Tetrahedron Vol. 48, No. 16, pp. 3353-3364, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

The "Cieplak" Effect: Hyperconjugative Interactions at Facially Dissymmetric π-Systems.

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(*Received in UK* 25 *February* 1992)

Abstract: *Molecular orbital calculations demonstrate that at the transition state for the addition of methanol to norbornanones,* **1a-d**, *the bond between the methanol oxygen and the carbonyl carbon is substantially formed. The bonds antiperiplanar to the approach of the methanol are little changed, but those antiperiplanar to the carbonyl oxygen are somewhat shortened in going to the transition state. In the presence of electron withdrawing substituents at C2 and C3 the anti C7-OMe bond is shorter than for* **1a**, *but does not change in the presence of electron donating ethyl groups. For the addition of methanol there appears to be little evidence that the Cieplak postulate is supported by semi-empirical calculations.*

Introduction

Following the work of le Noble[1] on a wide range of reactions of 5-substituted 2-adamantanones and Metha et al.,[2] on the reduction of 7-norbornanones, it is clear that electronic effects of substituents which are remote from the reactive site, and are therefore considered not to exert steric perturbations, influence diastereofacial selectivity at carbonyls.

An early approach to understanding the influence of electronic effects on π-facial diastereoselection was by Fukui[3] and focused on the analysis of ground state properties of the reactants. The faces of the π-system were considered to be differentiated by mixing of π and σ-orbitals resulting in a perturbation of the ground state HOMO and became known as non-equivalent orbital extension.[4] Hudec[5] has proposed that the preferred direction of approach to a carbonyl group is controlled by deviations in the angle by which the axis of the π* orbital of the carbonyl carbon atom is twisted thereby making the faces of the carbonyl diastereotopic.

Cieplak et al.[6], in a now widely quoted qualitative approach, have proposed that addition reactions to facially dissymmetric carbonyl systems are biased from steric and classical torsional control[7] by hyperconjugative stabilization (or electron delocalisation) of neighbouring-group electrons into the σ*-orbital of the incipient carbon-nucleophile bond. The approach of the nucleophile to the carbonyl, *syn* or *anti* to the substituent, is considered to be controlled by the electron density of the adjacent antiperiplanar bonds to the carbonyl π-system; the "Cieplak postulate" states that an incoming nucleophile will add to a carbonyl from the face that allows for the greater anti-periplanar hyperconjugative stabilization from an adjacent vicinal σ-bond. The direction of attack at cyclohexanones is therefore governed by which of the vicinal bonds is more electron donating, the C2-ax-H and the C6-ax-H bonds or the ring C2C3 and C5C6 σ-bonds (Figure 1). The most electron-rich vicinal bonds to the carbonyl of cyclohexanone are axial C-H bonds.[8] Axial addition of nucleophile to the carbonyl is thereby favoured antiperiplanar to the axial CH bonds which stabilize the electron deficient σ*-bond being formed between the nucleophile and the carbonyl carbon.[9] The argument has been used to explain[10] why axial attack of nucleophiles on cyclohexanones generally predominates even though the least hindered face is the equatorial face.[11] The Cieplak argument[12] is supported by the stereochemistry of reduction of C3-substituted cyclohexanones. An electron withdrawing group at C3 enhances axial attack; equatorial attack being disfavoured by a reduction in the electron donating ability of the C2C3 bond to the forming σ*-orbital. On the other hand when R is electron donating the antiperiplanar C2C3 bond is better able to donate electrons to the σ*-orbital of the forming equatorial carbon-nucleophile bond and equatorial attack is promoted. The hypothesis is also supported by le Noble's work on 5-substituted adamantan-2-one; attack of nucleophiles occurs at the *syn* face if the 5-substituent is an electron withdrawing group[13] and at the *anti* face if it is a donor.[14] Houk[15] has recently focussed attention, with some success, on the importance in reactions of carbonyls of torsional, steric and, in particular for polar substituted carbonyl compounds, on the influence of electrostatic effects between a charged nucleophile and the environment proximate to the carbonyl.

