PERKIN 2

The origin of Felkin–Anh control from an electropositive substituent adjacent to the carbonyl group †

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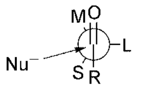
Ab initio calculations on the gas phase reaction of lithium hydride with 2-silylacetaldehyde, 2-silylpropionaldehyde, 2-trimethylsilylacetaldehyde, 2-trimethylsilylpropionaldehyde and 3-trimethylsilylbutan-2-one have been performed. For each of the substrates containing an SiH_3 group, the hydride approaches *syn* to the silyl substituent in the lowest-energy transition structure. In contrast, for each of the substrates containing the larger $SiMe_3$ group, the more conventional Felkin–Anh transition structure, in which the hydride attacks *anti* to this substituent, is lowest in energy. These results suggest that the diastereoselectivity of nucleophilic attack on a carbonyl group, adjacent to a stereogenic centre to which a trimethylsilyl group is attached, is largely controlled by the size of this substituent, rather than by the electronic effect of the electropositive silicon it contains. Other influences on the preferred conformations of the reactants and transition structures are discussed.

Introduction

The validity of the Felkin–Anh explanation[1] for diastereocontrol in nucleophilic attack on aldehydes and ketones (Cram's rule)[2] is well established when the substituents on the adjacent stereogenic centre exert only steric effects. The incoming nucleophile attacks more or less antiperiplanar to the large substituent, with the medium-sized substituent 'inside', between the incoming nucleophile and the carbonyl group, as shown in structure **1**.



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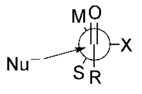

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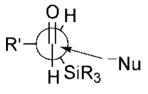
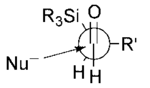
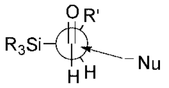


3a R' = H
b R' = Me



4a R' = H
b R' = Me



5a R' = H
b R' = Me

The explanation of the stereochemistry differs slightly when one of the substituents either is, or is attached by, an electronegative atom. The electronegative group, X, is deemed to be the large substituent, whatever its actual size relative to the other groups. Anh's hypothesis, that the best approach for an incoming nucleophile is antiperiplanar to the electronegative atom, as in structure **2**, is supported by much experimental evidence. The preference for this trajectory of approach has also been supported by several computational studies, beginning with that of Anh and Eisenstein in 1977,[3] and including the more recent and more thorough computational studies of Wong and Paddon-Row[4] and of Frenking and co-workers.[5,6]

In spite of the wide availability of synthetic methods for introducing electropositive substituents, such as silyl and stannyl, mechanistic studies, both experimental and computational, have usually examined only the stereoelectronic effects of alkyl, aryl, and electronegative substituents. Whether electropositive substituents provide very different stereoelectronic effects has not been systematically investigated. The only computational paper that does examine this point in the context of nucleophilic attack on a carbonyl group, is that of Wong and Paddon-Row.[7] These authors performed RHF and MP2 calculations on the stereochemistry of lithium hydride attack on 2-silylacetaldehyde as a model, and they found attack *syn* to the silyl group to be preferred. The trajectory shown in **3a** was computed to be lower in energy than that depicted in **4a**.

This result is surprising, because, in considering how an α-silyl group would influence the diastereoselectivity of attack on a carbonyl group in the Felkin–Anh steric model **1**, anyone would almost certainly choose the arrangement in structure **5a**. The silyl group is the largest substituent attached to the α-carbon; so, in the Felkin–Anh model, nucleophilic attack should occur *anti* to this group. Yet this trajectory of attack is not the one found to be preferred by the calculations of Wong and Paddon-Row.

Attack *syn* to the silyl group is, however, the trajectory that ought to prevail if Anh and Eisenstein's argument is strictly applied. Of the three substituents on the α-carbon atom in 2-silylpropionaldehyde, the methyl group is the most electronegative. Therefore, attack ought to take place *anti* to the methyl group, with the silyl group either 'outside', as in **3b**, or, more likely, 'inside', as in **4b**. Anh and Eisenstein did not consider electropositive substituents, but the prediction that **3** or **4** should be favoured over **5** is a logical extension of their rule for electronegative substituents. Therefore, we shall call this prediction, based on relative substituent electronegativities, the Anh–Eisenstein rule for ease of reference.

It might be argued that Si–C bonds are not strongly polarised, but *the electronegativity difference between silicon and carbon is actually greater than that between carbon and chlorine.* Using Allen's electronegativities (1.92, 2.54 and 2.97),[8] the differences are 0.62 and 0.43, respectively. The origin of the common misconception that Si–C bonds are not strongly polarised is probably the confusion between bond polarisation and molecular polarity. It is certainly true that most organosilanes are not polar, whereas most alkyl halides are. However, the reason that organosilanes have small or no dipole moments,

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† Geometries of the stationary points and their absolute RHF, MP2, and zero-point energies are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b008409n/

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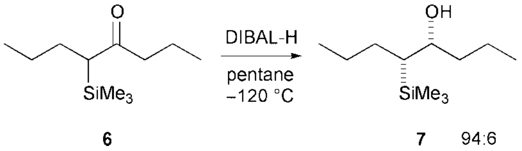
despite the four polar C–Si bonds that they contain, is that the four substituents attached to a silicon atom are tetrahedrally disposed. For the same reason, tetrahalomethanes do not have dipole moments, despite the fact that the four C–X bonds in them are each strongly polarised.

There are seven reports in which the sense of nucleophilic attack by hydride or organometallic carbon nucleophiles on α-silyl aldehydes and ketones has been determined experimentally, usually by treating the β-silyl alcohol products with acid or base to induce stereospecific elimination. Six of these papers report, more often than not, high diastereoselectivity, and always in the sense expected from the Felkin–Anh steric rule (structure **5** favoured), rather than the Anh–Eisenstein electronic rule with silyl 'inside' (structure **4** favoured).[9,10] The reaction **6** ⟶ **7** in Scheme 1 is the first example.[9]



Scheme 1

The seventh paper reports several anomalous examples in which the diastereoselectivity was in the opposite sense,[11] but in this study, unlike the case in all the others, there was an alkoxy substituent on the silicon atom. It was suggested by the authors of this paper that the exceptional behaviour they observed was caused by coordination of the selectride reagent to the oxygen atom, and that the preferred transition structure was the one expected for control of stereochemistry by chelation. However, in this study, dramatic changes were seen in the sense of attack upon quite minor changes in the structures of the α-silyl ketones.

