

THEORETICAL INTERPRETATION OF 1-2 ASYMMETRIC INDUCTION. THE IMPORTANCE OF ANTIPERIPLANARITY

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ABSTRACT. — A detailed M. O. study, which takes into account the counterion, the solvent effect and the stereoelectronic control of the reagent's approach, has been made for the following reactions: ($\text{MeCHCl-CHO} + \text{H}^-$) and ($\text{Et-CHMe-CHO} + \text{H}^-$). *Ab initio* (STO-3G) calculations show that there are at most 6 low-energy transition states, the geometries of which are very similar to those considered by Felkin and his co-workers. A qualitative interpretation of Felkin's model, based on perturbational arguments, is suggested which stresses the importance of the *antiperiplanar effect*: a transition state is stabilized if the incipient bond between the nucleophile and the carbonyl group is antiperiplanar to an adjacent sigma bond.

Except for the works of Ruch-Ugi² and of Salem³, all the other studies of 1-2 asymmetric induction⁴⁻⁹ in nucleophilic additions to chiral carbonyl compounds take into account only a limited number of conformers of the chiral substrate. This drastic simplification is a practical necessity, if one wishes to avoid a mathematical treatment which may mask the physical nature of the problem. However, one may wonder whether this restriction to a few conformers is theoretically justified. If it is so, which conformers should be retained and for what reasons?

It may be recalled here that the conformers considered in Cram's, Cornforth's, Karabatsos's and Felkin's models are all different. In Cram's model⁴ the only conformer retained is that in which the CO group bisects the adjacent CM and CS bonds (L, M, S being respectively the large, medium and small substituents on the chiral center). The major product results from a nucleophilic attack on the side of the small substituent (1). Cornforth's model⁵ is a variant of Cram's model which is used when one of the L, M, S substituents is a highly polar group (e. g. a halogen atom). It is assumed that, in order to

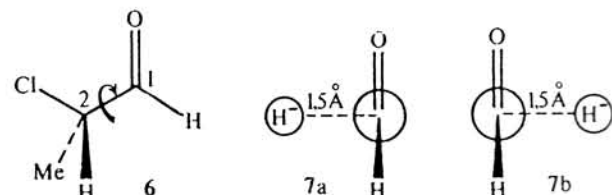
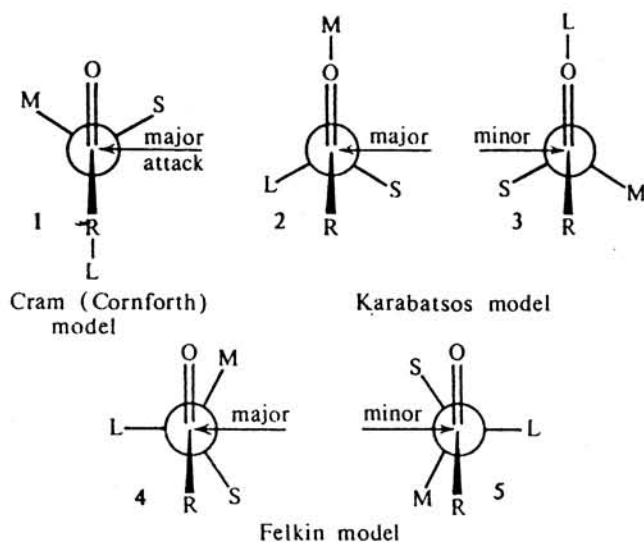
minimize dipolar interactions, the halogen and the oxygen atoms will stay as far apart as possible. In other words, the halogen atom will play the role of the L substituent.

Karabatsos' model⁶ uses the 2 conformers in which the carbonyl group eclipses either the CM or the CL bond (2 and 3). It is supposed that the nucleophilic reagent always approaches from the less hindered side. In Felkin's model⁷, the favoured transition states are considered to be those where the incipient bond between the carbon atom and the nucleophilic reagent bisects the CM and CS bonds (4 and 5). Steric and torsional repulsions between the reagent and the substrate are then at a minimum.

Reaction of 2-chloropropanal with a hydride ion (Fig. 1)

To compare these models and to see if it is theoretically justified to select only a few conformers of the carbonyl compound, we have proceeded in the following manner.

Consider the 2-chloropropanal molecule 6. When the C1-C2 bond is rotated by increments of 30°, 12 conformers of 6 are generated. Each conformer gives rise to two diastereoisomeric transition states represented by 7a and 7b, in which a hydride ion is placed at 1.5 Å from the carbonyl bond in a direction perpendicular to the CO axis. Twenty-four diastereoisomeric transition states are thus obtained and their energies calculated by an *ab initio* (STO-3G) method¹⁰. Standard geometries¹¹ are used throughout, unless otherwise specified.



In Figure 1, the relative energies of the different transition states have been plotted against the rotation angle. The full (dashed) line corresponds to the transition

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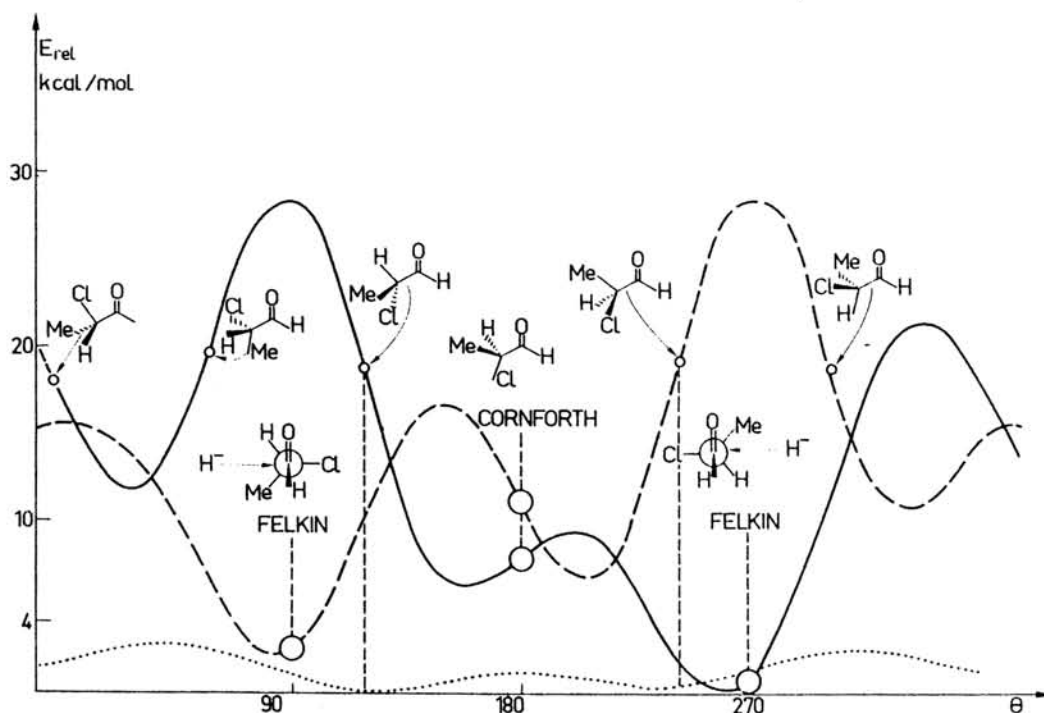


