The Importance of Electrostatic Effects in Controlling π-Facial Stereoselectivity in Nucleophilic Additions to Carbonyl Compounds: an *ab initio* MO Study of a Prototype Chelation Model

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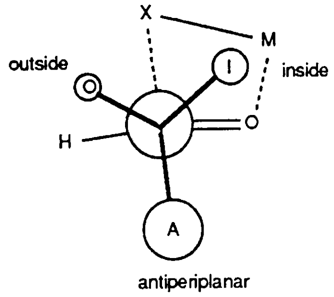
Ab initio MO calculations on the complete set of diastereoisomeric transition structures for the addition of lithium hydride to fluoroethanal and 2-fluoropropanal revealed that the most stable transition structure for each system is dominated by electrostatic attraction between Li and F and this results in the formation of the Cram chelation control product for the latter aldehyde.

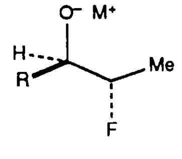
Recently, we reported results of an *ab initio* MO study of all six diastereoisomeric transition structures for the addition of cyanide anion to 2-fluoropropanal.[1] The most stable transition structure was found to have the allylic fluorine, methyl and hydrogen ligands occupying the antiperiplanar (A), inside (I) and outside (O) positions, respectively (see **1a**). This result is in agreement with the Felkin model,[2] supplemented by the Anh–Eisenstein[3] electronic argument for placing the strongest acceptor ligand (in this case, F) antiperiplanar to the forming bond which maximizes stabilization of the transition structure by negative hyperconjugation. The major product predicted from this addition is the Cram non-chelation product[4] **2a**, rather than **3a**.

It was noted,[1] however, that the preference for C–F to adopt the antiperiplanar conformation in the most favoured transition structure for addition of cyanide anion to 2-fluoropropanal is also expected on electrostatic grounds since the adverse ion–dipole repulsion obtaining between the cyanide anion and the C–F bond is minimized when the latter is in the antiperiplanar position. We now present results of *ab initio* MO calculations on the transition structures for addition of LiH to fluoroethanal and 2-fluoropropanal which show that interactions between the lithium and fluorine atoms, presumably electrostatic in origin, outweigh Anh–Eisenstein electronic effects, and lead to the formation of the Cram chelation control diastereoisomer.[5] This work has obvious relevance to the current intense interest in the question of whether putative chelates are genuine intermediates in Cram's chelation rule.[6,7]

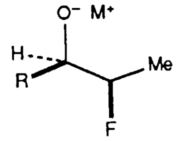
The complete set of diastereoisomeric transition structures for LiH addition to propanal, fluoroethanal and 2-fluoropropanal were fully optimized[8] using the HF/3-21G[9] and HF/6-31G(d)[10] theoretical models. All transition structures were characterized by analytical harmonic frequency calculations at the HF/3-21G level. Improved single point energies for these structures were obtained using second-order Møller–Plesset theory[11] (frozen core) and the 6-31+G(d)[12] basis set [MP2(FC)/6-31+G(d)//HF/6-31G(d)]. Selected transition structures and their relative energies are shown in Fig. 1. More detailed energies are given in Table 1. The following important conclusions can be drawn from our results.



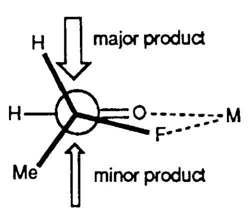
1a X = CN⁻; M = nothing
1b X = H; M = Li



2a R = CN; M = nothing
2b R = H; M = Li



3a R = CN; M = nothing
3b R = H; M = Li



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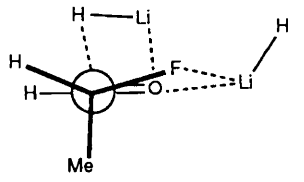

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(*i*) The lowest and highest energy transition structures for LiH attack on propanal have the methyl group in the inside and antiperiplanar positions, respectively. These results are in accord with those for addition of NaH[13] and cyanide anion[1] to propanal.

(*ii*) Despite an extensive search of the energy surface, only two of the three expected transition structures could be located for LiH attack on fluoroethanal, corresponding to the fluorine substituent adopting either the inside, **4a**, or outside position, **4b**. The third transition structure, having F in the antiperiplanar position, appears not to exist, although it was easily located in the case of cyanide anion attack on fluoroethanal. This is surprising since, according to the Anh–Eisenstein model, the antiperiplanar-F transition structure should be the most stable of all three structures, as in the case for cyanide anion attack on fluoroethanal.[1] The more stable transition structure **4a** reveals a significant interaction between the fluorine atom and the lithium cation, since the latter is substantially skewed towards the former (*cf.* **4a′** and **4b′**, making the F···Li distance only 2.27 Å. The origin of the F···Li interaction is probably electrostatic, as has been proposed to explain the nature of the F···Li 'bonds' in HF···LiH and HF···LiF complexes.[14] Such bonds in these complexes are quite strong (*ca.* 56 kJ mol^{-1}), although that in **4a** is expected to be weaker, owing to the greater F···Li

