn* transition state and its

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[36] The uneven orbital extension can be observed by plotting the value of the LUMO coefficient at a given distance from the atom onto an electron density surface, as supported by SPARTAN.

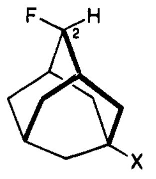
smaller torsional strain. The better interaction enthalpy is consistent with the more favorable antiperiplanar relationship of the *syn* (175°) compared to the *anti* (172°).

For AlH_3 addition to cyclohexanone *ab initio* calculations[37] of the enthalpy reaction surface result in transition state structures which similarly show lengthening of the σ-bonds antiperiplanar to the nucleophile.[38] Furthermore visualisation of the $\pi_{C=O}$ MO surfaces of the transition orbitals for axial addition reveals participation of the $C_\alpha-H_{ax}$ bond, but not the $C_\alpha-C_\beta$ in axial attack; the transition state for equatorial addition shows $C_\alpha-C_\beta$ bond mixing, but not $C_\alpha-H_{ax}$ in the HOMO.[39] Similar extensions are observed in the cyclohexanone LiH transition states.[1c]

An *ab initio* study of the 2-adamantyl cation[40] supports the conclusion that a more parallel alignment of the carbonyl π orbitals with $C_\alpha-C_\beta$ bonds can result in stabilization. The "classical" structure (C_{2v} symmetry) was calculated as a transition state, with the ground state geometry having a significant bending of the $C_\alpha-C^+-C_\alpha$ bridge toward one face of the cation (17.3°). Pyramidalization of the C^+-H bond occurs in the same direction (11.1°). The $C_\alpha-C_\beta$ bonds were unequal (1.542 and 1.603 Å (6-31G*), with the longer on the side closer to the C^+ bridge. These calculations support the proposal that, in the cation, preferential C−C hyperconjugation exists on one side of the ring, consistent with NMR data.[41] Since hyperconjugation is more important with increasing positive charge, we expect less bond lengthening in the transition state of AlH_3 reduction than in the 2-adamantyl cation, but more than would be found in the ground state ketone, if it were constrained to similar geometry. To test this hypothesis we have calculated the 3-21G* geometry of ground state ketone **2** which has been distorted by bending the carbonyl to the same degree as is found in the transition states for reduction. When **2** is deformed to resemble the *syn* AlH_3 transition state (O−C−C−H constrained to 32.6°, as in Figure 17), the resulting $C_\alpha-C_\beta$ bond lengths are 1.555 and 1.533 Å on the rings *anti* and *syn* to the nitrogen, respectively. The 1.555 Å bond length corresponds to 0.58% bond extension, compared to 1.564 Å (1.16%) lengthening found in the *syn* transition state (Figure 17). Deforming ketone **2** by bending the carbonyl in the other direction to resemble the *anti* AlH_3 transition state (O−C−C−H constrained to 29.1°, as in Figure 18) showed no lengthening of the $C_\alpha-C_\beta$ bonds (1.543 Å *anti* and 1.545 Å *syn*) from the values of **2**. The degree of hyperconjugation therefore depends on the extent of positive charge on the carbonyl carbon, the electron density in the participating bonds, and the degree of overlap.

Additional evidence for hyperconjugation in the transition state for reactions of **1** and **2** can be obtained by observation of the surface of the bonding MO which involves formation of the incipient $H_{Nu}-C_{C=O}$ bond. The favored *syn* amine oxide transition state shows hyperconjugative participation of the more electron-rich $C_\alpha-C_\beta$ bond with the forming bond; the *anti* counterpart shows participation of the electron-deficient $C_\alpha-C_\beta$ bond and the amine oxide functional group, all of which are antiperiplanar. This alignment is consistent with NMR chemical shift and coupling evidence in adamantanones.[42]

A wide range of chemical shifts and five-bond long-range coupling is observed[43−45] for derivatives of **5** but not **6** indicative of optimal alignment for through-bond transmission in the former.