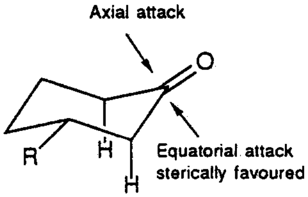


Figure 1. Nucleophilic attack at cyclohexanone

By analogy with the "Cieplak effect" for carbonyls, Diels-Alder reactions of 1-substituted cyclopenta-2,4-dienes would be predicted to occur *anti* to the adjacent substituent σ-bond which is the better hyperconjugative donor. Molecular orbital calculations of the transition states for the reactions of the 1-substituted cyclopenta-2,4-dienes with ethylene using the AM1 Hamiltonian show the diene C-X bond length for *anti* addition of the dienophile is longer than the comparable bond length when the X-substituent is *syn* to the approaching dienophile.[16] The lengthening of the C-X bond for *anti* addition is consistent with hyperconjugative stabilization involving the donation of electron density from the σ-bond of the *anti* substituent to the forming σ*-orbital and with these interactions being important in determining facial selection for Diels-Alder reactions. In order to test the generality of this postulate we now report our studies of hemiacetal formation.

Results and Discussion

The present study seeks to establish a more quantitative definition of the electronic interactions at the transition state. This study is directed to investigating if the Cieplak hypothesis is supported by semi-empirical calculations. Frontier molecular orbital theory[17] focuses on the more stabilizing orbital interactions between reactants; the interaction which contributes most to the offset of torsional, steric and bending components of transition state energy. Combining this principle with the Hammond postulate it is possible to conclude that the more exothermic the reaction the more the transition state will reflect the starting geometry and frontier orbital analysis of reactant orbitals might be expected to be a better predictor of relative transition state orbital interaction than for a less exothermic process. Because of the principle of microscopic reversibility it is appropriate to consider a frontier orbital analysis of the reverse reaction, particularly for endothermic reactions where such a frontier orbital analysis will be a better indicator of stabilizing orbital interactions at the transition state.

For addition to a carbonyl compound the important frontier orbital interaction is between the HOMO of the nucleophile and the π^*-orbital of the carbonyl. The principle of microscopic reversibility dictates that the transition states for axial and equatorial nucleophilic addition can be approached by considering addition to the carbonyl or by loss of Y^- from the epimeric adducts (Figure 2). For the loss of Y^-, the most important frontier orbital interaction will be between the C-Y σ-orbital (the HOMO) and the C-Y σ^*-orbital (the LUMO). The effect of proximate structure to the carbonyl and its influence on the frontier orbitals for addition and retroaddition could reflect in diastereoselection. It is known that electron withdrawing R groups favour axial attack and electron donating R groups favour equatorial attack. The basis underlying the Cieplak postulate[18] is that the nucleophile, Y^-, will be more rapidly lost from the epimeric product where hyperconjugative stabilization (lowering in energy) of the respective C-Y σ^*-orbital (LUMO) is the more favoured. Since it is assumed that C-H bonds are better than C-C bonds as electron donors, axial departure of Y from the top face of the molecule is considered to be favoured and hence the postulate says the reverse process namely addition of a nucleophile to a carbonyl will be more favoured from the axial face.[19]

It is important to realise that the frontier orbital approach to addition or retroaddition will be the better predictor of the transition state of the reaction the nearer in geometry and electronic configuration the transition state is to the reactant or product respectively. Since the addition reaction to carbonyls is normally considered to be exothermic the frontier orbital interaction best able to represent the transition energy is the orbital interaction of ketone LUMO and nucleophile HOMO.[20] This should be a better approximation to the transition state than considering the frontier orbitals of the reverse reaction. The orbital picture, particularly for addition, but also for retroaddition, is however complex (Figure 2). We have not been able to develop a simple predictive pictorial frontier orbital analysis of how adjacent molecular orbitals and substituents to the carbonyl account for facial selectivity in the addition reaction. The Cieplak hypothesis considers that hyperconjugative stabilization (lowering in energy) of the respective C-Y σ*-orbital (LUMO) is the more favoured for axial reaction as C-H bonds are better than C-C bonds as electron donors into the σ* LUMO. Most reactions for which this hypothesis has been applied are exothermic in nature and such a hypothesis should, because of the Hammond postulate, be a better predictor the more endothermic the addition since it concentrates on electron donation to the σ*-orbital. The Cieplak postulate might therefore be expected to have limited application for exothermic addition reactions to carbonyls and in reactions where there is little charge development and therefore little σ-demand at the reaction center.