Figure 1. — Reaction of H^- with $\text{Me}-\text{CHCl}-\text{CHO}$. Plot of transition states energies versus θ , angle of rotation around $\text{C1}-\text{C2}$. Full (dashed) line corresponds to transition states leading to the major (minor) product, according to Cornforth's rule. Dotted curve: conformational energy curve of $\text{Me}-\text{CHCl}-\text{CHO}$.

states which lead to the major (minor) product, according to Cornforth's rule⁵. Now, these curves are nothing else than the conformational energy curves of the diastereoisomeric "supermolecules" (chloropropanal + hydride ion). It is therefore necessary to check whether our method of calculation is able to reproduce at least qualitatively various rotational barriers. Using standard geometries, we have found for acetaldehyde a barrier of 1065 cal/mol, in good agreement with the experimental value (1100 ± 60 cal/mol)¹². For 2-chloropropanal and 2-methylbutanal, the calculated relative minima correspond to conformations where the carbonyl group eclipses an adjacent sigma bond (Fig. 1 and 2, dotted curves), in good agreement with the conformational analysis of this type of compounds¹³.

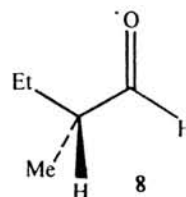
Being now reasonably sure that the calculated extrema are not artefacts, we return to the full and dashed curves of Figure 1. It is clear that the Cornforth transition states contribute but little to the formation of the final products, as they are quite energetic (more than 4 kcal/mol of relative energy). Assuming a Boltzmann distribution for the transition states, this means that less than one molecule, out of a thousand, goes through the Cornforth transition states. On the other hand, the two Felkin transition states are among the most stable.

It might be argued that this stability is due to a smaller coulombic repulsion between the chlorine atom and the hydride ion. To remove this objection, the same calculations are performed with 2-methylbutanal **8** as the chiral substrate.

Reaction of 2-methylbutanal with a hydride ion (Fig. 2)

Again, it can be seen (Fig. 2) that the Felkin transition states are practically localized on the relative minima,

while the Cram transition states and the Karabatsos transition states lie much higher (more than 2.7 kcal/mol of relative energy). In other words, less than 1% of the molecules goes through the Cram or the Karabatsos transition state. The 6 hachured areas in Figure 2 correspond to transition states having no more than 2.7 kcal/mol of energy above the more stable one. It may be noted that these areas are centered on "Felkin-type transition states", i. e. transition states where the incipient $\text{C1}-\text{H}^-$ bond is antiperiplanar to an adjacent sigma bond.



The foregoing calculations have been done for gas-phase reactions between the naked substrate and the naked nucleophile. This is not a very realistic representation of organic reactions which are usually run in solution and in the presence of the (counter) cation. Furthermore, we have assumed a perpendicular attack of the nucleophile on the carbonyl group (see 7 a and 7 b) and this assumption may not be justified. Therefore we shall discuss successively the influences of the cation, of the stereoelectronic control and of the solvent.

Influence of the counter cation (Fig. 3)

Recently, Pierre and Handel¹⁴ have found that, in the absence of alkali cations, cyclohexanone is not reduced by LAH or NaBH_4 . It is then essential to verify that our

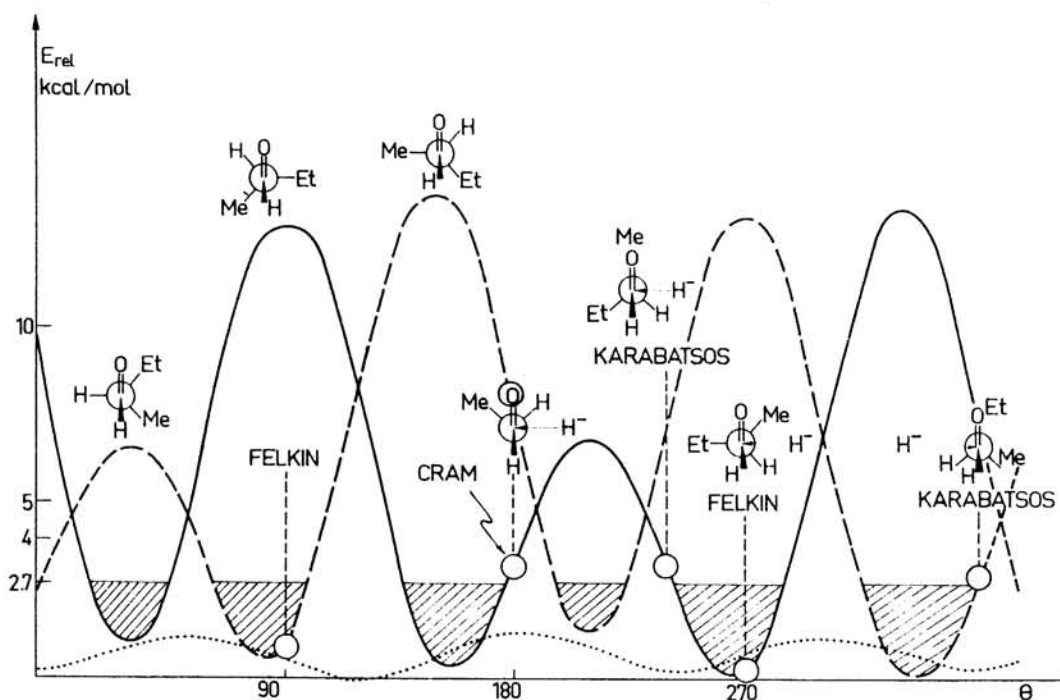
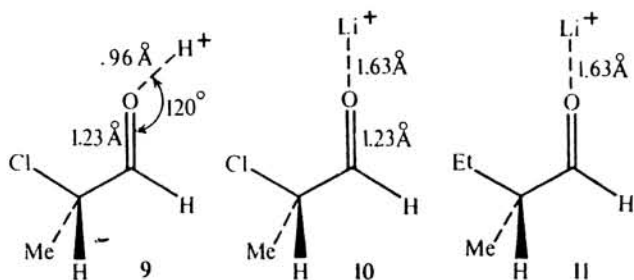


Figure 2. — Reaction of H^- with $\text{Et}-\text{CHMe}-\text{CHO}$. Same conventions as in Figure 1.

previous results are not modified when carbonyl complexation by the cation is taken into account.