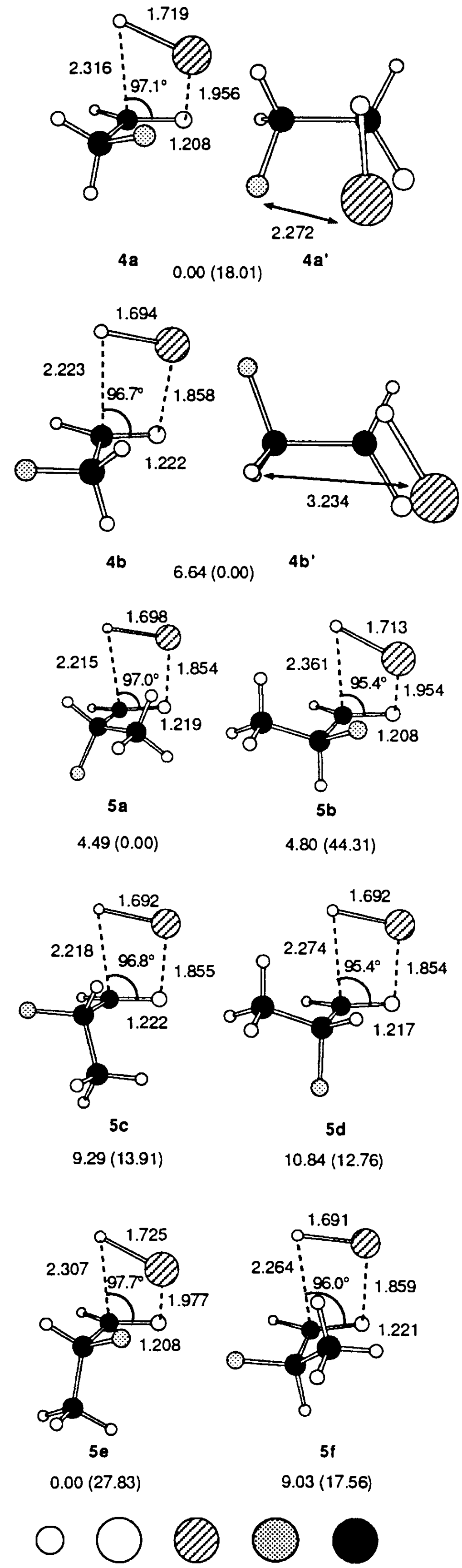

Fig. 1 HF/6-31G(d) optimized transition structures for lithium hydride attack on fluoroethanal **4** and 2-fluoropropanal **5**. Bond lengths in Å and angles in degrees. MP2(FC)/6-31+G(d)//HF/6-31G(d) relative energies (vibrationless) in kJ mol^{-1}. Relative energies with Li$^+$ removed are in parentheses.

Table 1 Absolute energies (hartrees),[a] relative energies (kJ mol^{-1})[b]

Structure	I[c]	O[c]	A[c]	HF/6-31G(d)//HF/6-31G(d)	MP2(FC)/6-31+G(d)//HF/6-31G(d)[d]
	H	H	Me	−199.95604 (4.49, 3.94)	−200.54694 (5.93, 5.38)
	Me	H	H	−199.95775 (0.00, 0.00)	−200.54920 (0.00, 0.00)
	H	Me	H	−199.95660 (3.02, 2.28)	−200.54725 (5.12, 4.38)
4a	F	H	H	−259.76433 (0.00, 0.00)	−260.39808 (0.00, 0.00)
4b	H	F	H	−259.76249 (4.83, 2.68)	−260.39555 (6.64, 4.49)
5a	Me	H	F	−298.80502 (5.25, 4.86)	−299.57312 (4.49, 4.10)
5b	F	Me	H	−298.80572 (3.41, 3.41)	−299.57300 (4.80, 4.80)
5c	H	F	Me	−298.80448 (6.67, 5.43)	−299.57129 (9.29, 8.06)
5d	H	Me	F	−298.80283 (11.00, 9.66)	−299.57070 (10.84, 9.50)
5e	F	H	Me	−298.80702 (0.00, 0.00)	−299.57483 (0.00, 0.00)
5f	Me	F	H	−298.80457 (6.43, 5.28)	−299.57139 (9.03, 7.88)

[a] 1 hartree = 2625 kJ mol^{-1}. [b] Relative energies in parentheses, vibrationless and with zero-point energy correction, respectively. [b] I = inside, O = outside and A = antiperiplanar positions. Refer to structure **1b**. [d] Electron correlation using the frozen core (FC) approximation.

separation in this system, compared to that in the HF···LiH and HF···LiF complexes (*ca.* 1.88 Å). Nevertheless, the electrostatic interaction in **4a** is still strong enough to 'drag' the antiperiplanar-F conformation into the inside position without barrier.† The MP2(FC)/6-31+G(d)//HF/6-31G(d) energies of **4a** and **4b** were recalculated in the absence of the lithium cation. In this case, the outside conformation **4b** is now preferred energetically over the inside conformation **4a** by 18 kJ mol^{-1}.

