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On the Origin of π-Facial Diastereoselectivity in Nucleophilic Additions to Chiral Carbonyl Compounds. 2. Calculated Transition State Structures for the Addition of Nucleophiles to Propionaldehyde 1, Chloroacetyldehyde 2, and 2-Chloropropionaldehyde 3.

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Summary : The transition state structures for addition of LiH to **1**, **2**, and **3** are computed and analyzed at MP2/6-31G(d)//HF/6-31G(d). Three factors are found to be important for the relative energies of the transition state structures; (i) the conformational energy of the aldehyde; (ii) the interactions between the nucleophile and the aldehyde; (iii) the counter ion effect. The relative energies of the lowest lying transition state structures for addition of LiH and CN^- to **3** leading to the major and minor product are not determined by the interactions between the attacking nucleophile and the aldehyde, but by the conformational energies of the aldehyde in the two transition states. The interaction between LiH and **3** is in fact more favorable in the transition state leading to the minor isomer.

Introduction

In the preceeding paper[1], we presented the calculated rotational profiles for propionaldehyde **1**, chloroacetyldehyde **2**, and 2-chloropropionaldehyde **3**. We discussed the structures of the conformational minima in terms of electrostatic, steric, and electronic interactions and showed the change in the eigenvalue ϵ of the LUMO of **1**, **2**, and **3** as a function of the rotation around the C-C(=O) bond. In this paper we present the calculated transition state structures for addition of LiH as model nucleophile to **1**, **2**, and **3**. In order to gain insight into the various factors which influence the relative energies of the transition states, we analyze the calculated results and present a thorough discussion of the theoretical data.

Theoretical Methods

Details of the theoretical procedures are described in the preceeding paper[1] and may be taken from there. Unless otherwise noted, energy values given in this paper are calculated at MP2/6-31G(d)//6-31G(d).

Propionaldehyde

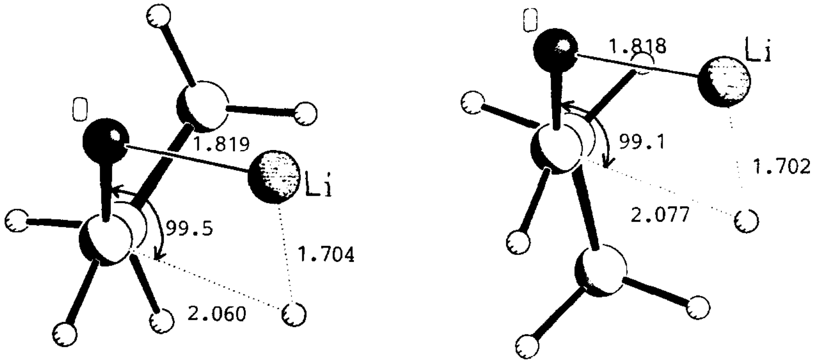
Figure 1 shows the optimized transition state structures for the addition of LiH to propionaldehyde **1*****a**, **1*****b**, and **1*****c** and their relative energies. The calculated energies are shown in Table 1. The energetically lowest lying form is **1*****a**, which has a hydrogen anti to the attacking hydride anion. In contrast, structure **1*****c**, which has a methyl group anti to the hydride anion, is the energetically highest lying form, 1.6 kcal/mol higher than **1*****a**. Very similar results have been reported for the addition of NaH to propionaldehyde by Wu and Houk[2a] and for the addition of CN^- to propionaldehyde by Wong and Paddon-Row[2b].

Table 1. Calculated total energies E_{tot} (hartrees), relative energies E_{rel} (kcal/mol) and zero-point vibrational energies ZPE (kcal/mol) scaled by 0.89.