The six sets of experimental results that follow the Felkin–Anh pattern could indicate either that electronic effects of the Anh–Eisenstein type do not exist for α-silyl substituents or that, unexpectedly, **3** is favoured over **4**. The experimental findings would be consistent with the computational results of Wong and Paddon-Row,[7] but only if **3**, with hydrogen 'inside', were preferred over the alternative structure with R′ 'inside'. The experimental results could also be seen as supporting a suggestion made by Cieplak[12] that an incoming nucleophile should approach antiperiplanar to the best electron donor, as in **5**. On the other hand, if Cieplak's suggestion is accepted, the stereochemistry of attack on carbonyl compounds that are substituted with electronegative substituents must be viewed as being anomalous.

In order to sort out these possible explanations of the experimental results and to determine the factors that actually do influence the stereochemistry of nucleophilic attack on carbonyl compounds that have electropositive α-substituents, we have carried out the computational study described in this paper. We have not only repeated the calculations of Wong and Paddon-Row on 2-silylacetaldehyde and on the transition structure for addition of lithium hydride to it; but we have also extended their study to 2-silylpropionaldehyde, a molecule that contains a stereogenic centre. In addition, we have investigated the effects of replacing the SiH_3 group in each of these compounds with trimethylsilyl; and we have located the transition structures for LiH reduction of 3-trimethylsilylbutan-2-one. This last reaction, which involves reduction of a ketone with a trialkylsilyl group attached to the stereogenic centre, is closest to the reactions that have actually been studied experimentally.

Computational methodology

Geometries were optimised and transition structures found using RHF calculations with the 6-31G* basis set.[13] Stationary points were identified as minima or transition structures and unscaled zero-point energy (ZPE) corrections were made by vibrational analyses at this level of theory.

Table 1 Basis set effects on the relative energies of transition structures **A–F** for the addition of lithium hydride to 2-silylpropionaldehyde

	$\Delta E_{MP2} + \Delta ZPE_{RHF}$/kcal mol^{-1}			
	6-31G*	6-31G**	6-31+G*	6-31++G**
E	0.00	0.00	0.00	0.00
A	0.19	0.55	0.10	0.33
D	0.73	0.79	0.71	0.67
B	1.27	1.58	1.06	1.28
F	2.07	2.10	1.94	1.96
C	2.29	2.68	2.78	3.03

For consistency with the computational methodology used by Frenking and co-workers[5,6] and by Wong and Paddon-Row,[7] single-point energies were computed at these geometries at the MP2 level of theory. The ZPE-corrected MP2/6-31G* relative energies are given in the Figures. In order to investigate the effects of inclusion of polarisation functions on hydrogen and of diffuse functions on all atoms, single-point MP2 energies were also computed with the 6-31G**, 6-31+G*, and 6-31++G** basis sets for the LiH reduction of 2-silylpropionaldehyde. The results of these calculations, which are reported in Table 1, indicated the adequacy of the 6-31G* basis set for this study.

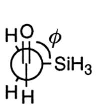
Geometries of the stationary points and their absolute RHF, MP2, and zero-point energies are available as supplementary information.† All calculations were performed with the Gaussian 98 package of electronic structure programs.[14]

In order to analyse the factors that affect the relative energies of the transition structures, we took advantage of the approach developed by Frenking and co-workers[5,6] and by Wong and Paddon-Row[7] in their calculations on reductions of α-substituted aldehydes. Like these authors, we performed single-point calculations at the geometries of the transition structures for LiH reductions, but with Li^+ and with LiH deleted. Although the geometries of the resulting species were not reoptimised following these deletions, these calculations provided valuable information about the relative energies of these geometries as, respectively, transition structures for addition of bare H^- and conformations of the carbonyl compound reactants.

Results and discussion

Rotational profiles of α-silyl aldehydes

We plot the energies of the rotamers of 2-silylacetaldehyde (**8**)



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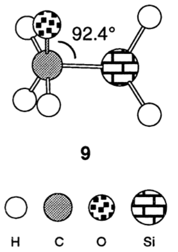

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against the Si–C–C–O dihedral angle, φ, in Fig. 1. Like Wong and Paddon-Row,[7] we find the global minimum **9** at φ = ± 92.4° and a local minimum at φ = 0.0°. Without ZPE corrections, our calculations predict the former conformation to be below the latter by 0.17 kcal mol^{-1}; but with inclusion of ZPE corrections we find that the two conformations become essentially isoenergetic.

The global minimum **9** at φ = ± 92.4° is stabilised by hyperconjugative electron donation from the Si–C bond into the C=O π* orbital. This is reflected in the 0.01 Å longer Si–C bond at

$\varphi = 92.4°$ than at $\varphi = 180.0°$, where the silicon interacts least with the carbonyl group. At $\varphi = 0.0°$ it is the C–H bonds that hyperconjugate with the C=O π* orbital; and Coulombic attraction between the partial negative charge on oxygen and the partial positive charge on silicon probably also contributes to the stability of this conformation, relative to $\varphi = 180.0°$.

Without ZPE corrections, Wong and Paddon-Row found an MP2/6-31+G* energy difference of 1.26 kcal mol^{-1} between the $\varphi = \pm 92.4°$ and $\varphi = 0.0°$ energy minima in Fig. 1.[7] We find that addition of diffuse basis functions to the heavy atoms selectively lowers the energy of not only the minimum at $\varphi = \pm 92.4°$ but also the maximum at $\varphi = 180.0°$, relative to the minimum at $\varphi = 0.0°$. Without diffuse functions on the heavy atoms, the 6-31G* basis set seems to overestimate the stabilisation provided by the proximity of the negatively charged oxygen and the positively charged silicon at $\varphi = 0.0°$.

The electropositive silyl group makes the conformational preferences of 2-silylacetaldehyde very different from those for 2-chloro- or 2-fluoroacetaldehyde.[5–7] For example, Frenking finds that 2-chloroacetaldehyde has its global energy minimum at $\varphi = \pm 156°$, where the C=O and C–Cl dipoles are nearly antiparallel. A local minimum at $\varphi = 0.0°$ is 0.85 kcal mol^{-1} higher in energy. There is an energy maximum near $\varphi = \pm 65°$, a geometry at which the Cl–C bond is hyperconjugated with the carbonyl group.