(*iii*) All six diastereoisomeric transition structures **5a**–**5f** were located for LiH addition to 2-fluoropropanal, including the pair of antiperiplanar-F structures **5a** and **5d**.‡ The first three structures **5a**–**5c** give the Cram product **2b**, and the remaining three structures **5d**–**5f** give the anti-Cram diastereoisomer **3b**. However, the Felkin–Anh–Eisenstein transition structure **5a** is only the second most stable transition structure, the most stable being **5e**, having fluorine inside and methyl antiperiplanar. As with **4a**, the stability of **5e** is due to F···Li electrostatic interactions, since the F···Li distance in **5e** is only 2.14 Å. The other inside-F structure **5b** is also stabilized by electrostatic interactions and is almost as stable as the Felkin–Anh–Eisenstein structure **5a**.

(*iv*) Single point MP2(FC)/6-31+G(d)//HF/6-31G(d) calculations were carried out on **5a**–**5f** in which the lithium ion was deleted from each structure. The resulting relative energies (given in parentheses in Fig. 1) reveal that the Felkin–Anh–Eisenstein 'transition' structure **5a**, minus Li$^+$ is now energetically the most favoured structure, being 28 kJ mol^{-1} more stable than **5e**, minus Li$^+$, which is in agreement with the results obtained for cyanide anion attack on 2-fluoropropanal.[1]

(*v*) Our calculations predict that the major product resulting from LiH attack on 2-fluoropropanal should be **3b**, and that it is formed almost exclusively *via* **5e**. On the other hand, the minor product **2b** is predicted to be produced in approximately equal amounts from two different transition structures **5a** (the Felkin–Anh–Eisenstein transition structure) and **5b**. Replacement of methyl by larger alkyl groups should favour **5a**, relative to **5b**.

(*vi*) Interestingly, **3b** is the product expected using Cram's chelation control model **6**, and transition structures **5b** and **5e** may be regarded as relatives of **6**. The principal difference between our 'chelated' transition structures and **6** is that **5b** and **5e** still maintain Felkin staggering about the forming bond, whereas this is severely reduced in **6**. The predicted stereoselectivity based on transition structures **5e** *vs.* **5b** (and **5a**) is lower than that usually observed from reactions allegedly proceeding under chelation control.[6,7] It is possible that chelation in **5b** and **5e** could be made stronger by the addition of a second lithium cation or a second LiH molecule, perhaps along the lines indicated by **7**. This point is being currently investigated.

In summary, our studies on the addition of LiH to α-fluoroaldehydes have demonstrated that electrostatic or weak chelation effects dominate Anh–Eisenstein electronic effects in determining diastereoselectivity and they nicely complement the recent experimental evidence for the existence of chelate intermediates in Cram's chelation rule.[6,7] Our preliminary studies indicate that these conclusions may be generalized to cover the addition of metal-complexed nucleophiles to α-methoxyaldehydes as well as to α-fluoroaldehydes.[15] Indeed, our results for LiH and cyanide anion[1] attack on 2-fluoropropanal and other systems[16] suggest that electrostatic,§ rather than antiperiplanar hyperconjugative, effects could be more important in determining conformational preferences in nucleophilic additions, even under conditions of non-chelation control.¶ An elegant combination of theoretical and experimental studies have led Houk and his coworkers[16] independently to the same conjecture.

Finally, we emphasize that our results are strictly applicable to the gas-phase, in the absence of solvent. Solvation of the lithium cation would no doubt result in marked attenuation of the electrostatic effects in **4a**, **5b** and **5e**.‖

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† Our results have not been corrected for basis set superposition error (S. F. Boys and F. Bernardi, *Mol. Phys.*, 1970, **19**, 553). Although this error is expected to overemphasize the stability of structures such as **4a**, it should be small because of the high quality of the basis sets used in the calculations and the inclusion of correlation energy.

‡ Apparently, the methyl group must stabilize the two antiperiplanar-F conformers by imposing a rotational barrier to their conversion into the respective inside-F conformers.

§ The importance of electrostatic effects was anticipated by Felkin.[2a]

¶ Electrostatic interactions depend on both the nature of the nucleophile, whether free or complexed, and the polarity of the substituent, whether negative (O, F, Cl) or positive (Si). Thus **5e** is favoured over **5a** because the attractive Li$^+$···F interaction outweighs the repulsive H$^-$···F interaction (these opposing influences might be weaker for a Cl substituent). A silicon substituent should prefer the inside position for naked anion attack (attraction by both nucleophile and carbonyl O) and outside for attack by metal complexed nucleophiles (repulsion by metal cation), which is consistent with our preliminary calculations.[15]

‖ Indeed, in a theoretical study of NaH to hydroxyethanal, Wu found that the hydroxy group also favoured the inside position owing to electrostatic effects, whereas complexation of two water molecules to the sodium atom reduced the electrostatic effect to the extent that the antiperiplanar conformation was now energetically slightly favoured over the inside: Y.-D. Wu, PhD thesis, University of Pittsburgh, 1986.

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