	6-31G(d)//6-31G(d)			MP2/6-31G(d)//6-31G(d)	
	E_{tot}	E_{rel}	ZPE	E_{tot}	E_{rel}
1***a**	-199.9577	0.0	54.9	-200.5386	0.0
1***b**	-199.9566	0.7	54.8	-200.5365	1.3
1***c**	-199.9560	1.1	54.9	-200.5361	1.6
1***a** ($-Li^+$)	-192.4060	0.0		-192.9849	0.0
1***b** ($-Li^+$)	-192.4041	1.2		-192.9825	1.5
1***c** ($-Li^+$)	-192.4021	2.4		-192.9808	2.6
1***a** (-LiH)	-191.9443	0.0		-192.5090	0.0
1***b** (-LiH)	-191.9427	1.0		-192.5071	1.2
1***c** (-LiH)	-191.9431	0.8		-192.5079	0.7
2***a**	-619.8171	0.6	32.6	-620.3931	0.0
2***b**	-619.8152	1.8	32.6	-620.3903	1.7
2***c**	-619.8181	0.0	32.6	-620.3926	0.3
2***a** ($-Li^+$)	-612.3006	6.5		-612.8858	6.4
2***b** ($-Li^+$)	-612.3052	3.6		-612.8906	3.4
2***c** ($-Li^+$)	-612.3110	0.0		-612.8961	0.0

2^*a (-LiH)	-611.8060	0.7		-612.3663	0.6
2^*b (-LiH)	-611.8071	0.0		-612.3672	0.0
2^*c (-LiH)	-611.8069	0.1		-612.3665	0.4
3^*a	-658.8574	0.0	49.6	-659.5668	0.0
3^*b	-658.8544	1.9	49.3	-659.5640	1.8
3^*c	-658.8554	1.3	49.5	-659.5648	1.3
3^*d	-658.8547	1.7	49.4	-659.5644	1.5
3^*e	-658.8531	2.7	49.4	-659.5621	2.9
3^*a (-Li^+)	-651.3204	0.0		-652.0280	0.0
3^*b (-Li^+)	-651.3038	10.4		-652.0114	10.4
3^*c (-Li^+)	-651.3168	2.3		-652.0251	1.8
3^*d (-Li^+)	-651.3040	10.3		-652.0114	10.4
3^*e (-Li^+)	-651.3086	7.4		-652.0161	7.5
3^*a (-LiH)	-650.8460	0.0		-651.5395	0.0
3^*b (-LiH)	-650.8430	1.9		-651.5363	2.0
3^*c (-LiH)	-650.8426	2.1		-651.5364	1.9
3^*d (-LiH)	-650.8437	1.4		-651.5377	1.3
3^*e (-LiH)	-650.8460	0.0		-651.5395	0.0

Figure 1. Optimized transition state structures 1^*a, 1^*b, and 1^*c. Distances are given in Å, angles in degrees.



1^*a

0.0 kcal/mol

0.0 kcal/mol (- LiH)

0.0 kcal/mol (- Li^+)

α (OCCC) = 29°

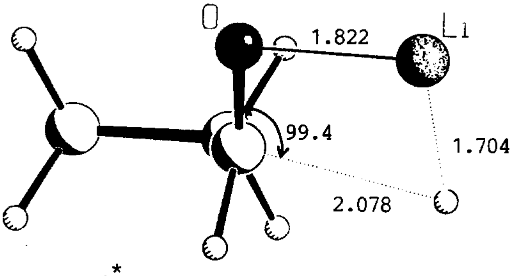
1^*b

1.3 kcal/mol

1.2 kcal/mol (- LiH)

1.5 kcal/mol (- Li^+)

α (OCCC) = 166°



1^*c

1.6 kcal/mol

0.7 kcal/mol (- LiH)

2.6 kcal/mol (- Li^+)

α (OCCC) = -85°

What determines the relative energies of the transition state structures **1^*a**, **1^*b**, and **1^*c**? The energy difference between the transition states **1^*a** and **1^*b**, which have a hydrogen atom anti to the attacking nucleophile, is nearly the same as the energy difference between the two structures calculated either without LiH or without Li^+ (Figure 1). This means that E_{rel} **1^*a** - **1^*b** is mainly determined by the conformation of **1** in the transition states. In fact, **1^*a** resembles most the major conformer **1a** and **1^*b** the minor conformer **1b** which are 1.4 kcal/mol different in energy (See Figure 6 of preceeding paper[1]). If the transition state structure **1^*c** is calculated without LiH, the energy difference **1^*a** - **1^*c** reduces from 1.6 kcal/mol to 0.7 kcal/mol. Thus, nearly half of the stabilization of **1^*a** relative to **1^*c** originates from the more favorable conformation of **1** in **1^*a**. Without the counter ion Li^+, **1^*c** becomes even more disfavored relative to **1^*a** and **1^*b**. In agreement with previous conclusions[2,3] we find that a C-H bond anti to the attacking nucleophile is more favorable than a C-C bond. However, the effect of the counter ion reduces the energy difference **1^*a** - **1^*c** from 2.6 kcal/mol to 1.6 kcal/mol. Thus, there are three different effects which establish the energy ordering of the transition states: (a) the conformation of **1** in the transition states which favors **1^*a** by 0.7 kcal/mol relative to **1^*c**; (b) the interaction of **1** with H^- which is worth an additional 1.9 kcal/mol in favor of **1^*a**; (c) the effect of the counter ion Li^+ which reduces the energy difference **1^*a** - **1^*c** by 1.0 kcal/mol. Our results indicate that all three effects have to be considered for a thorough discussion of nucleophilic additions to carbonyl compounds.