Our calculations on 2-trimethylsilylacetaldehyde find the lowest-energy conformation to be at $\varphi = \pm 85.9°$. As shown in Fig. 1, the shallow local minimum at $\varphi = 0.0°$ in 2-silylacetaldehyde disappears in 2-trimethylsilylacetaldehyde and is replaced by a local maximum, which is 1.08 kcal mol^{-1} above the minimum. Both of these stationary points are further below the maximum at $\varphi = 180.0°$ than the corresponding minima are in 2-silylacetaldehyde. Substitution of trimethylsilyl for silyl stabilises the minima near $\varphi = \pm 90.0°$ by 1.17 kcal mol^{-1} and the $\varphi = 0.0°$ conformation by 0.39 kcal mol^{-1}, relative to the maximum at $\varphi = 180.0°$.

The stabilisation of the $\varphi \sim 90°$ minimum by substitution of trimethylsilyl for silyl is due to the C–SiMe$_3$ bond being a better hyperconjugative electron donor than the C–SiH$_3$ bond (the SiMe$_3$ group has a low negative Hammett σ_p value of -0.03,[15] whereas the SiH$_3$ group has a low positive σ_p value of $+0.1$). Hyperconjugative electron donation removes electron density from the C–Si bond, thus increasing the positive charge on silicon. An isodesmic reaction that provides the relative stabilities of Me$_3$Si$^+$ and H$_3$Si$^+$ by comparing their hydride affinities finds the substituted silyl cation to be more stable than the unsubstituted cation by 38.9 kcal mol^{-1} at the MP2/6-31G* level.

Clearly, the 0.39 kcal mol^{-1} lowering of the energy at $\varphi = 0.0°$, relative to $\varphi = 180.0°$, that results from the substitution of SiMe$_3$ for SiH$_3$ has a different origin. The steric bulk of trimethylsilyl is larger than that of silyl; and the existence of a destabilising steric interaction between the SiMe$_3$ group and the carbonyl group at the $\varphi = 0.0°$ conformation is indicated by the fact that the O–Si distance is 0.093 Å longer in 2-trimethylsilylacetaldehyde than in 2-silylacetaldehyde. It is, therefore, rather surprising that substitution of SiMe$_3$ for SiH$_3$ actually stabilises the $\varphi = 0.0°$ conformation. In addition to the steric destabilisation of the $\varphi = 0.0°$ conformation, there must also be a stabilising O–Si attraction in this conformation that is stronger for SiMe$_3$ than for SiH$_3$. A likely candidate is an electrostatic attraction between the positively charged silicon and the negatively charged oxygen. Since methyl groups are inductively electron withdrawing, relative to hydrogen,[16] the silicon atom in an SiMe$_3$ group should be more positive than the silicon atom in an SiH$_3$ group. A Mulliken analysis confirms that this is, in fact, the case.

The larger Coulombic attraction between the positively charged silicon and the negatively charged carbonyl oxygen in 2-trimethylsilylacetaldehyde than in 2-silylacetaldehyde is reflected not only in the energies of the $\varphi = 0.0°$, relative to the $\varphi = 180.0°$ conformation of these two aldehydes but also in the geometries of the global energy minima. The Si–C–C–O dihedral angle of 85.9° in 2-trimethylsilylacetaldehyde is 6.5° smaller that the same dihedral angle in 2-silylacetaldehyde, making the O–Si distance 0.036 Å smaller in the former aldehyde than in the latter.

2-Silylpropionaldehyde (**10**) has no symmetry, and the rotational energy plot for **10** in Fig. 1 is correspondingly more complicated than that for 2-silylacetaldehyde (**8**). For **10** the global minimum **11** is at $\varphi = 108.0°$, and it benefits from the same type of hyperconjugation between the Si–C bond and the C=O π* orbital that exists in 2-silylacetaldehyde. In **11** the methyl group is 'inside', nearly eclipsing the carbonyl group, as expected from the Felkin–Anh picture **1**. The alternative conformation, with the methyl 'outside', has an energy minimum at $\varphi = -84.0°$ and is 1.19 kcal mol^{-1} higher in energy than conformation **11** with the methyl 'inside'. The conformation in which the silyl group eclipses the carbonyl group ($\varphi = 0.0°$) is

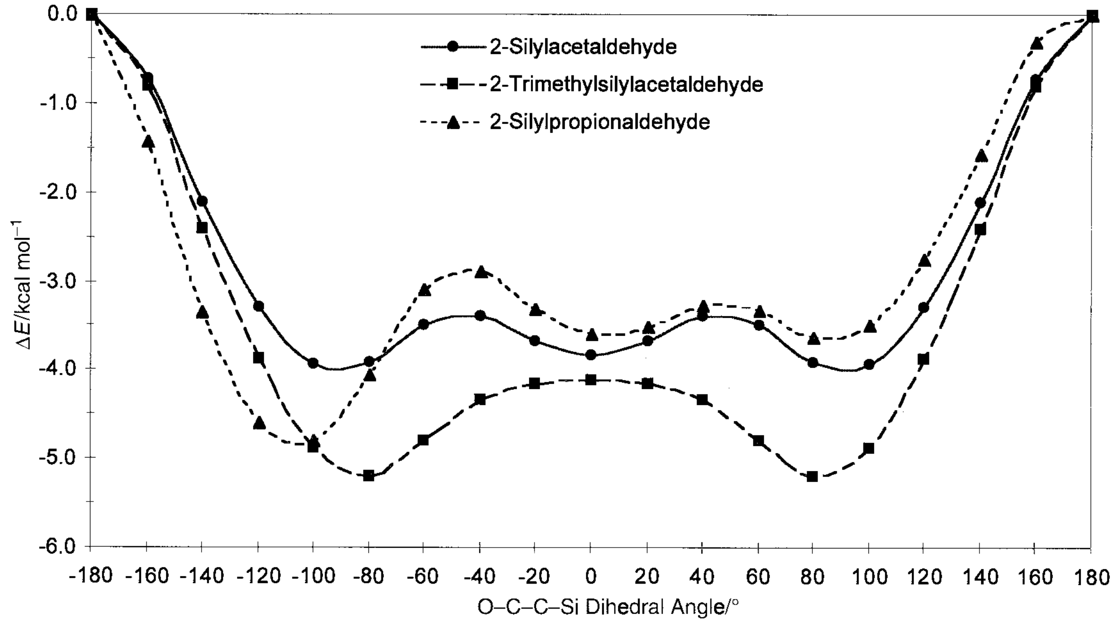
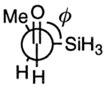


Fig. 1 MP2/6-31G*//HF/6-31G* rotational energy profiles for 2-silylacetaldehyde **8**, 2-trimethylsilylacetaldehyde, and 2-silylpropionaldehyde **10**.