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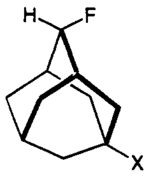

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Electrostatic effects have been implicated as a stereoinductive factor in reductions which contain remote polar substituents.[1c,14,18,19] Calculations which position charge at the location of the attacking nucleophile in the transition state can sometimes account for transition state enthalpy differences. In the case of the *syn* and *anti* transition states resulting from AlH_3 addition to **2**, the favored *syn* attack transition state resulting has a higher dipole moment (5.80 D) than the *anti* (4.61 D), indicating that there is less charge separation in the latter. Electrostatic effects do not appear to be major contributors in the stabilization of the *syn* over *anti* transition state from AlH_3 addition to **2**. If electrostatic effects played a significant role, a decrease in the stereoselection should be observed upon changing to a more polar solvent. Experimental results showed no decrease

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(37) A four-center cyclic transition state is located on the enthalpy surface for addition of AlH_3 to aldehydes and ketones. Since carbonyl reduction occurs with AlH_3, but generally not with LiH, this reaction has been proposed as complimentary to the latter for modeling facial selection in these reactions.[16,17]

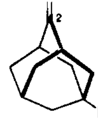
(38) In axial attack the $C_\alpha-H_{ax}$ bond is aligned with the $\pi_{C=O}$ orbital ($H_{Nu}-C_{C=O}-C_\alpha-C_\beta$ dihedral angle 179°). The $C_\alpha-C_\beta$ bond aligns better in the equatorial attack transition state ($H_{Nu}-C_{C=O}-C_\alpha-C_\beta$ dihedral 170°).[16]

(39) Experimental evidence of bond lengthening and shortening consistent with this hyperconjugation has been reported for crystal structures of cyclohexanone complexes, Laube, T.; Hollenstein, S. *J. Am. Chem. Soc.* **1992**, *114*, 8812−8817. Hyperconjugative has been implicated in the Diels−Alder reaction of 5-substituted cyclopentadienes with ethylene. Reaction occurs faster at the face of the diene which has the antiperiplanar orientation of the best donor ligand and the forming ring bonds in the transition state, Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136−1144. A semiempirical investigation revealed transition state bond extensions of the 5-substituent which is *trans* to the forming ring bonds. Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *48*, 651−654. Coxon, J. M.; McDonald, D. Q.; Steel, P. J. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT; 1994; Vol. 3, pp 131−166. No corresponding evidence was found for transition states of methanol addition to substituted 7-norbornanones.

(40) Dutler, R.; Rauk, A.; Sorensen, T. S.; Whitworth, S. M. *J. Am. Chem. Soc.* **1989**, *111*, 9024−9029.

(41) The preferential hyperconjugation provides a lower energy structure than is obtained by the more extended double hyperconjugation of the transition state cation. A MO surface was presented which showed that hyperconjugation of the C^+ with the adjacent C−C bond is almost entirely on one side of the molecule.

(42) A linear correlation between the C2 chemical shift and the magnitude of the deuterium isotope effect (change in chemical shift through four bonds) for several 5-deuterated derivatives of adamantanone (X = S; O; $C(CN)_2$; CH_2; $-OCH_2CH_2O-$; −Cl, −Cl; −Br, −Br; $-SCH_2CH_2S-$; −H, −H; $-CH_2CH_2-$), is interpreted as evidence that hyperconjugative interactions exist in the ground state in this system. Vinkovic, V.; Mlinaric-Majerski, K.; Marinic, Z. *Tetrahedron Lett.* **1992**, *33*, 7441−7444.



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in stereoselection in $NaBH_4$ reduction upon changing from methanol to water, or even saturated sodium chloride.[1e]

Conclusion

Ab initio calculations have provided structural evidence for hyperconjugative delocalization in the transition state for reduction of 2-adamantanones with AlH_3. The calculations show bond length changes in a four-center transition state which are consistent with hyperconjugative delocalization in the transition state. The $C_\alpha-C_\beta$ bond which is antiperiplanar to the incoming nucleophile is lengthened, and ring distortions consistent with torsional strain minimization and improvement of orbital alignment are present. These effects are also found in the *syn* and *anti* transition states of 5-azaadamantanone *N*-oxide with AlH_3. The greater bond lengthening occurs for *syn* addition consistent with the greater electron density in the adjacent periplanar bond and the more linear geometry of the bond and the nucleophile. The favored (*syn*) structure has an alignment of the nucleophile with the more electron-rich $C_\alpha-C_\beta$ bonds which is closer to the ideal antiperiplanar orientation and with less torsional strain than is found in the transition state for *anti* attack. The transition state MO surfaces which involve the incipient bond show an interaction with the antiperiplanar $C_\alpha-C_\beta$ bonds. The studies show that electronic as well as torsional effects contribute to facial selection and define the origin of this electronic effect.

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