We first calculated the geometries of the complexes ($\text{HCHO} + \text{H}^+$) and ($\text{HCHO} + \text{Li}^+$), optimizing the 3 cartesian coordinates of the cation and allowing a relaxation of the CO bond length¹⁵. We also assumed that the relative position of the cation, with respect to the carbonyl group, is conserved when formaldehyde is replaced by 2-chloropropanal or 2-methylbutanal. The usual calculations of transition states energies are then carried out with the complexed aldehydes **9**, **10** and **11** as chiral substrates.



No essential change is observed. The curves obtained for **9** or **10** (Fig. 3) are similar to the curves of Figure 1 and the curves obtained for **11** are similar to those of Figure 2. The calculated minima correspond to the same values of the rotation angle and the Felkin transition states remain among the most stable. These results suggest that complexation by the cation increases the rates of reaction but does not modify the geometries of the favoured transition states.

Influence of stereoelectronic control. Principle of optimal intermolecular overlap.

From crystallographic studies of several aminoketones, Bürgi, Dunitz and Shefter¹⁶ have found that the angle made by the nitrogen atom with the carbonyl group is always superior to 90° , with a mean value of 107° . Taking the view that these different structures of aminoketones, arranged in the right sequence, constitute a set of "snapshots" of the nucleophile's path of approach (the nucleophile being here the nitrogen lone pair) these authors concluded that there is a strong preference for non-perpendicular nucleophilic attack. Bürgi, Lehn and Wipff^{16, 17} have carried out *ab initio* (SCF-LCGO-MO) calculations for the nucleophilic addition of a hydride ion to formaldehyde and have found an angle ($\text{H}^- \cdots \text{C}=\text{O}$) of 109.5° for a distance $\text{H}^- \cdots \text{C}$ equal to 1.12 \AA .

At first sight, these results seem to be in contradiction with the so-called "stereoelectronic control" which is considered to favour perpendicular attack¹⁸. In fact, this contradiction is only apparent. The principle of stereoelectronic control states that, other things being equal, reactions will proceed along reaction paths corresponding to the most favourable (molecular) orbital overlap. Now, a perpendicular attack gives the best *interatomic* orbital overlap but not the best *intermolecular* orbital overlap, except when the two interacting atoms are both molecular centers of symmetry. This is certainly not a very usual case. Indeed, if we try to look for the reaction path with the best intermolecular overlap between the nucleophile and the carbonyl group, we are led inevitably to an angle of attack superior to 90° , in agreement with the results of Dunitz, Lehn and their respective co-workers.

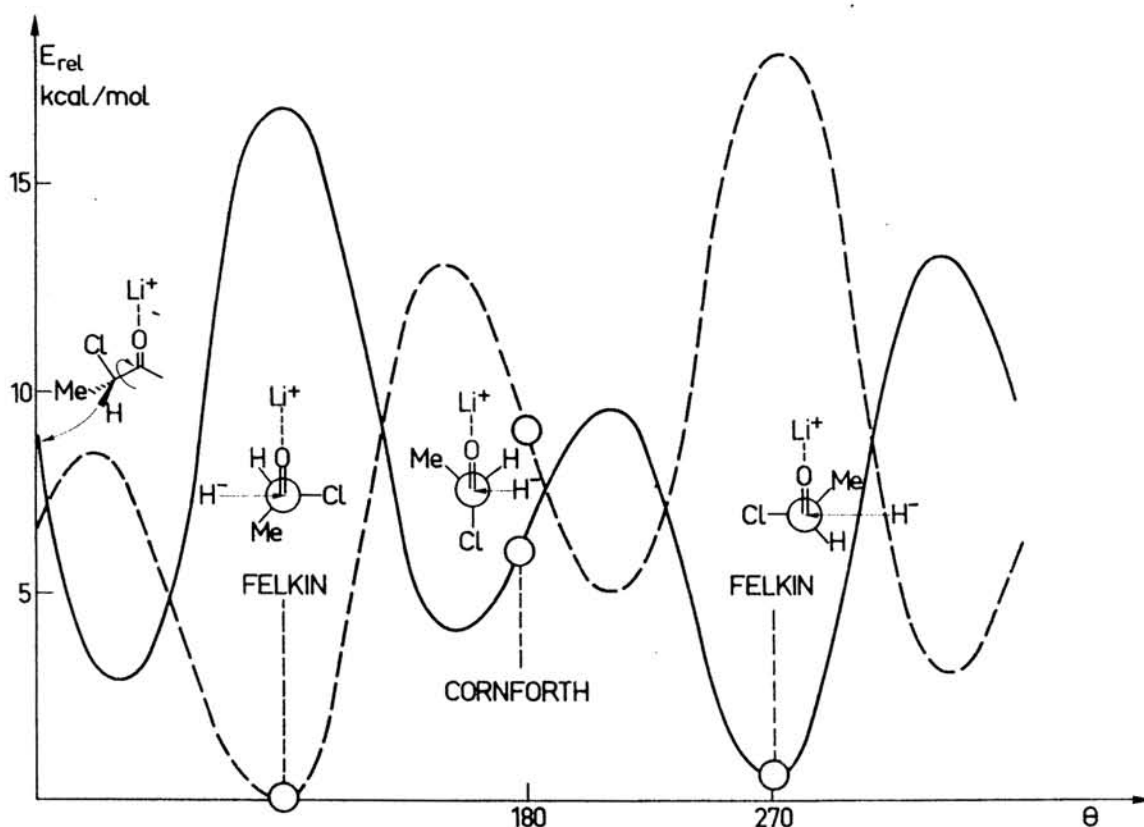


Figure 3. — Reaction of H^- with $(\text{Me}-\text{CHCl}-\text{CHO} + \text{Li}^+)$.