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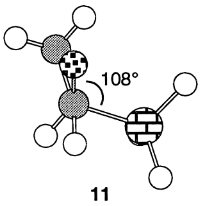

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also computed to be 1.19 kcal mol^{-1} above the global minimum at $\varphi = 108.0°$.

There appear to be two possible reasons why the methyl group prefers the 'inside' position, and both probably contribute to this conformational preference. First, the H–C bond is partially hyperconjugated with the carbonyl group when the methyl group is 'inside'; whereas, the Me–C bond is partially hyperconjugated with the carbonyl group when the hydrogen is 'inside'. Since the H–C bond is a better hyperconjugative electron donor than the Me–C bond,[12,17] the former conformation should be lower in energy than the latter. Second, there is probably a weak Coulombic attraction between the positively charged hydrogen atoms of the methyl group and the negatively charged oxygen atom. Evidence exists for a similar weak attraction, involving the methyl hydrogens and the fluorine, in 1-fluoropropane.[17]

Whatever its precise origin, the well known preference for the methyl group to be close to the carbonyl oxygen is seen most clearly in the lowest-energy conformation for propionaldehyde itself, in which the methyl group perfectly eclipses the carbonyl group. This global energy minimum is calculated to be between 1 and 2 kcal mol^{-1} below the pair of local minima in which the methyl group is rotated by 120°.[18]

Replacing the silyl group in 2-silylpropionaldehyde (**10**) with a trimethylsilyl group results in some small changes in conformational preferences that are similar to those found on making the same replacement in 2-silylacetaldehyde (**8**). In 2-trimethylsilylpropionaldehyde the global energy minimum, which has the methyl group 'inside', shifts from $\varphi = 108.0°$ to $\varphi = 102.2°$. The local minimum, with the methyl 'outside', is 0.83 kcal mol^{-1} higher in energy. At this minimum too, the replacement of SiH_3 by $SiMe_3$ shifts the optimised value of φ by *ca.* 6°, to $\varphi = -78.3°$. As is the case in 2-trimethylsilylacetaldehyde, the $\varphi = 0.0°$ conformation of 2-trimethylsilylpropionaldehyde, in which the C=O σ and the C–Si bonds are eclipsed, is not an energy minimum.

Types of transition structures for lithium hydride additions to α-silyl aldehydes

We have found it expedient to analyse the results of our calculations on lithium hydride additions in terms of idealised versions **A**–**F** of the six types of possible transition structures for the reaction of a nucleophile (represented by an arrow) with 2-silylpropionaldehyde. All the structures have been drawn from the same point of view, with the carbonyl group in front and pointing up and one group *anti* to the incoming nucleophile. The same absolute configuration at the α-carbon is shown throughout.

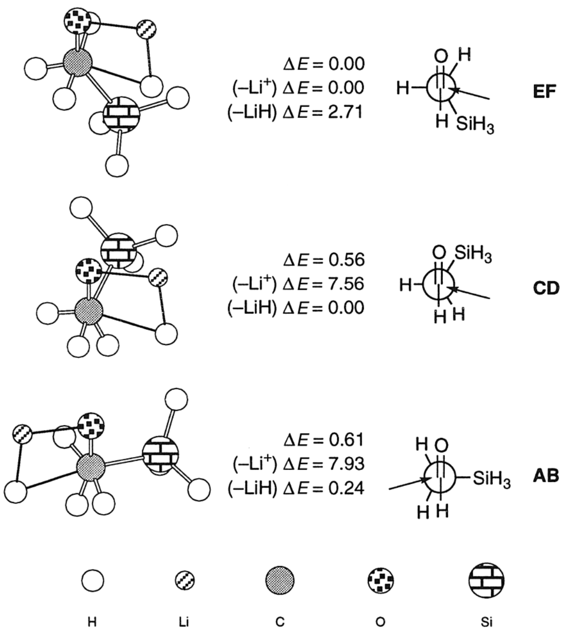
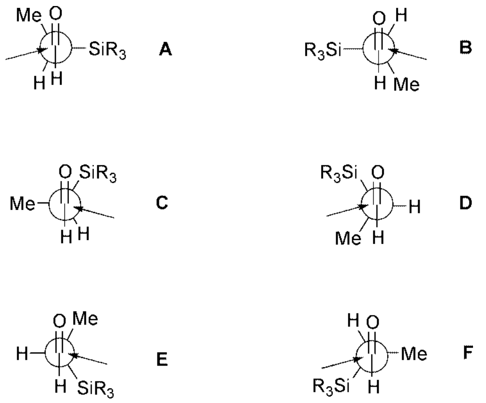


Fig. 2 MP2/6-31G*//HF/6-31G* transition structures for 2-silylacetaldehyde and lithium hydride and relative energies in kcal mol^{-1}.



Structure **A** has the strict Felkin–Anh geometry **5b**, with the silyl group *anti* to the nucleophile and the methyl group 'inside', between the incoming nucleophile and the carbonyl oxygen. Structure **C** is the conformation that is predicted to be favoured by the strictly applied Anh–Eisenstein rule, with the silyl group 'inside', close to the carbonyl group, and the nucleophile attacking *anti* to the methyl group, as in **4b**. Structure **E** appears to be very improbable, since it has the silyl group 'outside', the methyl group 'inside' and the nucleophile attacking *anti* to the hydrogen atom. Structures **B**, **D**, and **F** are each the same as, respectively, structures **A**, **C**, and **E**, except for the exchange of the positions of the methyl and the hydrogen that are attached to the stereogenic carbon. Nucleophilic attack from the left-hand side, as in structures **A**, **D**, and **F**, gives the diastereoisomer that is expected from the Felkin–Anh (*i.e.*, Cram) rule. Attack from the right-hand side, as in **B**, **C**, and **E** gives the anti-Felkin–Anh diastereoisomer.

Transition structures for lithium hydride addition to 2-silylacetaldehyde (8)

In 2-silylacetaldehyde the α-carbon is not a stereocentre. Therefore, there are only three types of energetically different transition structures, rather than six. Upon attack by an achiral nucleophile, each pair of equivalent transition structures gives a pair of enantiomers, rather than a pair of diastereoisomers. The three pairs of transition structures differ only in the orientation of the silyl group. In **A** and **B** SiH_3 is *anti* to the nucleophile; in **C** and **D** SiH_3 is 'inside', and in **E** and **F** it is 'outside'.