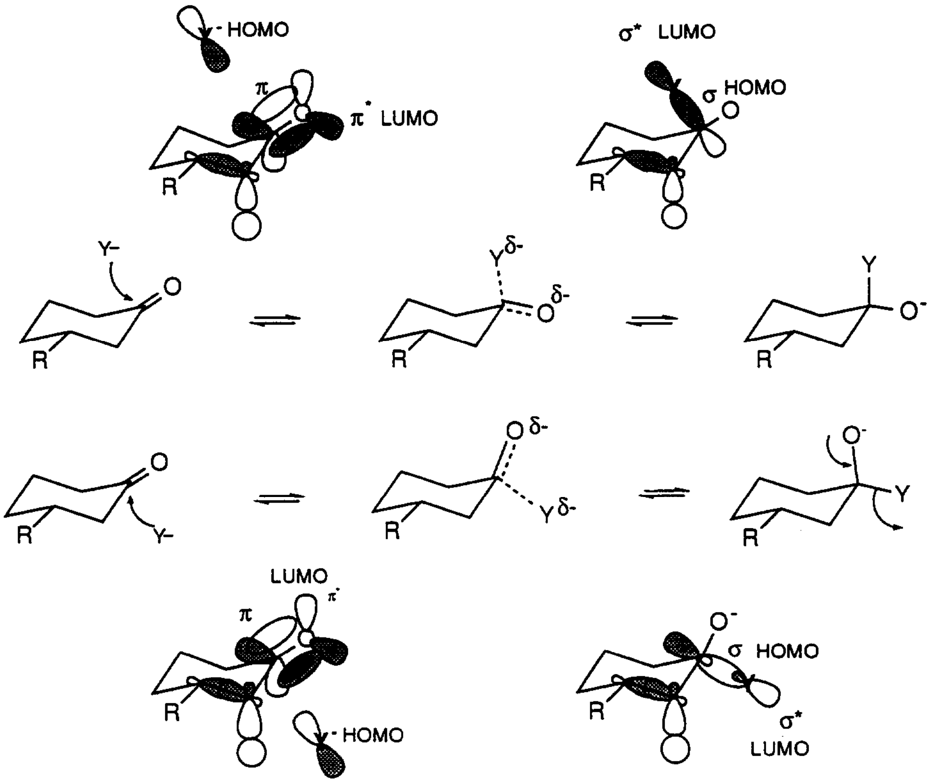
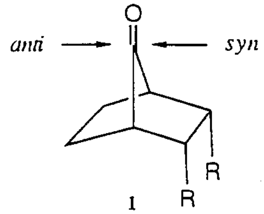


Figure 2. Axial and equatorial attack at 3-substituted cyclohexanones showing frontier and adjacent molecular orbitals.

With the increase in speed of computers semi-empirical molecular orbital calculations of diastereomeric transition states resulting from reaction at two nonequivalent faces of a trigonal center are possible for systems of sufficient complexity to be of relevance to organic chemists. We report such calculations[21] directed towards establishing the importance of hyperconjugative stabilization at the transition state for nucleophilic addition to facially dissymmetric ketones[22] and in particular the reactions of 7-norbornanones since experimental studies of reduction reactions are well documented.