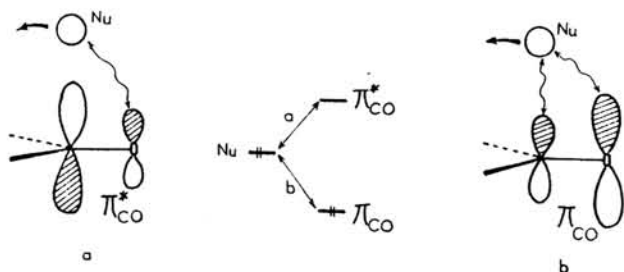
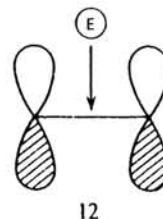


Figure 4. — Non perpendicular attack as a result of stereoelectronic control.

Let us consider the interaction between the nucleophile's HOMO and the π_{CO}^* orbital (Fig. 4 a). This is a two-electrons stabilizing interaction and we should look for the greatest overlap possible. As there is a negative out-of-phase overlap between the nucleophile and the oxygen atom (wavy double arrow), a lateral displacement of the nucleophile away from the carbon-oxygen region (arrow) will increase the stabilization. A similar conclusion is reached from the consideration of the interaction between π_{CO} and the nucleophile's HOMO. This is a four-electron destabilizing interaction. In order to minimize the repulsion, we must seek the smallest possible overlap. As the amplitude of the π_{CO} wave-function is larger on the oxygen atom than on the carbon atom, it is best to move the nucleophile away from the oxygen atom (arrow, Fig. 4 b). Both interactions ($\text{Nu}-\pi_{\text{CO}}^*$ and $\text{Nu}-\pi_{\text{CO}}$) therefore induce an increase of the $(\text{Nu} \dots \text{C}=\text{O})$ angle. A numerical check of this perturbation treatment has been done for the model reaction ($\text{HCHO} + \text{H}^-$). The $\text{H}^- \dots \text{C}$ distance is kept

constant (1.5 Å). The angle of attack varies from 90 to 115° by increments of 5°. The maximal overlap between H^- and π_{CO}^* is obtained for 105°, while the lowest energy of the "supermolecule" ($\text{HCHO} + \text{H}^-$) corresponds to an $\text{H}^- \dots \text{C}=\text{O}$ angle of 110°. This 5° difference may be attributed to the repulsive interaction between the hydride and the π_{CO} orbital. The deviation from perpendicular attack is therefore due almost entirely to the interaction with the π_{CO}^* orbital*.

Let us now return to the asymmetric induction problem. For each conformer of 2-chloropropanal, we have calculated the transition state energies for 3 values of the angle of attack: 90, 100 and 110°. The hybridization change at the carbonyl group has been neglected



12

* An interesting consequence of our interpretation of non-perpendicular nucleophilic attack is the following. For electrophilic additions to double bonds, the major interaction is that existing between the electrophile's LUMO and the ethylene π orbital. As the latter has its largest amplitude between the 2 carbon atoms, in order to obtain maximal overlap, electrophilic reagents must attack a double bond at its center, leading to the familiar triangular onium ions (12, $\text{E} = \text{Br}^+, \text{H}^+ \dots$). We would like to emphasize the fact that the cyclic onium ions and the non-perpendicular nucleophilic attack on carbonyls are but two facets of the same rule of optimal intermolecular overlap.

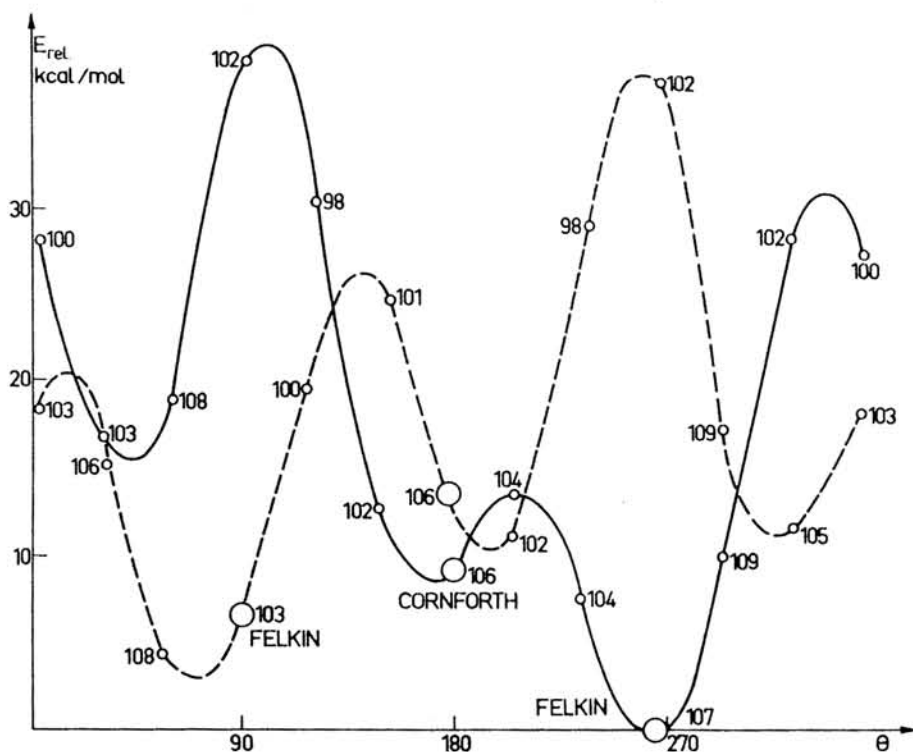


Figure 5. — Reaction of H^- with $\text{Me}-\text{CHCl}-\text{CHO}$. Angles of attack are optimized (corresponding value is given beside each point).

in all cases. Assuming a quadratic dependence of the transition state energy E on the angle of attack α :

$$E = a\alpha^2 + b\alpha + c,$$

we have deduced the optimal values for E and α . These results are reproduced on Figure 5¹⁹. The angles range from 98 to 109°, with an arithmetic mean value of 103°5. This is in good agreement with the value (105 ± 5°) suggested by Dunitz, Lehn and coworkers¹⁶.

