

Theoretical Evidence in Support of the Anh-Eisenstein Electronic Model in controlling π -Facial Stereoselectivity in Nucleophilic Additions to Carbonyl Compounds

Stephen S. Wong and Michael N. Paddon-Row*

Department of Organic Chemistry, University of New South Wales, P.O. Box 1, Kensington, N.S.W. 2033, Australia

Ab initio MO calculations on the complete set of diastereoisomeric transition structures for the addition of cyanide anion to propanal, fluoroethanal, and 2-fluoropropanal, revealed that the most stable transition structure has the C-F bond in the antiperiplanar position with respect to the forming carbon-nucleophile bond; this finding is consistent with the Anh-Eisenstein model for nucleophilic attack on chiral acyclic carbonyl compounds but not with the Cieplak model.

A useful model for explaining π -facial stereoselectivity in nucleophilic addition reactions to cyclic and chiral acyclic carbonyl compounds¹ is that based on the Felkin-type transition structure (1) (Table 1),² in which the α -carbon adopts a staggered conformation with the 'large' ligand, L, assuming a near antiperiplanar (or anti) disposition with respect to the forming bond.¹⁻⁴ The major stereoisomer then results from conformation (1), in which the 'medium' size group, M, occupies the sterically less congested inside position, rather than the more congested outside position.

A problem with this otherwise appealing model lies with the correct identification of the 'large' group, L, because the attribute 'large' incorporates not only obvious steric effects, but also electronic factors.³⁻⁵ In the context of frontier orbital theory, the latter mainly arise from stabilizing two-electron interactions in the transition structure (1). These are thought to be dominated either by mixing the filled $\sigma_{\text{C-L}}$ MO of the forming nucleophile-carbon bond with the vacant $\sigma_{\text{C-L}}^*$ MO of the C-L bond (Anh-Eisenstein model³), or by mixing the vacant $\sigma_{\text{C-L}}^*$ MO of the forming bond with the filled $\sigma_{\text{C-L}}$ MO of the C-L bond (Cieplak model⁵).

Thus, steric factors aside, the Anh-Eisenstein model assigns the best acceptor ligand to 'L', whereas the Cieplak model assigns the best donor ligand to 'L'. Which one of these electronic models is more realistic? Although both models have their fair share of adherents and critics,⁴⁻⁶ this issue has yet to be satisfactorily resolved. This problem can be tackled through an *ab initio* MO study of nucleophilic attack on a chiral carbonyl system in which the electronic demands of one of the three groups attached to the chiral centre, *e.g.*, F, are quite different from the remaining two groups, say H and Me. Herein, we report preliminary results of what we believe to be the first such study.[†]

The complete set of diastereoisomeric transition structures for the addition of cyanide anion to propanal, fluoroethanal, and 2-fluoropropanal were found[‡] using the HF/3-21G theoretical model.^{7a} Improved single point energies were obtained using second-order Møller-Plesset theory^{7b} and the

6-31+G* basis set.^{7c} Energetic details are given in Table 1, and the transition structures for the cyanide-2-fluoropropanal system are shown in Figure 1. The following important conclusions may be drawn from our data.