A comparison of the calculated torsion angles α for **1^*a**, **1^*b**, **1^*c**, and the LUMO as function of α (Figure 5, preceeding paper[1]) shows that the LUMO of **1** is higher at the torsion angle α calculated for $\mathbf{1^{*}a}$ (29°) than for $\mathbf{1^{*}b}$ (166°) and $\mathbf{1^{*}c}$ (-85°), although the interaction between **1** and LiH is strongest in $\mathbf{1^{*}a}$. This indicates that a simple consideration of the LUMO of the carbonyl compound in its ground state may be insufficient for an adequate discussion of the interactions with the nucleophile.

The optimized transition state structures $\mathbf{1^{*}a}$, $\mathbf{1^{*}b}$, and $\mathbf{1^{*}c}$ show that the angle between the C=O group and the hydride anion is 99.5° for $\mathbf{1^{*}a}$, 99.1° for $\mathbf{1^{*}b}$, and 99.4° for $\mathbf{1^{*}c}$, which is at the lower end of what was suggested (105 ± 5°) by Bürgi and Dunitz[4]. Slightly larger values have been calculated for the attack of NaH to **1** by Wu and Houk[2a], their values being 102.6° for $\mathbf{1^{*}a}$, 102.0° for $\mathbf{1^{*}b}$, and 102.7° for $\mathbf{1^{*}c}$. The small angle values seem to be caused by the counter ion. Wong and Paddon-Row[2b] report angles between 113.9° and 115.7° for the calculated transition states for the addition of CN^- to 2-fluoropropionaldehyde in the absence of a metal counter ion.

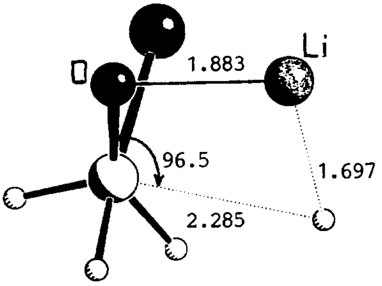
Our finding that the relative energies of the transition states $\mathbf{1^{*}a}$, $\mathbf{1^{*}b}$, and $\mathbf{1^{*}c}$ are strongly determined by the rotational profile of **1** in its gound state may be an explanation why in some cases the diastereoselectivity in the reaction of chiral aldehydes with achiral enolates could successfully be predicted using ground state energies and geometries.[5] Wuts and Walters concluded from their theoretical study using molecular mechanics methods that "the direction of enolate addition is dictated primarily by aldehyde structure and probably not by transition-state geometry".[5] It remains to be seen if this conclusion is also valid if substituents other than alkyl groups, in particular polar substituents, are involved.

Chloroacetaldehyde

Figure 2 shows the optimized transition states for the addition of LiH to chloroacetaldehyde $\mathbf{2^{*}a}$, $\mathbf{2^{*}b}$, and $\mathbf{2^{*}c}$. There are striking differences relative to the corresponding transition states $\mathbf{1^{*}a}$, $\mathbf{1^{*}b}$, and $\mathbf{1^{*}c}$. The transition state which resembles most the lowest lying ground state conformation **2b** is $\mathbf{2^{*}b}$ (Figure 2). However, $\mathbf{2^{*}b}$ is the energetically highest lying transition state, 1.7 kcal/mol higher than $\mathbf{2^{*}a}$ and 1.4 kcal/mol higher than $\mathbf{2^{*}c}$. Unlike the transition states in the $\mathbf{1^{*}}$ series, the energy sequence of the transition states $\mathbf{2^{*}a}$, $\mathbf{2^{*}b}$,

$\mathbf{2^*c}$ is determined by the interactions between the aldehyde **2** and LiH. This can be seem from the relative energies of $\mathbf{2^*a}$, $\mathbf{2^*b}$, and $\mathbf{2^*c}$ calculated <u>without</u> LiH, which shows that the conformation of chloroacetaldehyde is most favorable in $\mathbf{2^*b}$ and least favorable in $\mathbf{2^*a}$. (Figure 2).