Compared with the curves of Figure 1, those of Figure 5 are slightly distorted. However, it seems reasonably safe to conclude that two essential features have been conserved: 1) the Felkin transition states lie close to the minima; 2) they are more stable than the Cornforth transition states.

In reality, Felkin's model fares even better than Figure 5 indicates. As a matter of fact, we have until now studied separately the influences of cationic complexation (Fig. 3) and of stereoelectronic control (Fig. 5). If both effects are taken into account simultaneously, it turns out that the optimal angles of attack are smaller than those indicated on Figure 5. They range from 95°5 to 103°5, with an arithmetic mean value of 100° (compared with 98, 109 and 103°5 for Fig. 5). We obtain two curves intermediate in shape between those of Figure 3 and Figure 5. Similar results are obtained with 2-methylbutanal: the best angle of attack is 103° for the naked substrate and decreases to 99° for the complexed substrate.

That cationic complexation favours near-perpendicular attacks is another consequence of the principle of optimal intermolecular overlap. We shall

distinguish two cases, depending on whether the cation is a proton or not. If the cation is a proton, there is no conjugation with the carbonyl π system. The distortion of the π orbitals is entirely due to the increase of the oxygen electronegativity by protonation²⁰. This leads to a decrease of the oxygen coefficient in π_{CO}^* and of the carbon coefficient in π_{CO} . The repulsive interactions (Fig. 4) and accordingly, the deviation from perpendicular attack, are reduced.

If the cation is not H^+ , but say Li^+ , the π system suffers an additional distortion by conjugation. We have now three π orbitals for the model system ($\text{HCHO} + \text{Li}^+$):

$$\psi_1 = 0.49(p_z \text{C}) + 0.75(p_z \text{O}) + 0.109(p_z \text{Li}),$$

$$E_1 = -0.726 \text{ a.u.},$$

$$\psi_2 = 0.665(p_z \text{C}) - 0.283(p_z \text{O}) - 0.739(p_z \text{Li}),$$

$$E_2 = -0.061 \text{ a.u.},$$

$$\psi_3 = 0.597(p_z \text{C}) - 0.65(p_z \text{O}) + 0.684(p_z \text{Li}),$$

$$E_3 = 0.047 \text{ a.u.}$$

For the sake of comparison, we give here the unperturbed orbitals of formaldehyde

$$\pi_{\text{CO}} = 0.616(p_z \text{C}) + 0.671(p_z \text{O}),$$

$$E_\pi = -0.44 \text{ a.u.},$$

$$\pi_{\text{CO}}^* = 0.816(p_z \text{C}) - 0.771(p_z \text{O}),$$

$$E_\pi^* = 0.281 \text{ a.u.}$$

Table I lists the atomic overlaps of the hydride $1s$ orbital with the $2p_z$ orbitals of C, O and Li for various angles of attack α (see 13). We can now evaluate and compare the different intermolecular overlaps.

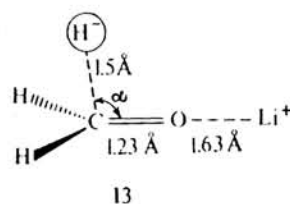


Table I. — Atomic overlaps of the hydride $1s$ orbital with the $2p_z$ orbitals of C, O and Li. For relative positions of the different atoms, see 13.

α	90°	95°	100°	105°	110°	115°
$\langle H C \rangle$	0.3126	0.3114	0.3079	0.302	0.2938	0.2833
$\langle H O \rangle$	0.0726	0.0598	0.0493	0.0406	0.0335	0.0276
$\langle H Li \rangle$	0.072	0.062	0.0533	0.0457	0.0391	0.0334

The carbon coefficient being smaller in ψ_1 than in π_{CO} , there is less repulsion between H^- and ψ_1 than between H^- and π_{CO} . This induces a slight decrease of α . But, as pointed out earlier, the main stereoelectronic control is due to the interactions of H^- with the vacant orbitals. The calculated maximal overlaps with H^- are obtained respectively at $\alpha=110^\circ$ for ψ_2 and at $\alpha=95^\circ$ for ψ_3 (105° for π_{CO}^*). The lowest energy for the system ($H^- + HCHO + Li^+$) corresponds to an $H^- \dots C=O$ angle of 105° (110° for the $H^- + HCHO$ system). Thus the decrease of the angle of attack α is not due to the LUMO ψ_2 but is due to the next higher M.O. ψ_3 . This is a typical example of "superjacent orbital control"²¹: the stereochemistry is not controlled by ψ_2 , albeit the nearest in energy to the nucleophile's HOMO. It is amusing to note that another common hypothesis, which assumes that the nearer a neighbouring atom the greater its influence, is also violated in this case. Although the oxygen atom is located next to the reaction center, it interacts less with the incoming H^- than does Li, which has a much more diffuse A.O. (cf. Table I).

Influence of the solvent (Fig. 7)

Before looking at the particular case of solvent effects in asymmetric induction, it is necessary to verify that our calculations are able to reproduce solvent effects in general. For that reason, we have calculated²² the orbital energies of a certain number of anions (F^- , Cl^- , HO^- , HS^- , MeO^- , MeS^- , CN^- ...), first naked, then solvated with an increasing number of solvent molecules. H_2O has been taken as a model of protic solvent and $HCHO$ as a model of dipolar aprotic solvent.

The following results are obtained. In the gas phase, the HOMOs of small anions (e. g. F^- , HO^-) have higher energies than those of larger anions (Cl^- , HS^-). Solvation by H_2O stabilizes small anions more than the large ones, so that for 3 or 4 molecules of solvent, the order of the HOMO energies is reversed (Fig. 6). Consider now the nucleophilic attack of such an anion on some substrate. When the nucleophilic anion is approached, the main interaction occurs between the LUMO of the substrate and the HOMO of the anion.

For a given substrate (i. e. for a given LUMO), the higher the HOMO, the stronger the interaction, and the more "nucleophilic" the anion. Our calculations thus suggest a reversal of the nucleophilicity order when one goes from the gas phase — where small anions are more reactive — to protic solutions, where larger anions are better nucleophiles. This is in good agreement with experimental results²². Dipolar aprotic solvents are less effective than protic solvents and the order of the HOMO levels remains the same as in the gas phase²².