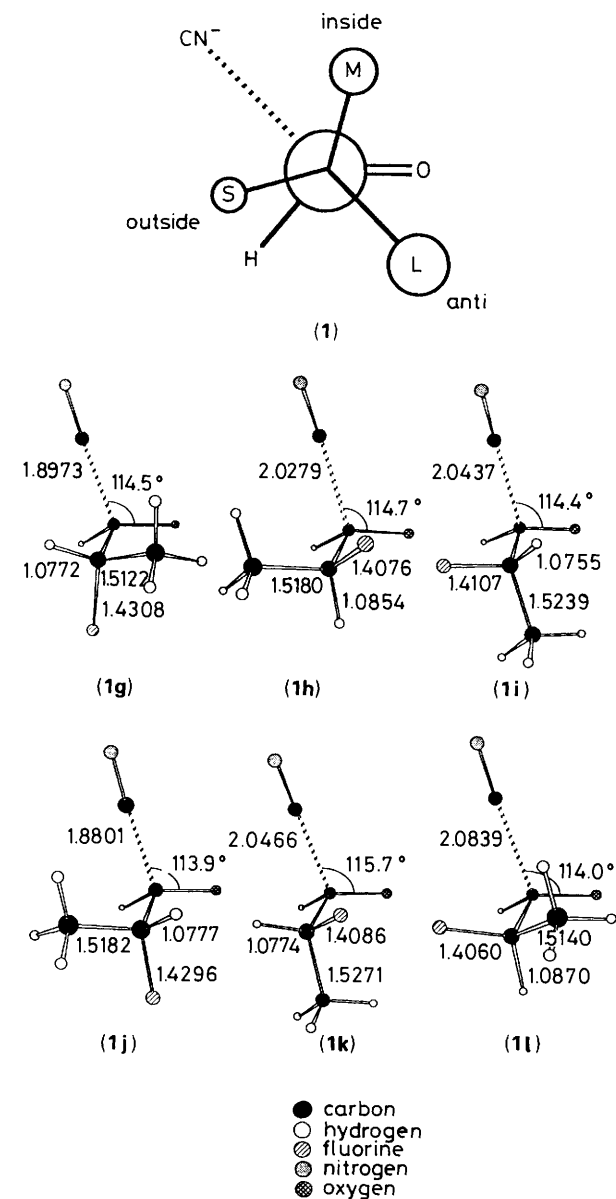


Figure 1. Optimized (HF/3-21G) transition structures for cyanide attack on 2-fluoropropanal. Lengths in Angstroms and angles in degrees.

[†] Previous MO studies have been restricted to achiral carbonyl systems having an alkyl substituent attached to the α -carbon atom.^{4b-d,6d}

[‡] (a) All transition structures were fully optimized and characterized by analytical frequency calculations at HF/3-21G. (b) M. J. Frisch, J. S. Binkley, H. B. Schlegel, K. Raghavachari, C. F. Melius, R. L. Martin, J. J. P. Stewart, F. W. Bobrowicz, C. M. Rohlfing, L. R. Kahn, D. J. DeFrees, R. Seeger, R. A. Whiteside, D. J. Fox, E. M. Fleuder, and J. A. Pople, GAUSSIAN 86, Carnegie-Mellon University, Pittsburgh, PA 15213, U.S.A.

[§] We are aware of the deficiencies of the 3-21G basis set in treating anions.^{7c} However, such deficiencies should be minimized in this study since we are only interested in comparing diastereoisomeric transition structures.

Table 1. Absolute energies (hartrees),^a relative energies (kJ mol⁻¹),^b and natural charges^c of transition structures.

| Structure | M | S | L | HF/3-21G//3-21G | MP2(FC)/6-31+G**/3-21G ^d | Natural charges |
|-----------|----|----|----|-------------------------|-------------------------------------|-----------------|
| (1a) | H | H | Me | -282.63454 (5.0, 4.5) | -285.12704 (4.1, 3.6) | -0.46 |
| (1b) | Me | H | H | -282.63646 (0.0, 0.0) | -285.12860 (0.0, 0.0) | -0.48 |
| (1c) | H | Me | H | -282.63242 (10.6, 9.3) | -285.12802 (1.5, 0.2) | -0.50 |
| (1d) | H | H | F | -342.13479 (0.0, 0.0) | -344.99516 (0.0, 0.0) | -0.52 |
| (1e) | F | H | H | -342.12739 (19.4, 19.3) | -344.98700 (21.4, 21.3) | -0.41 |
| (1f) | H | F | H | -342.13372 (2.8, 2.4) | -344.98975 (14.2, 13.8) | -0.37 |
| (1g) | Me | H | F | -380.96690 (0.0, 0.0) | -384.16965 (0.0, 0.0) | -0.47 |
| (1h) | F | Me | H | -380.95439 (32.8, 31.5) | -384.15967 (26.2, 24.9) | -0.37 |
| (1i) | H | F | Me | -380.96323 (9.6, 8.8) | -384.16392 (15.0, 14.2) | -0.35 |
| (1j) | H | Me | F | -380.95996 (18.2, 17.0) | -384.16701 (6.9, 5.7) | -0.48 |
| (1k) | F | H | Me | -380.95699 (26.0, 25.4) | -384.16066 (23.6, 23.0) | -0.36 |
| (1l) | Me | F | H | -380.96414 (7.2, 6.6) | -384.16468 (13.0, 12.4) | -0.32 |

^a 1 hartree = 2625 kJ mol⁻¹. ^b Relative energies in parentheses, vibrationless and with zero point energy correction, respectively. ^c Natural charges on the alkanal moiety calculated at HF/3-21G. ^d Electron correlation using the frozen core (FC) approximation.