Figure 2. Optimized transition state structures $\mathbf{2^*a}$, $\mathbf{2^*b}$, and $\mathbf{2^*c}$. Distances are given in Å, angles in degrees.



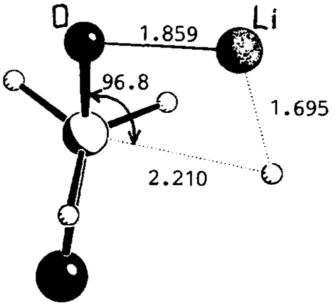
2^*a

0.0 kcal/mol

0.6 kcal/mol (- LiH)

6.4 kcal/mol (- Li^+)

α (OCCCl) = 17°



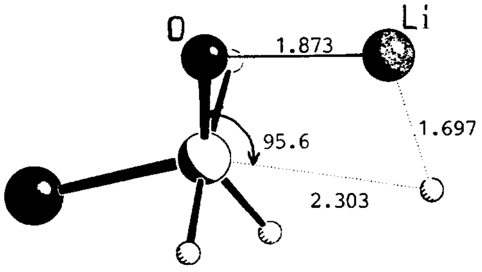
2^*b

1.7 kcal/mol

0.0 kcal/mol (- LiH)

3.4 kcal/mol (- Li^+)

α (OCCCl) = -170°



2^*c

0.3 kcal/mol

0.4 kcal/mol (- LiH)

0.0 kcal/mol (- Li^+)

α (OCCCl) = -103°

The transition state **2^*c** with the C-Cl bond anti to the hydride anion corresponds to the Felkin-Anh model. When the relative energies of structures **2^*a**, **2^*b**, and **2^*c** are calculated without the counter ion (Li^+), **2^*c** becomes by far the lowest lying transition state, 3.4 kcal/mol lower than **2^*b** and 6.4 kcal/mol lower than **2^*a** (Figure 2). This is in agreement with the results of Wong and Paddon-Row[2b] for the addition of CN^- to fluoroacetaldehyde. They calculated the relative energies of the transition states corresponding to **2^*c** , **2^*b**, and **2^*a** to be 0.0, 3.3, and 5.1 kca/mol.[2b] Thus, in the absence of specific counter ion effects discussed below, the "Felkin" transition state **2^*c** is energetically clearly favored.

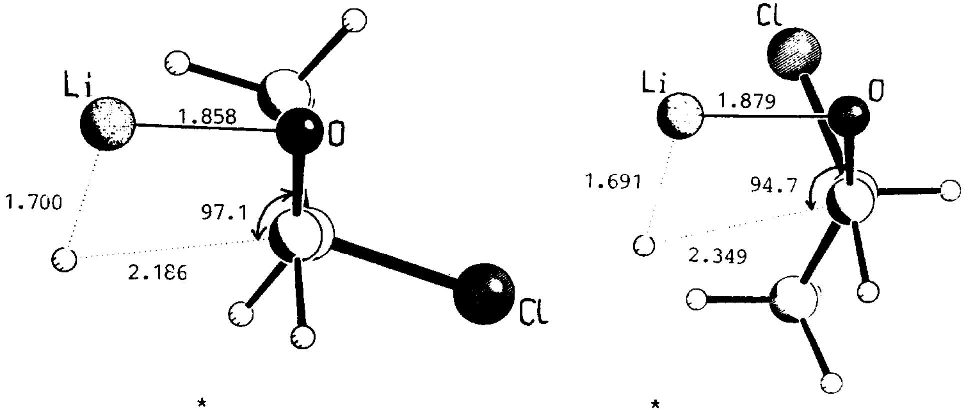
The much stronger influence of the interactions between LiH and aldehyde for the relative energies of the transition states **2^*** compared with **1^*** can be understood when the energy level of the LUMO for **2** (Figure 7, preceeding paper[1]) is compared with the LUMO of **1** (Figure 5, preceeding paper[1]). The LUMO of **2** shows a deep minimum at a torsion angle $\alpha \sim 75^o$ which indicates the importance of the C-Cl bond being perpendicular to the adjacent C=O bond as postulated by Felkin[6] and Anh[7]. The transition state **2^*c** is located at a torsion angle (-103^o) where **2** has a much lower lying LUMO than for **2^*a** and **2^*b**, thus enhancing strongly the HOMO-LUMO interactions. This agrees with the calculated strong stabilization of **2^*c** relative to **2^*a** and **2^*b** in the absence of the counter ion (Figure 2).