The 7-norbornanones are attractive for study since while C2 and C3 *endo* substituents exhibit electronic effects on the reaction center because of the rigid nature of the framework they do not alter the steric environment in the region of the molecule proximate to the reaction center. The complexity of the molecules, while being beyond reasonable cost *ab initio* methods for computation of the diastereomeric transition states, are able to be studied by semi-empirical molecular orbital calculations if the conformational flexibility of the substituents can be appropriately handled. These ketones have been shown by Mehta et al.[2] to be facially sensitive to the nature of the R substituents in reaction with nucleophiles. When the R groups are electron withdrawing, reduction with sodium borohydride is favoured *syn* to the substituents, while electron releasing groups promote reduction from the opposite face (Table 1). Thus the system allows electronic and steric effects to be delineated.



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	syn:anti ratios
R = H	50:50
R = ethyl	20:80
R = CO_2CH_3	84:16

Table 1. Reduction of 1 with $NaBH_4$

Experimental studies of anionic nucleophilic addition to carbonyl groups in the gas phase[23] proceed without an activation barrier. In fact Dewar[24] has suggested that all reactions of anions with neutral species will proceed without activation in the gas phase. In solution, desolvation of the anion is considered to account for the experimentally observed barrier to reaction. In semi-empirical and *ab initio* molecular orbital calculations no allowance is made for the interactions of the species of interest with solvent. Inclusion of solvent is costly and complex, particularly in transition state calculations.[25] The "transition states" for reactions such as hydride addition to carbonyl compounds cannot therefore be modelled by gas phase AM1 and PM3 procedures. To achieve our objective of studying the effect of substituents on facial selectivity it was necessary to find a reaction that had a calculated activation barrier in the gas phase such that the effect of substituents on that section of the reaction coordinate could be examined. Although the reactions of charged species with carbonyl containing compounds occur without activation in the gas phase, this is not necessarily the case for reaction with a neutral species. The gas phase hydration of formaldeyde has been studied by *ab initio*[26] and semi-empirical[27] molecular orbital methods and is predicted to occur with an activation barrier. For this reason it was decided to perform AM1 and PM3 calculations for hemiacetal formation from formaldehyde and methanol and then to establish the effect of the norbornyl structure, and in particular *endo* substituents, on the transition states for *syn* and *anti* hemiacetal formation at the bridgehead carbonyl. In this manner we expected to quantify the hyperconjugative interactions at the transition state for nucleophile driven addition. Product ratios of hemiacetals will reflect thermodynamic stabilities since they are formed in reversible reactions and therefore kinetic product ratios can not be obtained experimentally. The system is however excellent for theoretical study of substituent effects and these effects might be expected to be important in other addition reactions of carbonyls.

The results of PM3 and AM1 calculations for hemiacetal formation between methanol and formaldehyde are summarized in the reaction-energy profile diagram (Figure 3) which shows that the reaction occurs via a hydrogen bonded dimer.[28] The proton transfer to the carbonyl oxygen occurs in concert with attack by the methanol oxygen on the carbonyl carbon. AM1 calculated geometrical parameters for the transition state in the reaction of methanol and formaldehyde are shown below.[29] A frequency calculation of the transition state using the AM1 and PM3 methods each gave a single imaginary vibrational frequency, the major contributing vectors confirm the concerted nature of proton transfer with addition of the alcohol