(i) For cyanide attack on propanal, the lowest energy transition structure is (1b), in which the methyl group occupies the inside position. Of the remaining pair of transition structures, (1c), having C-Me in the outside position, is energetically preferred to (1a), having the C-Me group in the anti position. These results agree with those of recent studies on the addition of NaH to propanal.^{4b} Natural population (NP) analysis⁸ shows slightly more charge transfer from cyanide to propanal when C-H is in the anti position (Table 1). This result is inconsistent with the notion that C-H is a better donor than C-Me (required by the Cieplak model), but is consistent with the argument^{4b} that C-Me, being a better donor than C-H,⁹ causes destabilization of the electron-rich transition structure (1a), relative to (1b).

(ii) The lowest energy transition structure for the addition of cyanide to fluoroethanal is (1d), in which the C-F bond adopts the antiperiplanar conformation. This result is consistent with the Anh-Eisenstein model, but not with the Cieplak model, because C-F is a better acceptor than C-H. Indeed, NP analysis reveals substantially larger charge transfer from cyanide to the aldehyde moiety in (1d), with C-F in the antiperiplanar position, compared to either (1e) or (1f), in which C-H is antiperiplanar.

(iii) Of the six diastereoisomeric transition structures for cyanide attack on 2-fluoropropanal, three of them, (1g)–(1i), lead to formation of product (2), whereas the remaining three, (1j)–(1l), lead to the formation of the diastereoisomeric product (3). The most favoured transition structure is calculated to be (1g), in which the best acceptor, C-F, is antiperiplanar and the methyl group occupies the inside position.¶ This structure lies 12.4 kJ mol⁻¹ (including ZPE correction) below the Cieplak transition structure (1l). The predicted stereochemical outcome for this reaction, *via* (1g), is the formation of (2), which agrees with the Anh-Eisenstein

model. However, in contrast, the Cieplak model predicts formation of (3), *via* (1l). Interestingly, our calculations suggest that even the formation of (3) should occur *via* transition structure (1j), in which C-F is antiperiplanar, rather than *via* (1l). The greatest amount of charge transfer to the aldehyde group is observed in (1g) and (1j), when the C-F bond is in the antiperiplanar position. This is in accord with the stabilization of electron-rich transition structures by an electron withdrawing antiplanar C-F bond.†† Experimental support for our findings is found in the recent studies on nucleophilic addition reactions to 2-methoxypropanal and analogues,^{6a} although we do note that the results of those studies are also consistent with reactions proceeding *via* transition structures akin to (1h) or (1i).

(iv) We find that a particular bond is longer when it is in the antiperiplanar position than when it occupies either the inside or outside positions. Using transition structures (1g)–(1l), the computed average bond elongations are (%): C-F, 1.56; C-H, 0.86; C-Me 0.66. The observed trend in bond elongation, C-F > C-H > C-Me, is consistent with stabilization of an electron-rich transition structure by an antiperiplanar acceptor group, but is inconsistent with the Cieplak model, which requires the following order: C-H > C-Me > C-F.

In summary, we find that the electronic component to the determinant of π -facial stereoselectivity in the nucleophilic addition to α -halogenated carbonyl groups is better represented by the Anh-Eisenstein hypothesis than by the Cieplak model.‡‡¶¶ Strictly speaking, our results are applicable to gas phase nucleophilic additions by free anions. The effect of complexation is currently being studied, although we note here that attack on propanal by cyanide anion and NaH lead to identical conclusions (*vide supra*).^{4b}

†† The NP analyses should be treated with caution since the degree of charge transfer also appears to be a function of the incipient carbon-nucleophile bond length. Perhaps this is the reason for the greater degree of charge transfer observed for (1i), with C-Me in the antiperiplanar position, compared to (1l), with C-H in the antiperiplanar position.

‡‡ The Cieplak model,⁵ however, has been successful in treating nucleophilic and electrophilic attack on more rigid cyclohexyl and adamantyl systems. Whether such attacks are due to electronic (Cieplak⁵) or torsional (Felkin,² Houk^{4b}) effects has yet to be resolved satisfactorily.

¶¶ The preference for C-F to adopt the antiperiplanar conformation could also be due in part to adverse dipole effects between the cyanide group and the C-F bond when in the outside or inside positions. This point will be addressed in future studies.

¶ Electronic, and not steric factors must be responsible for the observed conformational preference since F is sterically smaller than Me; L. N. Ferguson, 'The Modern Structural Theory of Organic Chemistry,' Prentice-Hall, London, 1963, p. 214.

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