The sizable stabilization by 6.7 kcal/mol of **2^*a** relative to **2^*c** is due to the calculated chelating ability of Li^+. If one of the substituents R of the chiral aldehyde has lone-pair electrons such as chlorine in **2**, the counter ion may act as a bridging ligand between the carbonyl oxygen and chlorine, thus enforcing a low-lying transition state with a chelate structure as **2^*a**. In **2^*a**, the interatomic distance between the positively charged Li and the negatively charged Cl is only 3.50 Å, while it is 4.86 Å in **2^*c** and 4.69 Å in **2^*b**. This indicates favorable Li-Cl interactions with the sequence **2^*a** > **2^*b** > **2^*c**. By using appropriate ligands such as alkoxy groups capable of participating in bidendate chelates as intermediates, the stereochemical course of the addition reactions of chiral α-alkoxy carbonyl compounds can be controlled[8] in a direction which is subject to Cram's cyclic model.[9] The important conclusions from the calculated results for **2** and **2^*** is that (i) the relative energies of the transition states **2^*a**, **2^*b**, **2^*c** are determined mainly by the interactions between **2** and LiH, and not by the conformational profile of the aldehyde as in case of **1**; (ii) in the absence of the chelating effect of the counter ion, the energetically lowest lying transition state is **2*****c**, which has the C-Cl bond trans to the attacking nucleophile. It follows that a C-Cl bond anti to the attacking nucleophile is much more favorable than a C-H bond.

2-Chloropropionaldehyde

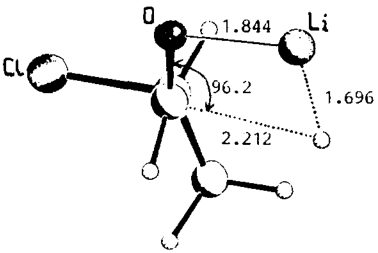
We calculated the transition states for addition of LiH to **3**. Theoretically there should be six transition state structures, three leading to the threo product and three to the erythro isomer. We located three saddle points on the LiH + **3** potential energy surface yielding the threo isomer, but only two transition states, **3*****a** and **3*****b**, that lead to the erythro diastereomer. The five transition states **3*****a**, **3*****b**, **3*****c**, **3*****d** and **3*****e** are shown in Figure 3. The energetically lowest lying form is **3*****a**, which leads to the erythro isomer and has a C-Cl bond trans to the attacking nucleophile (Figure 3). The other transition state yielding the erythro product is **3*****b**, which has a C-H bond anti to the hydride anion. **3*****b** is 1.8 kcal/mol higher in energy than **3*****a**. A transition state with a methyl group anti to hydride leading to the erythro product could not be found.

Figure 3. Optimized transition state structures **3*****a**, **3*****b**, **3*****c**, **3*****d** and **3*****e**. Distances are given in Å, angles in degrees.