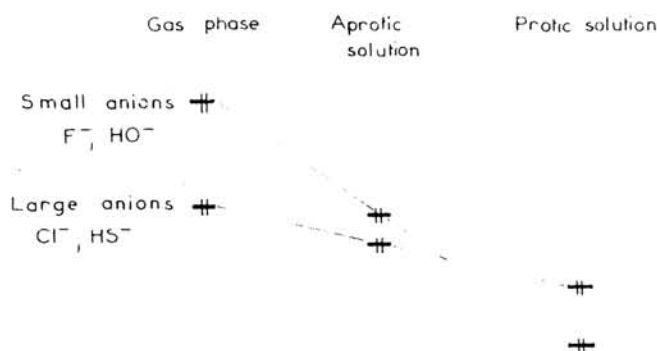
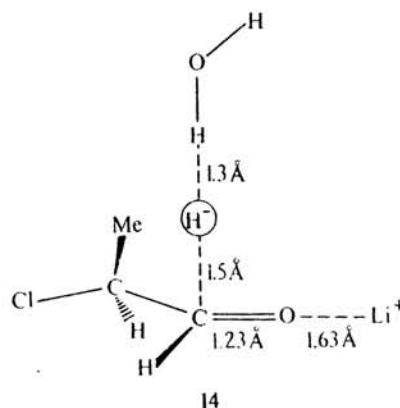


Figure 6. — HOMO levels of anions.

From these calculations, it may be concluded that our very coarse model of solvation can reproduce qualitatively the phenomenon and that the major effect of solvating an anion is a lowering of its HOMO level. It is therefore possible, in order to observe the general trend, to solvate the anion with just one molecule of solvent. Figure 7 shows the transition state energies for the reaction of ($Me-CHCl-CHO + Li^+$) with ($H^- + H_2O$) (see 14). Perpendicular attack is assumed for the sake of simplicity. Not surprisingly, the curves of Figure 7 are very similar to those of Figure 1 or Figure 3. As a matter of fact, complexation by Li^+ lowers the energy of π_{CO}^* while solvation lowers the energy of H^- . The net result is a mere shift of the 2 frontier orbitals and no essential change from Figure 1 is anticipated.



Interpretation of Felkin's model. The antiperiplanar effect

As more than 10 series of calculations lead to the same results, it seems reasonable to admit that:

1) it is possible to take into account only a limited number (<6) of conformers for the chiral substrate;

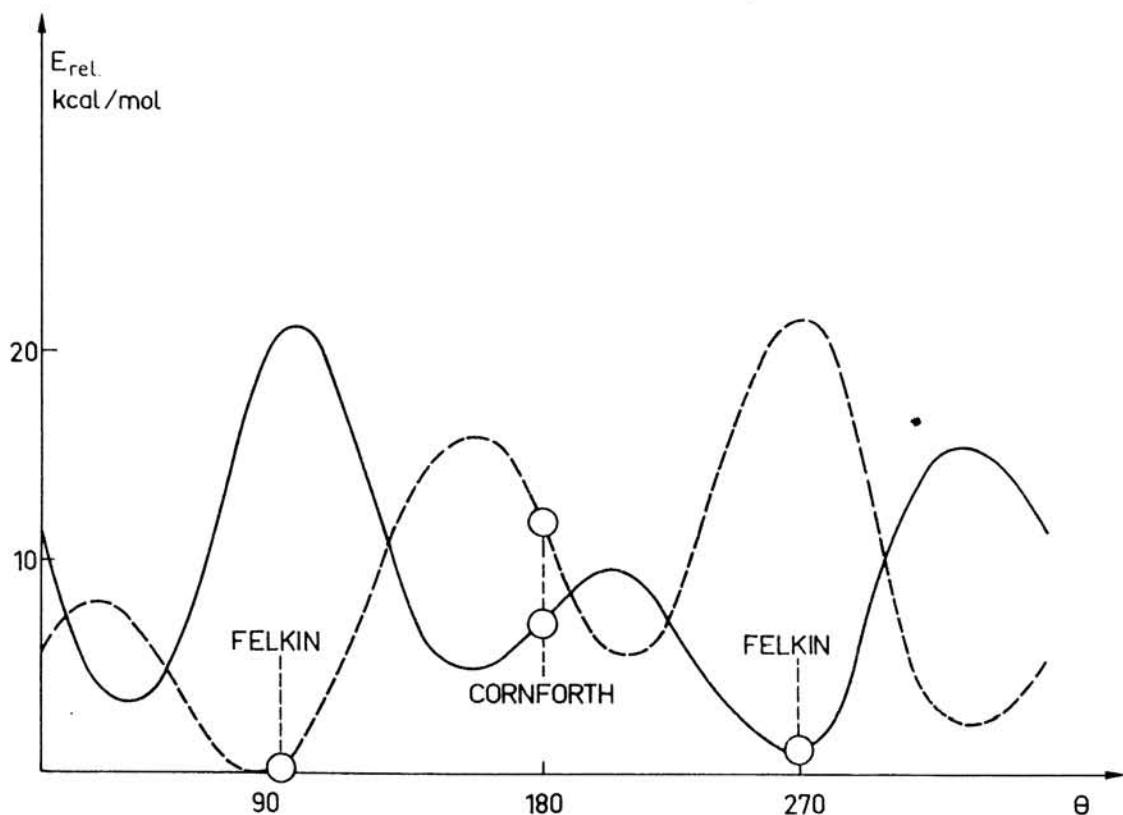


Figure 7. — Reaction of $(\text{H}^-, \text{H}_2\text{O})$ with $(\text{Me}-\text{CHCl}-\text{CHO} + \text{Li}^+)$. Perpendicular attack of the nucleophile is assumed.

2) of the 4 models under study, Felkin's seems to be the best one. The other models give rise to rather energetic transition states and for this reason, should be considered as mnemotechnical schemes.

The low relative energy of the Felkin transition state arises from the antiperiplanarity of the $\text{C1}-\text{H}^-$ and $\text{C2}-\text{L}$ bonds. As we have mentioned before, the principal interaction is that occurring between the nucleophile's HOMO and the $\pi_{\text{C=O}}^*$ orbital of the substrate. Any effect which lowers $\pi_{\text{C=O}}^*$ will increase this interaction and stabilize the transition state. Now, when $\text{C1}-\text{H}^-$ and $\text{C2}-\text{L}$ are antiperiplanar, there is a good overlap between $\pi_{\text{C=O}}^*$ and $\sigma_{\text{C2-L}}^*$, leading to a stabilization of the former²³. This good overlap between $\pi_{\text{C=O}}^*$ and $\sigma_{\text{C2-L}}^*$ also occurs for a synperiplanar attack. This stereochemistry is however disfavoured for 2 reasons:

1) while anti attack with respect to L leads to an in-phase overlap between H^- and $\sigma_{\text{C2-L}}^*$ (at C2), syn attack leads to an out-of-phase overlap between H^- and $\sigma_{\text{C2-L}}^*$ (Fig. 8)²⁴;

2) syn attack implies an eclipsing of $\text{C1}-\text{H}^-$ and $\text{C2}-\text{L}$ bonds.