We show in Fig. 2 the transition structures calculated for the addition of lithium hydride to 2-silylacetaldehyde (**8**), and, next to each, a drawing of the nearest schematic version. The transition structures are presented in the order of increasing energy, with the lowest-energy structure at the top. The relative energy of each structure in kcal mol^{-1} is the top line of the three energies next to it. The second line shows the relative energy, computed for the frozen geometry with the lithium ion removed; and the third line gives the relative energy of the frozen structure with both the lithium and the hydride removed.

We see immediately, as Wong and Paddon-Row saw before us,[7] that the lowest-energy transition structure **EF** has neither the Felkin–Anh **AB** nor the strict Anh–Eisenstein **CD** geometry. In **EF** the hydride approaches the carbonyl group from the more hindered direction, *syn* to the silyl group. The Anh–Eisenstein transition structure **CD** is 0.56 kcal mol^{-1} higher in energy, and the Felkin–Anh structure **AB** is 0.05 kcal mol^{-1} higher still.

Without vibrational corrections, the MP2/6-31+G* calculations of Wong and Paddon-Row found **CD** to be 0.80 kcal mol^{-1} higher than **AB**. When diffuse functions are added to the 6-31G* basis set that we used, the 0.85 kcal mol^{-1} change in the energy difference computed between these two transition structures parallels, but is smaller in magnitude than, the increase in the energy difference between the analogous conformations of 2-silylacetaldehyde.

Although the energy differences between the three transition structures in Fig. 2 are small, whatever causes the **EF** transition structure to have the lowest energy must override the rather high relative energy (2.71 kcal mol^{-1}) that this conformation of 2-silylacetaldehyde **8** has without the lithium hydride. Like Wong and Paddon-Row, we ascribe the rather surprising preference for transition structure **EF** over both **AB** and **CD** to the Coulombic attraction between the negatively charged hydride and the positively charged silicon. This interpretation is supported by the much lower energy of **EF**, relative to conformations **AB** and **CD**, when the lithium cation is removed.

The finding, first published by Wong and Paddon-Row, that transition structure **EF** is computed to be favoured for reduction of 2-silylacetaldehyde by lithium hydride, shows that some modification of both the Felkin–Anh and Anh–Eisenstein rules must be seriously considered for electropositive substituents. This finding also poses the question, already raised in the introduction, of why experiments on the reduction of α-silyl-substituted carbonyl compounds are found to give the products predicted by the Felkin–Anh rule.[9,10]

It should be noted, however, that the experimentally observed diastereoselectivity is not necessarily inconsistent with the computational finding that transition structure **EF** is favoured for reduction of silylacetaldehyde. For example, in the reduction of 2-silylpropionaldehyde, if transition structure **F**, in which hydrogen is 'inside', were unexpectedly favoured over **E**, in which methyl is 'inside', the experimental results would be rationalised. On the other hand, it is possible that replacement of the computationally convenient SiH_3 group with the bulkier, trisubstituted silyl groups (*e.g.*, $SiMe_3$) that were actually used in the experiments might disfavour transition structures **EF**, relative to the Felkin–Anh transition structures **AB**.

In order to investigate these different possibilities, we carried out calculations on the lithium hydride reduction of 2-silylpropionaldehyde **10** and on the effects of replacing the SiH_3 groups in **8** and **10** with $SiMe_3$. The results of these calculations are described in the following sections.

Transition structures for lithium hydride addition to 2-silylpropionaldehyde (10)

The results of our calculations on the reduction of **10** are summarised in Fig. 3. As in our calculations on reduction of 2-silylacetaldehyde, in the lowest-energy transition structure hydride attacks *syn* to the silyl group. However, this structure, which most nearly resembles **E**, is only 0.19 kcal mol^{-1} lower in energy than a transition structure that is close to the idealised Felkin–Anh geometry **A**.

The transition structure resembling **E** is lowest in energy, in spite of having the third highest energy when lithium hydride is removed. Obviously, this conformation is not favourable for propionaldehyde in the absence of lithium hydride. The proximity of the hydride to silicon again appears to be responsible for the low energy of this transition structure; for it becomes, by far, the most favourable structure when only the lithium cation is removed.

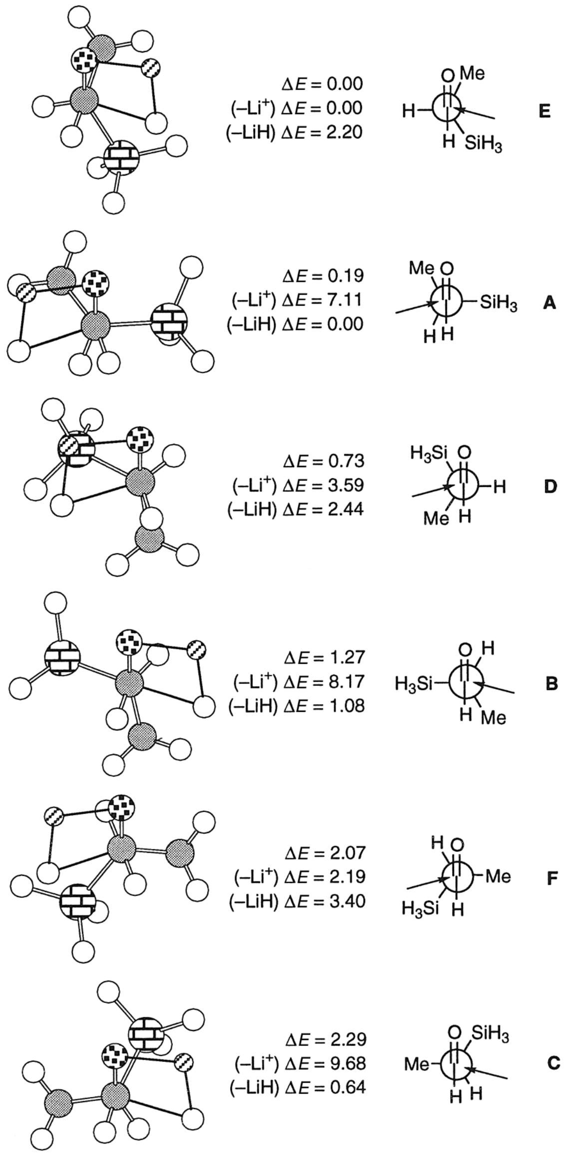


Fig. 3 MP2/6-31G*//HF/6-31G* transition structures for 2-silylpropionaldehyde and lithium hydride and relative energies in kcal mol^{-1}.