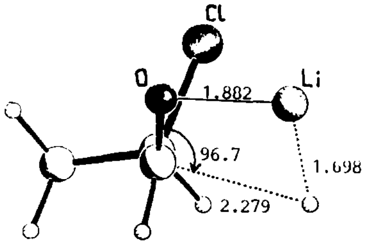
3^*a
0.0 kcal/mol
0.0 kcal/mol (- LiH)
0.0 kcal/mol (- Li^+)
α_1(OCCCl) = -104°
α_2(OCCC) = 17°

3^*b
1.8 kcal/mol
2.0 kcal/mol (- LiH)
10.4 kcal/mol (- Li^+)
α_1(OCCCl) = 24°
α_2(OCCC) = 151°



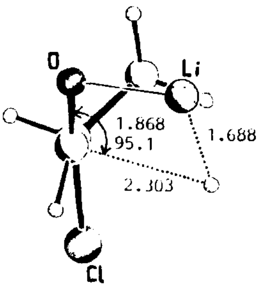
3^*c

1.3 kcal/mol
1.9 kcal/mol (- LiH)
1.8 kcal/mol (- Li^+)
α_1(OCCCl) = -84°
α_2(OCCC) = 156°



3^*d

1.5 kcal/mol
1.3 kcal/mol (- LiH)
10.4 kcal/mol (- Li^+)
α_1(OCCCl) = 22°
α_2(OCCC) = -101°



3^*e

2.9 kcal/mol
0.0 kcal/mol (- LiH)
7.5 kcal/mol (- Li^+)
α_1(OCCCl) = 175°
α_2(OCCC) = 48°

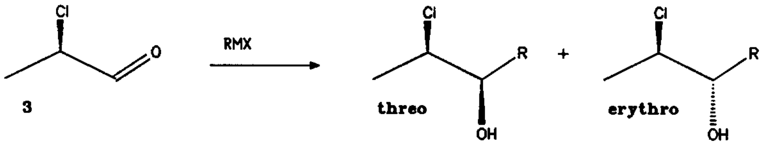
The energetically lowest lying transition state leading to the threo product **3^*c** also has a C-Cl bond in an anti position (Figure 3). **3^*c** is 1.3 kcal/mol higher in energy than **3^*a**. Two other structures give the threo product, **3^*d** with a trans methyl group and **3^*e** with a trans hydrogen. **3^*d** and **3^*e** are 1.5 kcal/mol and 2.9 kcal/mol higher in energy than **3^*a** . The ratio of erythro to threo products was then calculated by assuming a Boltzmann's distribution of the transition states leading to the two diastereomers[10]:

$$\text{erythro/threo} = \Sigma e^{-\Delta Ee/RT} \;/\; \Sigma e^{-\Delta Et/RT} \qquad (1)$$

ΔEe : relative energy of the erythro transition state.
ΔEt : relative energy of the threo transition state.

Using the relative energies for **3^*a**, **3^*b**, **3^*c**, **3^*d**, and **3^*e** (MP2/6-31G(d)//HF/6-31G(d) + ZPE, the theoretically predicted ratio erythro/threo[10] is 92 : 8. This is in good agreement with the experimentally observed[11] results (Table 2) in which methylmetal reagents were used as nucleophile, showing E/T ratios between 77 : 23 and 88 : 12, depending on the nucleophilic agent and reaction conditions. Of course, this agreement is fortuitous since the experimental results are obtained for reactions in solutions while our theoretical results refer to gas phase reactions. The good agreement means that the interactions of the reactants and the solvent have about the same magnitude in the reactions yielding the major and minor isomers, and thus cancel each other.

Table 2. Experimentally obtained[a] diastereoselectivity for the reaction of **3** with various reagants.



RMX	solvent	yield	E/T selectivity
MeTi(OiPr)$_3$	CH_2Cl_2	90%	85:15
MeMgCl	Et_2O	90%	88:12
nBuTi(OiPr)$_3$	Et_2O	80%	80:20
nBuMgCl	Et_2O	80%	77:23

[a] Ref. 11

The energetically lowest lying transition states which lead to the major isomer via 3***a** and to the minor isomer via 3***c** correspond to the Felkin model[6] and with Anh's hypothesis[7] that an electronegative substituent trans to the attacking nucleophile is favored. Our results do not agree with the Cieplak model[3] which predicts that an electron releasing group in the trans position should be favored. The Cieplak model has also been critisized by others.[2] The calculations by Houk et al.[2b] were restricted, however, to achiral coumpounds.