Two verifications have been made. First, if our frontier-orbital interpretation of Felkin's model is correct, the fluctuations of the total energy of the supermolecule $(\text{Me}-\text{CHCl}-\text{CHO} + \text{H}^-)$ should follow closely those of its HOMO level²⁵. This is indeed the case: compare the curves of Figure 9 and of Figure 1.

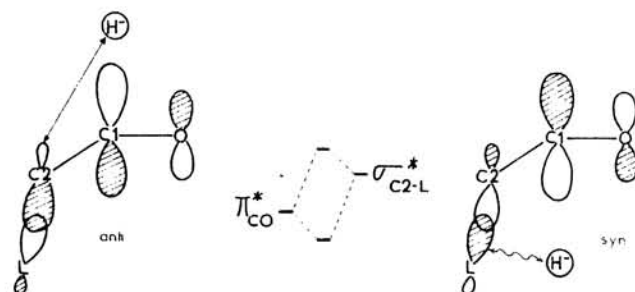


Figure 8. — Secondary interactions for anti- and syn-periplanar attacks.

Secondly, we have calculated the overlaps between $1s_{\text{H}^-}$ and $\sigma_{\text{C2-L}}^*$ for anti or syn attack, with various values of the $\text{H}^- \cdots \text{C}=\text{O}$ angle. As Table II shows, the "anti" overlaps are 5 to 10 times larger than the "syn" overlaps.

Table II. — Overlaps between $1s_{\text{H}^-}$ and $\sigma_{\text{C2-L}}^*$ for syn- and anti-periplanar attacks (cf. Fig. 8).

Angle of attack	"anti" overlap	"syn" overlap
90°	0.044	0.006
95°	0.048	0.005
100°	0.051	0.005
105°	0.054	0.006
110°	0.057	0.008
115°	0.058	0.011

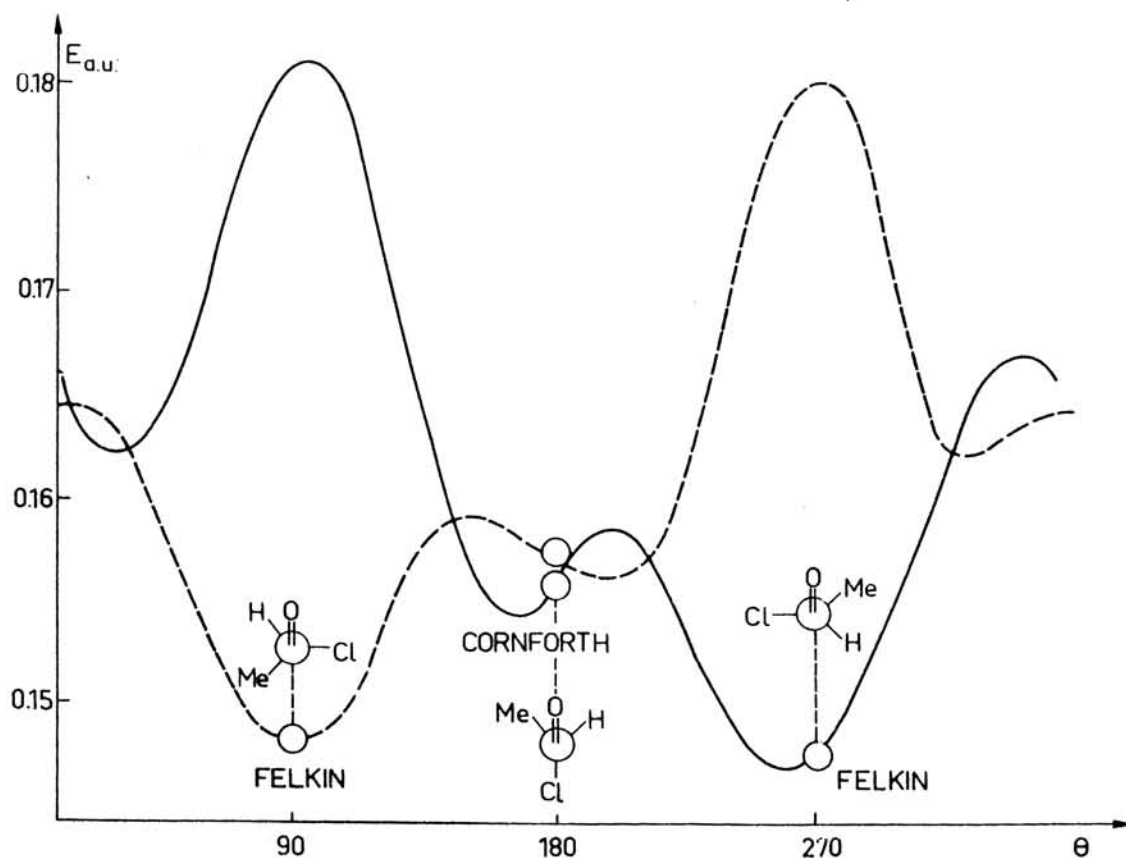
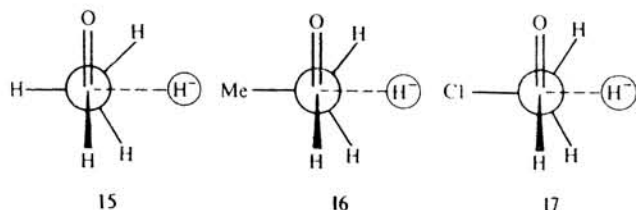


Figure 9. — HOMO energies of the system $(\text{Me}-\text{CHCl}-\text{CHO} + \text{H}^-)$ plotted against the angle of rotation around $\text{C1}-\text{C2}$.