The third lowest transition structure also has the hydride close to the silyl group. Its geometry most resembles idealised structure **D**. This structure remains the third lowest in energy when the lithium cation is removed, but it becomes the second highest conformation in the absence of both lithium and hydride.

Interchanging the positions of the methyl group and the hydrogen that are attached to the stereogenic carbon gives the three transition structures of highest energy. The conformational preference in 2-silylpropionaldehyde, discussed above, for placing methyl rather than hydrogen close to the carbonyl oxygen, contributes to the lower energy of the transition structures **E** and **A**, relative to **F** and **B**, respectively. The energy differences between these pairs of structures amounts to 2.07 kcal mol^{-1} for the **E-F** pair and to 1.08 kcal mol^{-1} for the **A-B** pair. These energy differences remain largely unchanged when the lithium cation is removed; but, on removal of lithium and hydride the **E**–**F** and **A**–**B** energy differences are both in the range of 1.1–1.2 kcal mol^{-1}. This difference is close to the 1.19 kcal mol^{-1} energy difference between the fully optimised methyl 'inside' and methyl 'outside' conformations of 2-silylpropionaldehyde.

The remaining pair of transition structures actually differ by more than a methyl–hydrogen interchange. The highest energy structure does, indeed, resemble **C**; but in the structure with the third lowest energy, which most closely resembles **D**, the hydride nucleophile is much closer to silicon than in **C**. In fact, with the lithium cation removed, the structure that most resembles **D** remains third lowest in energy; but **C** has the highest energy of all six structures. In contrast, with both lithium and hydride removed, **C** is the second lowest-energy conformer, presumably because it places the positively charged silyl group close to the negatively charged carbonyl oxygen, as in the $\varphi = 0.0^\circ$ conformation of 2-silylpropionaldehyde.

Basis-set effects on the relative energies of the transition structures

As discussed in the section on the conformations of 2-silylacetaldehyde, comparison of our MP2/6-31G* relative energies with the MP2/6-31+G* relative energies of Wong and Paddon-Row shows that addition of diffuse functions to the basis sets for the non-hydrogen atoms stabilises a geometry in which the Si–C bond hyperconjugates with the carbonyl, relative to a geometry in which the silyl group eclipses the carbonyl. A similar basis set effect, but of smaller magnitude, was noted in the relative energies of the transition structures for lithium hydride addition to 2-silylacetaldehyde. In order to determine whether augmentation of the 6-31G* basis set would significantly alter the relative MP2/6-31G* single-point energies computed for transition structures **A–F** in attack of lithium hydride on 2-silylpropionaldehyde, we carried out MP2/6-31G**, MP2/6-31+G* and MP2/6-31++G** calculations.

The results of these single-point MP2 calculations with all three basis sets are given in Table 1. Addition of polarisation functions to the hydrogens (6-31G* ⟶ 6-31G**) stabilises **E** more than all the other transition structures. The amount by which each transition structure is stabilised, relative to **E**, generally decreases with the distance between the hydride nucleophile and the silyl group. For example, **A** and **B** are stabilised less than **D** and **F**. Thus, it would appear that the major effect that addition of polarisation functions to the hydrogens has on the relative energies of the transition structures is due to an improvement in the description of the SiH_3–H^- interaction.

In contrast, addition of diffuse basis functions to the heavy atoms (6-31G* ⟶ 6-31+G*) stabilises most of the transition structures relative to **E**. Structures **A** and **B** are stabilised the most. This finding is consistent with the comparisons, made in the sections on 2-silylacetaldehyde **8** and on the addition of lithium hydride to **8**, between our 6-31G* results and the 6-31+G* results of Wong and Paddon-Row.

Addition of polarisation functions to the hydrogens and diffuse functions to the heavy atoms have opposite effects on the energies of most of the transition structures, relative to that of **E**. An exception is transition structure **C**, for which the effects of both types of basis set expansion add. For the other four transition structures, going from 6-31G* to 6-31++G** changes their MP2 energies, relative to that of **E**, by less than ± 0.15 kcal mol^{-1}. Consequently, the results in Table 1 validate the use of the 6-31G* basis set for computing, with at least semi-quantitative accuracy, the relative energies of the transition structures for gas-phase addition of lithium hydride to α-silyl carbonyl compounds.

Transition structures for lithium hydride additions to carbonyl compounds containing α-trimethylsilyl groups

Shown in Fig. 4 are the transition structures calculated for the combination of lithium hydride with 2-trimethylsilylacetaldehyde. Now the Felkin–Anh transition structure **AB** is the lowest in energy. The transition structure **EF**, in which hydride attacks *syn* to the silyl group, becomes the highest in energy of the three transition structures, although the energy difference between it and **CD** is not very large.

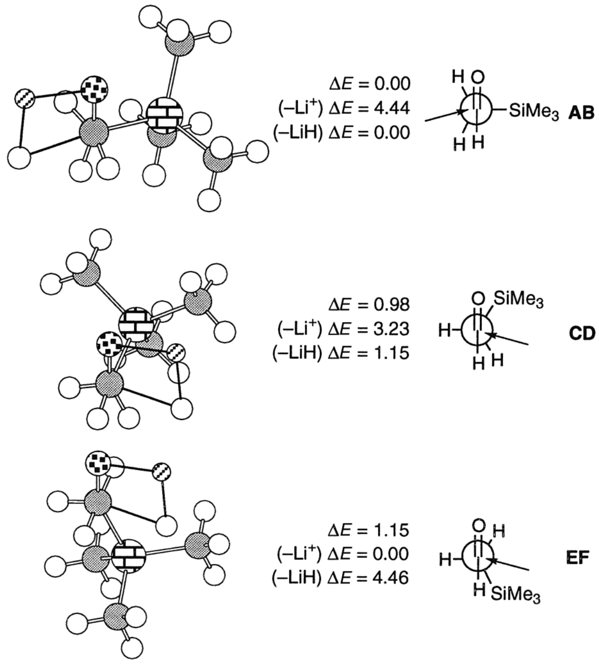


Fig. 4 MP2/6-31G*//HF/6-31G* transition structures for 2-trimethylsilylacetaldehyde and lithium hydride and relative energies in kcal mol^{-1}.

Transition structure **EF** is by far the lowest in energy when the lithium cation is removed, but comparison of the relative energies in Figs. 2 and 4 suggests that the attraction between the hydride ion and the $SiMe_3$ group is weaker than that between hydride and SiH_3. This decrease is responsible for the change from **EF** being favoured over **AB** by 0.61 kcal mol^{-1} for lithium hydride addition to 2-silylacetaldehyde to **AB** being favoured over **EF** by 1.15 kcal mol^{-1} for the same reaction of 2-trimethylsilylacetaldehyde.