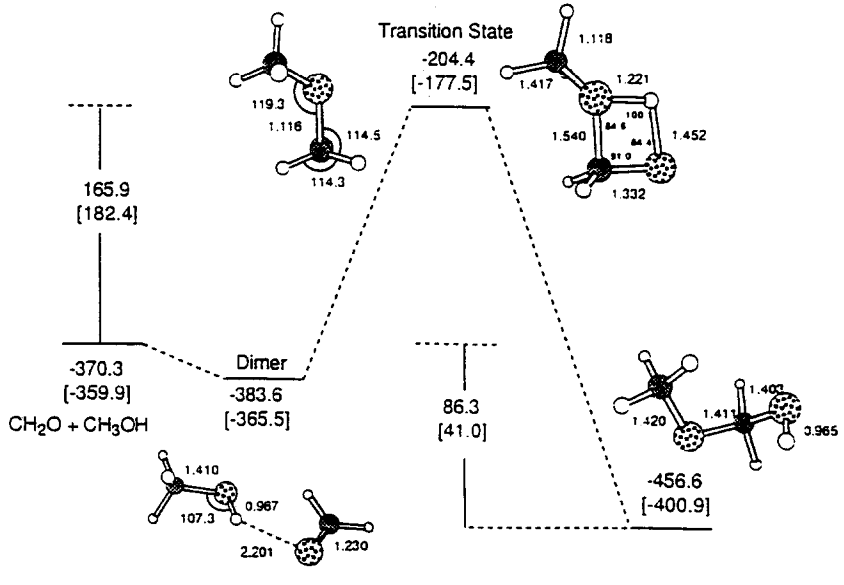


Figure 3. The AM1 and PM3 [square brackets] calculated reaction energy profile for the addition of methanol to formaldehyde. Heats of formation in kJ mol^{-1}.

oxygen to the carbonyl group. The major contributing vectors of the single imaginary frequency of the transition state are shown in Figure 4. The transition state geometry reveals that the bond between the oxygen of the methanol and the carbon of the aldehyde is well developed at the transition state, being 1.54Å compared to a product bond length of 1.42Å. At the transition state the hydrogen being transferred from methanol to the ketone oxygen is still preferentially bound to the methanol (1.22Å) when compared to the distance from the carbonyl oxygen (1.45Å) which suggests the hydrogen transfer occurs relatively late with respect to the primary bond formation.

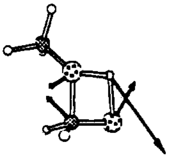
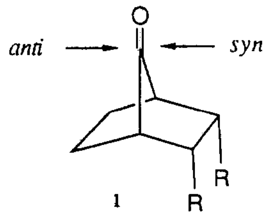


Figure 4. Contributing vectors of the single imaginary frequency of the transition state.

The AM1 method was used to investigate the addition of methanol to 2,3-disubstituted 7-norbornanones. The calculated transition structure for hemiacetal formation from formaldehyde and methanol was used as a starting geometry for the reaction center to determine the transition structure for hemiacetal formation in the addition of methanol to 2,3-disubstituted-7-norbornanones. Transition states were located for both *anti* and *syn* addition of methanol. Full gradient optimization procedures were applied to all geometrical parameters and frequency calculations on each of the resulting stationary points confirmed them to be transition structures. For the conformationally flexible substituents (R = CO_2CH_3 and R = CH_2CH_3) molecular mechanics calculations using the MM2 force-field were performed for the parent ketone with a procedure involving the systematic rotation of each rotatable bond at 60° intervals. The conformational search was carried out using the programs BAKMDL (KS 2.96)[30] and BKM.[31] In both cases a single conformation was identified which would account for ca. 70% of the conformer population at room temperature and this substituent geometry was used as a starting geometry for the AM1 transition state calculations. The calculated enthalpies of activation for the diastereotopic transition states and the calculated percentage *syn* reaction at 25° are shown in Table 2.



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	AM1 calculated activation enthalpy.		
	syn	*anti*	*syn:anti* ratios (25°)
1a R = H	215.9	215.9	50:50
1b R = ethyl.	217.2	215.5	33:67
1c R = CO_2CH_3	213.8	207.2	7:93
1d R =F	213.4	206.9	7:93

Table 2. AM1 calculated enthalpies of activation (kJ mol^{-1}) for the reaction of methanol and 2,3-disubstituted 7-norbornanones **1a-d**.