What is now needed to confirm the importance of the antiperiplanar effect is an estimate of its magnitude. Examination of Figures 1, 2, 3, 5, 7, 9 shows that a deviation of 20° from the optimal value of θ (angle of rotation around $\text{C1}-\text{C2}$) leads to an energy increase of 5-10 kcal/mol. We have also calculated **15**, **16**, **17** and compared their energies with those of the isolated reactants. It is found that approaching the nucleophile causes a stabilization of 35.5 kcal/mol for **15**, 37.4 kcal/mol for **16** and 59 kcal/mol for **17**. Although these numbers are not to be taken at their face values, the general trend is clear: it is best to have Cl antiperiplanar to H^- , and Me is the second best choice. It may be noted that in **15**, **16** and **17**, the steric and torsional repulsions between H^- and the substrates are the same. Therefore the differences observed are due entirely to the antiperiplanar effect: σ_{CC1}^* is lower than σ_{CC}^* which in turn is lower than σ_{CH}^* .



In view of these results, we suggest tentatively a value of 5-10 kcal/mol for the antiperiplanar effect. If this estimation is correct, an obvious consequence follows: in

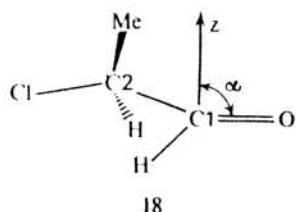
any reaction with asymmetric induction, a search for antiperiplanarity²⁶ between the incipient bond and an adjacent sigma bond should lead naturally to the most favourable transition states, all other things being equal.

Comparison of antiperiplanar effect and orbital distortion effect.

Recently, it has been suggested that orbital distortion may partially control the direction of reagent approach toward the substrate²⁷. For a chiral carbonyl compound, the π electron density is greater on one diastereotopic face than on the other. Attack on the positive face is favoured at first because of coulombic attraction. Then, as the reaction progresses, the carbonyl group suffers a hybridization change which usually also favours attack on the positive face. This hybridization change, being of a much greater magnitude, supersedes the initial orbital distortion. Therefore the energy differences for attacks on diastereotopic faces tend to disappear as the reaction progresses. In other words, orbital distortion may play a role if the transition state is reached rapidly, but its importance will diminish in reactions with late transition states.

This idea is confirmed by a model calculation in which we took 2-chloropropanal in a Cram conformation (**18**) and pyramidalized the Cl atom. Table III shows the energy changes, due to pyramidalization, of the naked substrate and of the supermolecule (substrate + H^-).

Clearly, orbital distortion is important only in the early stages of the reaction and, even then, does not



exceed 2 kcal/mol. This is small, compared with the 5-10 kcal/mol extra-stabilization given by the antiperiplanar effect. It follows that if the initial conformation with maximum orbital distortion is not a Felkin conformation, conformational change will occur during the reaction.

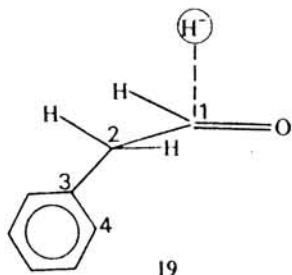
Table III. — Energy changes of **18** and (**18** + H⁻) due to C1 pyramidalization. The angle α is the common value of the 3 angles \angle C1—O, \angle C1—C2 and \angle C1—H (see **18**).

α (°)	Relative energy	
	2-chloropropanal (kcal/mol)	2-chloropropanal + H ⁻ (kcal/mol)
75	21.37	-40.31
80	9.09	-35.40
85	2.02	-21.59
90	0	0
95	2.31	-19.82
100	9.59	-34.71
105	21.91	-40.13

Antiperiplanar effect and "effective sizes" of substituents

A crucial problem associated with the Cram, Cornforth, Karabatsos or Felkin models is the ordering of the substituents with respect to their polarity and "effective size"²⁸. Our interpretation of Felkin's model now supplies a simple rule: the X, Y, Z substituents should be ordered according to the energies of the antibonding σ_{C2-X}^* , σ_{C2-Y}^* and σ_{C2-Z}^* orbitals.

However, this rule should be applied cautiously if a substituent has low-lying vacant orbitals, as it may be necessary to introduce secondary orbital interactions. Consider a phenyl substituent. Its π^* orbitals may interact through space with π_{CO}^* and stabilize the transition state. Table IV shows the relative energy of the supermolecule **19** (H⁻ + 2-phenylacetaldehyde) as a function of ϕ , the C1—C2—C3—C4 dihedral angle. It is possible that the extra-stabilization obtained for $\phi = 90^\circ$ is responsible for the large effective size of the phenyl group which sometimes acts as if it is bigger than the t-butyl group²⁸.



Comparison of the two Felkin transition states: a chemical consequence of the rule of non perpendicular attack

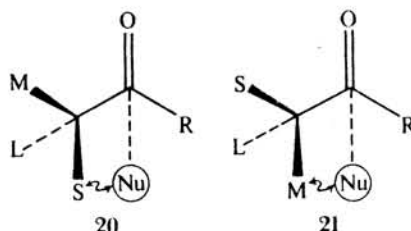
A last point remains to be clarified: why should transition state 4 be preferred to transition state 5? It is

Table IV. — Relative energy of (H⁻ + 2-phenylacetaldehyde) as a functions of the dihedral angle C1—C2—C3—C4.

ϕ	E_{rel} (kcal/mol)
0	4.09
45	0.77
90	0
135	2.27

obvious that, if *perpendicular attack* is assumed, the intermolecular steric and torsional interactions between the nucleophile and the substrate are identical in both cases: all distances (Nu—O, Nu—R, Nu—S, Nu—M) being the same in **4** and **5**. In their original papers⁷, Felkin and his co-workers postulated that the interactions of substituents M and S are stronger with R than with O. It is not clear why this should be so, considering that the oxygen atom is probably complexed with solvent molecules and/or a cationic species. Furthermore, the predominance of R over O must hold, even when R=H. Nevertheless, this hypothesis discriminates between **4** and **5**, agrees well with the observation that selectivity increases with the bulkiness of R, and for these reasons, has not been questioned.

However, the same conclusion may be reached, if non-perpendicular nucleophilic attacks are assumed. It is clear that the steric hindrance encountered by Nu is much more serious in **21** than in **20** (wavy arrow). It is also clear that non-perpendicular attacks increase the Nu—R interaction and decrease the Nu—O interaction, thereby accounting for the predominance of R over O, even when R=H.



Therefore, we suggest the replacement of the third premise of Chérest, Felkin and Prudent⁷ ("the important steric interactions involve Nu and R rather than the carbonyl oxygen") by the assumption of non-perpendicular attack.

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