As discussed in the section on aldehyde conformations, the silicon atom is actually more positively charged in $SiMe_3$ than in SiH_3. Therefore, the 1.76 kcal mol^{-1} change in the relative energies of **EF** and **AB** on substitution of trimethylsilyl for silyl is presumably due to the larger size of $SiMe_3$ compared to SiH_3, rather than to an electronic effect. In fact, the Si–H^- distance in **EF** increases by 0.277 to 3.086 Å, on replacement of SiH_3 by $SiMe_3$. This increase is consistent with the existence of a destabilising interaction between the methyl groups of $SiMe_3$ and the hydride, which raises the energy of transition structure **EF**, relative to that of **AB**.

In Fig. 5 we summarise the results of our calculations on the reaction of lithium hydride with 2-trimethylsilylpropionaldehyde. Again the Felkin–Anh transition structure **A** is the lowest in energy. The next lowest in energy is its partner **B**, with the methyl group 'outside', instead of 'inside'. The 1.07 kcal mol^{-1} energy difference between **A** and **B** is nearly the same as the 1.08 kcal mol^{-1} energy difference between the analogous pair of **A**–**B** transition structures in the lithium hydride reduction of 2-silylpropionaldehyde **10** and similar to the 1.19 kcal mol^{-1} energy difference between the methyl 'inside' and methyl 'outside' conformations of **10**.

The third lowest-energy transition structure is **E**, which has the hydride *syn* to the silyl group. This structure again becomes the lowest in energy if the lithium ion is removed but one of the highest if the lithium and the hydride are both removed. The Si–H^- distance in transition structure **E** increases by 0.260 to 3.073 Å, when SiH_3 in **10** is replaced by $SiMe_3$. This increase in the Si–H^- distance is again consistent with a destabilising interaction between the hydride and the methyl groups of $SiMe_3$ being responsible for raising the energy of transition structure **E**, relative to those of structures **A** and **B**, when SiH_3 is replaced by $SiMe_3$.

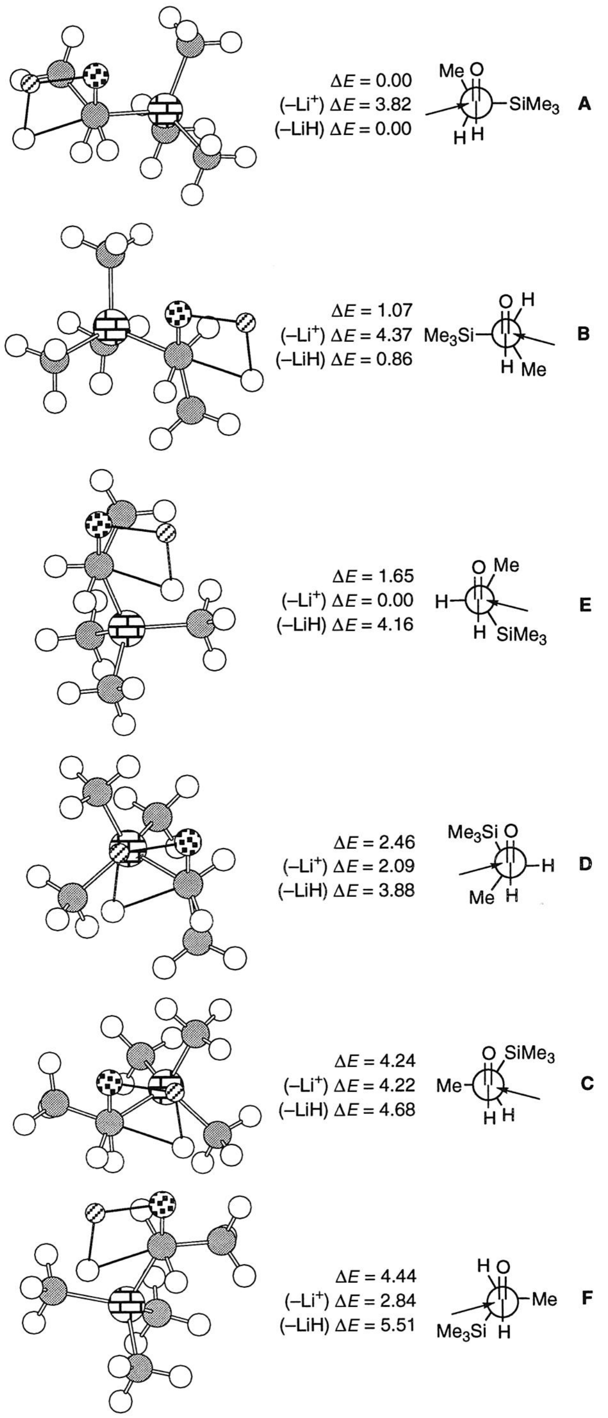


Fig. 5 MP2/6-31G*//HF/6-31G* transition structures for 2-trimethylsilylpropionaldehyde and lithium hydride and relative energies in kcal mol^{-1}.

It is noteworthy that, in the lithium hydride addition reactions of both 2-silylacetaldehyde and 2-silylpropionaldehyde, replacement of SiH_3 by $SiMe_3$ destabilises not only structure **E**, but also structures **C**, **D**, and **F**, relative to structures **A** and **B**. Unlike the case in **A** and **B**, in **D–F** the hydride attacks *syn* to the silyl group; and the silicon–hydride interactions in **D–F** are obviously disfavoured by replacement of SiH_3 by the bulkier $SiMe_3$ group.

Finally in Fig. 6 we show the transition structures calculated for the combination of lithium hydride with 3-trimethylsilylbutan-2-one. Of the reactions on which we have performed calculations, this reaction is closest to most of those that have been studied experimentally. There are some changes in the relative energies in Fig. 6 from those in Fig. 5, but the reason for each of the changes can be easily understood.