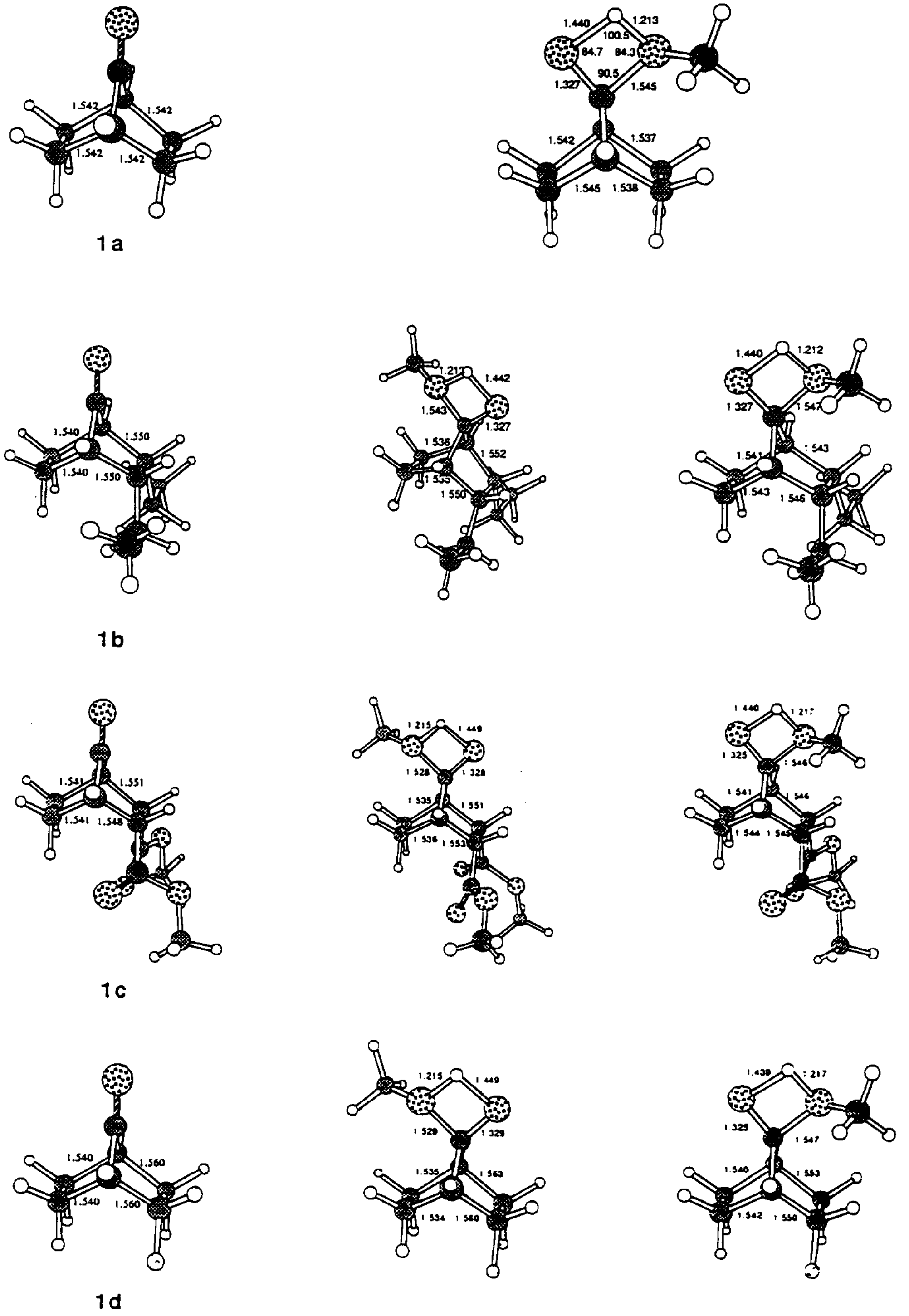

Figure 5. The calculated bond lengths and geometries of ketones 1a-d and the transition state geometries for *syn* and *anti* addition of methanol .