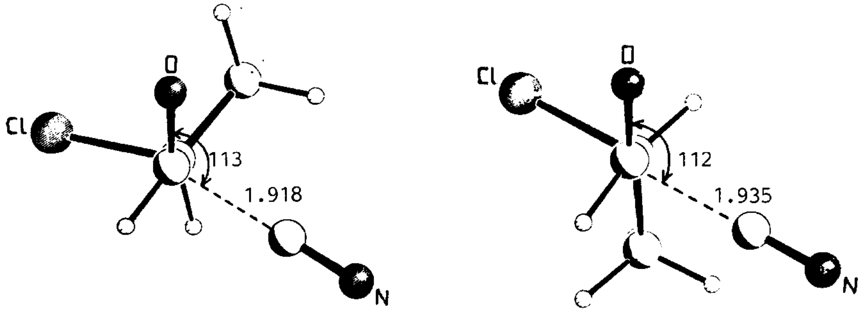
What in fact determines the relative energies of the series 3*? Let us begin with the structures 3***a** and 3***b** yielding the erythro product (Figure 3). The energy difference 3***a** - 3***b** changes very little from 1.8 kcal/mol to 2.0 kcal/mol when the two species are calculated without LiH. This means that the interactions between **3** and LiH have the same magnitude in 3***a** and 3***b**. But the similarity in the computed energy difference is deceptive! 3***b** profits strongly from the chelating ability of the Li^+ counterion, as is revealed by the computed relative energies of 3***a** and 3***b** without Li^+ (Table 1 and Figure 3). Without Li^+, 3***b** is 10.4 kcal/mol higher in energy than 3***a**. Similar results are found for the transition state 3***d**, which is also subject to the chelating effect. The energy difference 3***a** - 3***d** changes dramatically to 10.4 kcal/mol in the absence of Li^+ (Table 1, Figure 3), while the energy changes only little when the two structures are calculated without LiH. Thus, the energy gain due to the chelate effect is worth 8.6 kcal/mol in the case of 3***b** and 8.9 kcal/mol in the case of 3***d**.

Transition state 3^***e** also shows a counter ion effect. Without LiH, the transition state 3^***e** has the same energy as 3^***a**. This is because the conformation of 3 in both structures is close to the energy minimum 3**a** (see Figure 3). Without the counter ion, 3^***e** is 7.5 kcal/mol higher in energy than 3^***a**, indicating less favorable interactions between H^- and 3 in 3^***e**. The energy difference of 2.9 kcal/mol between 3^***a** and 3^***e** indicates a stabilization due to the presence of Li by of 4.6 kcal/mol. The counter ion effect runs parallel to the Li-Cl interatomic distances, which are 3.40 Å (3^***d**), 3.44 Å (3^***b**), 4.56 Å (3^***e**), 4.75 Å (3^***c**), and 4.86 Å (3^***a**).

The energy difference between the "Felkin transition states" 3^***a** and 3^***c** changes little when the two species are calculated without LiH or Li^+ (Table 1, Figure 3). In fact, the energy difference in favor of 3^***a** is <u>reduced</u> in the presence of H^- or LiH, which indicates that the interactions between 3 and LiH is <u>more</u> favorable in 3^***c** than in 3^***a** . This is contrary to the model proposed by Felkin [6] and Anh[7] who argued that 3^***a** is favored over 3^***c** because of better interactions of 3 with the attacking nucleophile. <u>Our calculated results indicate that the difference between</u> 3^***a** <u>and</u> 3^***c** <u>is only due to the conformation of</u> 3 <u>in the two transition states</u>. This is illustrated in Figure 3. The conformation of 3 in the transition state structure 3^***a** is close to the energy minimum conformation 3**a** (compare the torsion angle α with Figure 9 of the preceeding paper[1]), while in 3^***c** it is closer to an energy maximum. The transition states 3^***a** and 3^***c**, which are stabilized mostly be the interactions with H^- (Figure 3), have torsion angles α_1 which are close to the minima for the LUMO of 3, while 3^***b**, 3^***d**, and 3^***e** are found at much higher LUMO values.