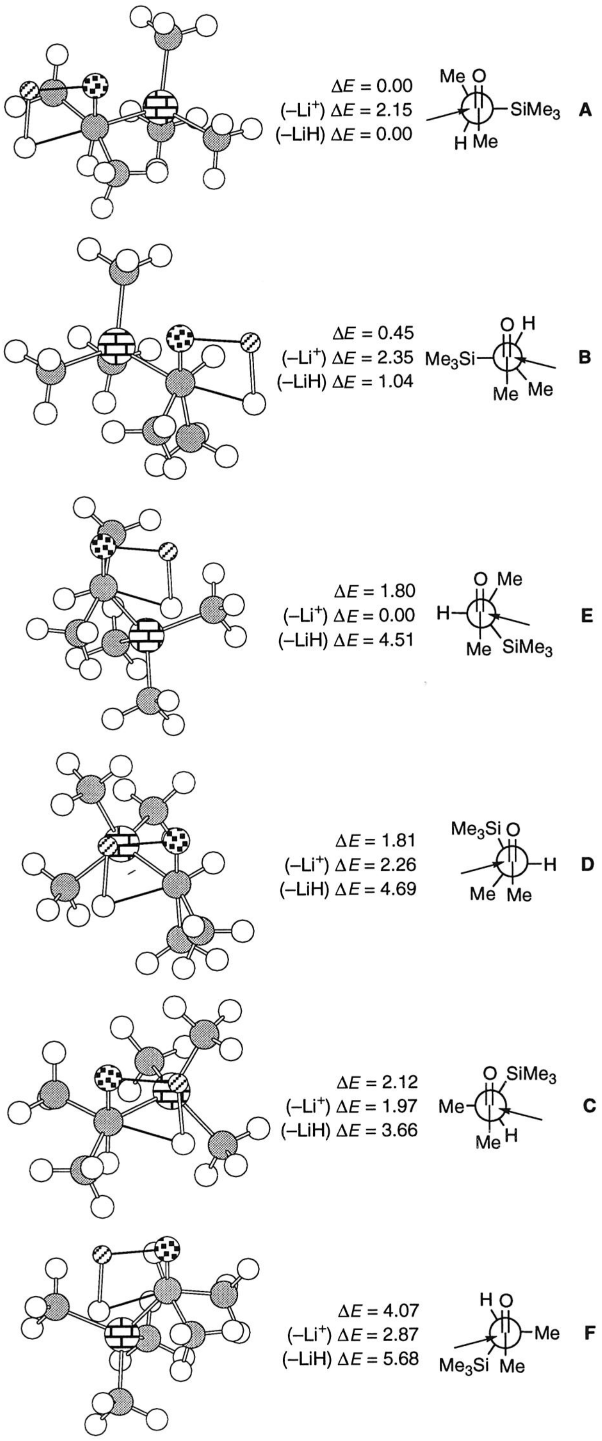


Fig. 6 MP2/6-31G*//HF/6-31G* transition structures for 3-trimethylsilylbutan-2-one and lithium hydride and relative energies in kcal mol^{-1}.

The Felkin–Anh transition structure **A** is again the lowest in energy and remains the lowest when the lithium hydride is removed. However, its partner, transition structure **B**, which has the methyl group 'outside', is now only 0.45 kcal mol^{-1} higher in energy than **A**. This energy difference between transition structures **A** and **B** in the reaction of lithium hydride with 3-trimethylsilylbutan-2-one is 0.62 kcal mol^{-1} smaller than the 1.07 kcal mol^{-1} difference between the analogous pair of transition structures in the addition of lithium hydride to 2-trimethylsilylpropionaldehyde.

The reason for this 0.62 kcal mol^{-1} change in the relative energies of **A** and **B** is almost certainly that the methyl group attached to the carbonyl carbon in the ketone is closer to the trimethylsilyl group in transition structure **A** [Me–C(O)–C–Si = 83.2°] than in transition structure **B** [Me–C(O)–C–

Si = 94.7°]. Steric repulsion between these two groups in transition structure **A** for reduction of the ketone is also apparent in the fact that this same dihedral angle is 9.0° larger than the corresponding H–C(O)–C–Si angle of 74.2° in transition structure **A** for reduction of 2-trimethylsilylpropionaldehyde. This conformational difference rotates the methyl group on the stereogenic centre away from its favoured position, close to the carbonyl group, in the lowest-energy transition structure for lithium hydride addition to the ketone. The dihedral angle of Me–C–C=O = 50.3° in transition structure **A** for reduction of the ketone is more than 10° larger than that of Me–C–C=O = 40.0° in transition structure **A** for reduction of the aldehyde.

The third lowest transition structure for lithium hydride addition to 3-trimethylsilylbutan-2-one is again **E**, in which the hydride is *syn* to the trimethylsilyl group. Like structure **A**, structure **E** is destabilised, relative to structure **B**, by the interaction between the methyl group attached to the carbonyl carbon and the trimethylsilyl group. The energy difference between structures **E** and **B** is 0.77 kcal mol^{-1} larger for lithium hydride addition to 3-trimethylsilylbutan-2-one than for the same reaction of 2-trimethylsilylpropionaldehyde.

On the other hand, the trimethylsilyl group is projected away from the carbonyl methyl in transition structures **C** and **D** for the lithium hydride reduction of the ketone. Consequently, the energies of **C** and **D**, relative to **B**, are not significantly higher in lithium hydride addition to 3-trimethylsilylbutan-2-one than to 2-trimethylsilylpropionaldehyde. In fact, in **C** the carbonyl methyl eclipses the hydrogen at the stereogenic centre, rather than the methyl group attached to this centre, as in **B** and **D**. Therefore, transition structure **C** is actually stabilised by 1.50 kcal mol^{-1}, relative to **B**, and by 1.47 kcal mol^{-1}, relative to **D**, in lithium hydride attack on the ketone, compared to the aldehyde.

Conclusions

We find the factors that play a role in determining the relative energies of the different transition structures for lithium hydride additions to α-silylaldehydes are: (a) Si–C hyperconjugation with the carbonyl group, (b) O–Si attraction, (c) electrostatic attraction between the incoming hydride and the SiH_3 group, (d) the favourability of having the carbonyl oxygen and a methyl group at the α-carbon in close proximity, and (e) greater steric bulk of $SiMe_3$ compared to the SiH_3. Electronic factors (b) and (c) confer on SiH_3 a very different set of predicted conformational preferences from the halide substituents in the calculations of Frenking and co-workers and of Wong and Paddon-Row. Nevertheless, because the bulk of the trimethylsilyl group is large enough to mitigate effects (b) and (c), lithium hydride reduction of both 2-trimethylsilylpropionaldehyde and 3-trimethylsilylbutan-2-one is predicted by our calculations to follow the Felkin–Anh rule, as has been found experimentally in the carbonyl addition reactions of related aldehydes and ketones. In the reduction of 3-trimethylsilylbutan-2-one, our calculations find that repulsion between the carbonyl methyl and the trimethylsilyl group also plays a role in determining the energy difference between the six possible transition structures.

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