The predicted *syn* to *anti* ratio of 33:67 for **1b** parallels the experimental results obtained by Mehta for the reduction of the C7-ketone with sodium borohydride, where the electron releasing ethyl substituent was found to promote reaction *anti* to the substituent. The AM1 results for the electron withdrawing carbomethoxy substituents in **1c** on methanol addition are at variance with the experimental observations for borohydride reduction. The AM1 calculations for methanol addition predict predominantly *anti* reaction, whereas in the experimental studies on borohydride reduction carbomethoxy groups were shown to promote reaction at the *syn* face. The apparent failure of AM1 calculations for methanol addition to parallel borohydride reduction experiments and reproduce the small energy differences observed for the diastereotopic transition states could be a result of the reactions being sufficiently different in character[32] for comparison since one involves a neutral and the other a charged nucleophile.

The Cieplak postulate requires that the activation barrier for *anti* addition to an electron donating group should fall relative to *syn* addition. The AM1 calculated activation barrier for *anti* addition of methanol to **1b** is not significantly lower than the barrier to addition to **1a**. On the other hand the calculated barrier to *syn* addition at **1b** increases over **1a**. While the calculated product ratio is consistent with the Cieplak hypothesis that electron donating substituents will increase *anti* addition the reason appears not to concern the barrier to *anti* addition but rather to result from an increase in the barrier to *syn* addition. For **1c** and **1d** the Cieplak postulate would favour *syn* addition to the electron withdrawing substituents. The barrier to *syn* addition does fall, but the energy difference is small relative to that for **1a**. The calculated barrier to *anti* addition is however substantially lowered. Direct interaction between the incoming methanol for *syn* addition and the C2 C3 substituents may be overestimated in the AM1 treatment and this would account for the calculated preference for *anti* face reaction. The calculated bond lengths and geometries of ketones **1a-d** along with the transition state geometries for *syn* and *anti* addition of methanol are shown in Figure 5. For **1a** the antiperiplanar σ-bond to the adding methanol is little changed (ca 0.1% bond lengthening) but in the direction expected by the Cieplak postulate.[33] However the bonds antiperiplanar to the carbonyl oxygen are shortened by ca. 0.3% in the transition state. For **1b-d** the antiperiplanar bond to the adding methanol is again only slightly lengthened ca. 0.1-0.16%, but the antiperiplanar carbon-carbon bonds to the carbonyl oxygen are again shortened in the transition state 0.3-0.5%. One of the requirements for hyperconjugative stabilization to be important is that at the transition state the reacting carbon be highly electron deficient. The calculations show that the reaction is mildly exothermic and that at the transition state the forming C7-OMe bond is well developed and hyperconjugation by antiperiplanar bonds will therefore be of lesser importance than in a reaction where the reacting center is considerably electron deficient at the transition state. An analysis of the calculated geometry of the four transition atoms centered at C7 reveals that in the presence of electron withdrawing substituents as in **1c** and **1d** the *anti* C-OMe bond is shorter than for **1a**. This bond length does not change, relative to that in **1a**, in the presence of the electron donating ethyl groups in **1b**. There are no other bond changes of significance. The shortening of the *anti* C7O-Me bond in **1c** and **1d** is consistent with a tighter transition state. It is possible that this is a consequence of a reduction by carbomethoxy and fluoro substitution of the C1C2 and C3C4 bonds to donate electron density to C7. The Cieplak postulate would ascribe this to lessening in the ability to donate electron density to the σ^*-bond of the C-OMe bond. The shortening of the *anti* C7O-Me bond in **1c** and **1d** is reflected in a marginally greater increase in the C1C2 and C3C4 bond lengths of **1c** and **1d** compared to **1b** but the differences are barely significant. The data demonstrate that in the addition of methanol to **1a-d** there appears to be no evidence that the Cieplak postulate is supported by semi-empirical calculations. Addition of methanol to carbonyl containing compounds, although it proceeds with a calculated activation barrier in the gas phase, has yet to be established as a satisfactory model for comparing the importance of hyperconjugative stabilization in the additions of charged nucleophiles such as hydride ion.