What about the attack of nucleophiles without the presence of counter ions? Figure 4 shows the energetically lowest lying transition state structures for addition of nitrile anion CN^- to 3 leading to the major (3^***f**) and minor (3^*g) isomer. 3^***f** is calculated 2.4 kcal/mol lower in energy than 3^*g. The energy difference between the two conformations of 3 calculated with the frozen geometries of 3^***f** and 3^*g without CN^- shows that the conformational difference is 1.3 kcal/mol. Unlike the addition of LiH, the attack of CN^- leading to the major isomer is also favored by the interactions between 3 and the nucleophilic agent. The angle between the attacking nucleophile and the carbonyl group is significantly larger in case of CN^- (Figure 4) than for LiH (Figure 3), which leads to stronger torsional strain. Also, the interatomic distance between carbon atom of the attacking nucleophile (CN^-) and the carbonyl C atom is clearly smaller than between the hydride atom and carbonyl C in case of LiH addition (Figure 3). This indicates a much "later" transition state for the addition of CN^- than for LiH addition. But more than half of the energy difference between **3*f** and **3*g** still comes from the conformational difference of **3** in the transition states.

Figure 4. Optimized transition state structures **3*f** and **3*g**. Distances are given in Å, angles in degrees.



3^*f
0.0 kcal/mol
0.0 kcal/mol (- CN^-)
α_1(OCCCl) = -81°
α_2(OCCC) = 39°

3^*g
2.4 kcal/mol
1.3 kcal/mol (- CN^-)
α_1(OCCCl) = 64°
α_2(OCCC) = 176°

The most important conclusion that arises from our theoretical data is that the energy difference between the transition states leading to the major (**3*a**, **3*f**) and minor isomer (**3*c**, **3*g**) is mainly determined by the difference in the conformational energy of **3** in the two geometries. The difference in the interaction energies of **3** with the attacking nucleophiles are less important. In the case of LiH addition the calculated data indicate even a preference for **3*c**, the transition state yielding the minor isomer.

Conclusions

The calculated transition state structures for addition of LiH to **1**, **2**, and **3** show that in the case of **1** a hydrogen atom trans to the attacking nucleophile is energetically preferred over a methyl group. This preference is partly due to the more favorable conformation of **1** in the corresponding transition state **1*a**. For the addition of LiH to **2**, the most favorable transition state structure **2*a** also has a hydrogen trans to the attacking nucleophile. However, **2*a** profits strongly from favorable interactions between the neighbouring Li and Cl atoms. In the absence of Li^+, the transition state structure **2*b** with the chlorine trans to the nucleophile is clearly favored. The energetically lowest lying transition state structures for addition of LiH to **3** have the chlorine atom trans to LiH. The transition state structure **3*a**, which leads to the major isomer, is 1.3 kcal/mol lower in energy than **3*c**, which leads to the minor product. The energetic preference of **3*a** over **3*c** is caused by the more favorable conformation of **3** in the transition state **3*a**. The interactions between LiH and **3** are more stabilizing in **3*c** than in **3*a**. Also for the attack of CN^- to **3**, the difference between the transition states leading to the major (**3*f**) and minor (**3*g**) isomer is mainly caused by the conformation of **3** in the transition states.

There are several factors which influence π-facial diastereoselectivity in nucleophilic additions to chiral carbonyl compounds, such as steric, electronic, conformational, and electrostatic effects, the importance of which is dependent on the reactant, the nucleophile, the solvent, and the reaction conditions. Since the energy difference favoring one reaction course over the other is often very small, it is difficult to single out a particular effect as being solely responsible for the stereoselectivity. The best one may achieve is to find a model which allows the rationalization of the experimental results for a certain class of compounds (which may hopefully be very large), and to predict the results of new experiments. In contrast to previous leading models[2,3,6,7] based on electronic and/or steric interactions between the carbonyl compound and the nucleophile, our study reveals that the most important factor for the π-facial diastereoselectivity in nucleophilic addition reactions to carbonyl compounds originates from simple conformational effects. We are currently studying the question whether this conclusion also pertains to other systems such as 2-phenyl, 2-alkoxy, and 2-amino propionaldehyde as well as substituted cyclohexanones. Work on this is in progress.

After this work was completed, a study by Xie and Saunders[12] was published on the reaction of 2-pentanone with dialkylamide bases. The hydrogen-transfer reaction was explained using a model in which the electrostatic and conformational effects are the dominant factors in the reactant-like transition state structure, rather than steric effects which previously been suggested for this reaction[13]. Electrostatic effects have also been identified as important for the nucleophilic addition to carbonyl compounds by Wong and Paddon-Row[2c,d] in a recent reeximation of their earlier work[2b]. The reflection of ground state substrate conformations in transition states of certain radical reactions has been emphasized by Burke[14].

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