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9. Equatorial attack to the carbonyl would be stabilized by the C2C3 and C5C6 bonds which are antiperiplanar to the developing σ-bond with the nucleophile, but since these CC bonds are considered poorer electron donors than C-H bonds, equatorial addition is less favoured.
10. A more classical torsional effect between adjacent σ-bonds was first delineated by von Schleyer and also favours axial addition vs equatorial attack since for the former an unfavourable torsional interaction is avoided.[7]
11. The more bulky a nucleophile the more important attack from the more open equatorial face becomes.

12. The qualitative argument first delineated by Cieplak has been widely used to rationalise experimental observations, though not without controversy. Lodge, E.P.; Heathcock, C.H. *J. Am. Chem. Soc.*, **1987**, *109*, 3353. See also reference 15.
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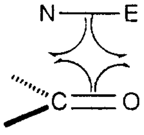
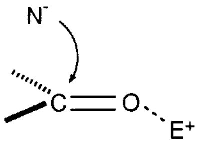
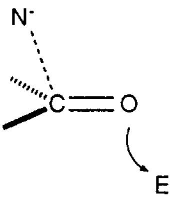
17. For reaction of an electrophile and a nucleophilic it is the interaction of the HOMO of the nucleophile and the LUMO of the electrophile that results in the more important frontier orbital interaction, consistent with donation of electron density of the nucleophile to the electrophile.
18. The authors have emphasised this in this paper since to their knowledge no similar analysis of the Cieplak postulate has appeared.
19. In the presence of a C3 substituent which is electron donating equatorial cleavage will become more favoured. Similarly an electron withdrawing substituent at C3 will favour rupture of the adjacent axial σ-bond.
20. It should be noted that Cieplak always considers the microscopic reverse process namely the interaction of antiperiplanar orbitals with the σ*-orbital, the LUMO orbital of the bond undergoing cleavage. The reaction specificity is thereby assumed to be strongly effected by this interaction which is influenced by proximate antiperiplanar bonds. This reaction is generally endothermic and this treatment should be less satisfactory as a predictor of transition state energy than considering the frontier orbitals for the forward exothermic reaction.
21. AM1 and PM3 as implemented in MOPAC, version 6.0. Quantum Chemistry Program Exchange (QCPE), Program Number 455, 1990.
22. Addition to carbonyls can occur by (i) a non allowed [$\pi 2 + \sigma 2$] pathway or by (ii) an electrophile or (iii) nucleophile driven mechanism.







The relative energy difference of the HOMO of the nucleophile relative to the π* LUMO of the carbonyl compared to the LUMO of the electrophile and the HOMO n-orbital of the carbonyl will be a factor in establishing whether the reaction is electrophile or nucleophile driven. In the case of a reaction catalysed by acid the reaction is considered to be electrophile driven and reaction of the nucleophile occurs to the protonated carbonyl.

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28 The characterised species and the reaction energy profile are similar to those calculated for the hydration reaction.[27]

29. A comparison of semi-empirical and *ab initio* results for addition of water to formaldehyde concluded that the AM1 was better than the PM3 method in treating these types of reactions. These results are similar to those obtained from *ab initio* and semi-empirical calculations for the hydration of formaldehyde.[31]
30. The program, BAKMDL (KS 2.96) was run on a VAX and provided by Professor Kosta Steliou, University of Montreal. BKM, the Unix version, was run on a IBM Risc 6000 320. The program is a steric energy minimization program which uses the MODEL MM2 force field and operates in batch mode. The conformational search was carried out using a grid search procedure. The calculations were carried out using the full force field screening for bad 1,5 C-C VDW interactions, using a minimum cut off distance of 3.5A.
31. BKM can be obtained from Serina Software.
32. Reproducing the small energy differences observed for the diastereotopic transition states for **1c** is a demanding test for any molecular orbital procedure. It is perhaps more important to examine the bond lengths of the diastereotopic transition states.

33 The increase in bond length at the transition state is given as a percentage increase in bond length relative to the bond length of the same bond in the starting ketone.

Acknowledgements: We thank the UGC and the New Zealand Lottery Board for support.