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On the Origin of π-Facial Diastereoselectivity in Nucleophilic Additions to Chiral Carbonyl Compounds 3. Rotational Profiles of 2-Methoxypropanal and 2-N,N-Dimethylaminopropanal.

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Summary: The rotational profiles of 2-methoxypropanal and 2-N,N-dimethylaminopropanal are theoretically predicted using ab initio methods at the MP2/6-31G*//3-21G level of theory. The conformational energies show a strong dependence on the torsion angle not only around the C-C bond but also around the C-R (R=OMe, NMe_2) bond.

Introduction

In our previous work, we investigated the rotational profiles[1a] of propanal, chloroacetaldehyde and 2-chloropropanal and the transition state structures[1b] for the addition of LiH to these molecules. In this and the following paper[2] we present theoretical results for other substituted propanals, namely 2-methoxypropanal (1) and 2-N,N-dimethylaminopropanal (**2**). Derivates of **1** and **2** have been extensively studied in experimental work by Reetz et al.[3] Here we present the theoretically predicted rotational profiles around the C-C bond (torsion angle α) and the C-R (R=OMe, NMe_2) bond (torsion angle β, Figure 1). Unlike 2-chloropropanal, the conformational space of **1** and **2** involves the rotation around two bonds. The question we address is how the rotation around β affects the barrier around the C(Carbonyl)-C single bond. There are no experimental results for the conformations of **1** and **2** available.

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Figure 1. Structures of the molecules studied in this paper. The values for α and β in the conformations shown are α=0°, β=180°

1 **2**

Theoretical Details

The calculations were carried out using the CONVEX and Silicon Graphics versions of GAUSSIAN 88 and GAUSSIAN 90 series of programs[4]. Optimized geometries and theoretical vibrational frequencies were obtained at the Hartree-Fock level using the 3-21G basis set[5]. Single point calculations at 6-31G(d) level were used for estimating the relative energies. Correlation energy was calculated using Møller-Plesset perturbation theory[6] terminated at second order. Thus, the highest level of theory is denoted MP2/6-31G(d)//3-21G. Unless otherwise noted, energy values are given at that level of theory.

Results and Discussion

The following definitions and notations will be used throughout this paper. The torsion angle α is defined as the value for the clockwise rotation around the C-C bond looking from C=O along the C-C axis (Figure 1). The torsion angle β is defined as the value for the clockwise rotation around the C-R bond (R = OMe for **1**, R = NMe_2 for **2**) looking from the carbon side of the bond towards the heteroatom (O or N). A value of α = 0° corresponds to an eclipsed arrangement of the C=O and C-R groups, a value of β = 0° corresponds to an eclipsed arrangement of the C-CHO and O-Me groups for **1** and eclipsed conformation of the C-CHO group and a dummy (Du) atom on the bisector of the angle Me-N-Me for **2**.

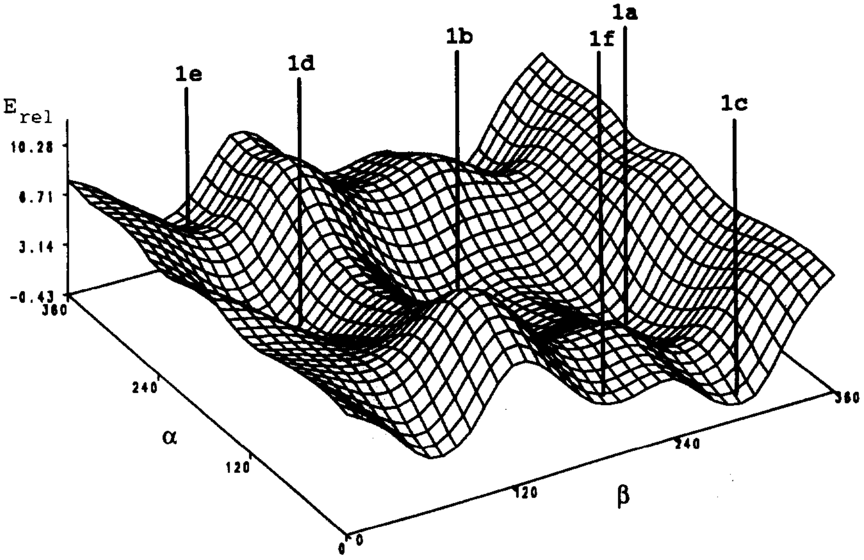
2-Methoxypropanal (1)

Figure 2 shows the calculated potential energy surface for rotation of 2-methoxypronanal **1** around α and β. Six energy minima **1a**-**1f** could be located which are shown in Figure 3. Calculated energies are listed in Table 1.

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

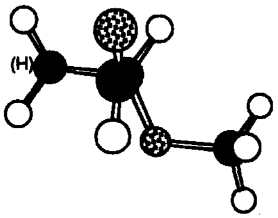
	HF/6-31G(d)//3-21G			MP2/6-31G(d)//3-21G	
	E_{tot}	E_{rel}	ZPE	E_{tot}	E_{rel}
1a	-305.82428	0.0	70.2	-306.69225	0.0
1b	-305.82399	0.2	70.3	-306.69178	0.3
1c	-305.82168	1.6	70.4	-306.69086	0.9
1d	-305.82144	1.8	70.5	-306.69010	1.4
1e	-305.81797	4.0	70.6	-306.68731	3.1
1f	-305.81788	4.0	70.2	-306.68665	3.5

Figure 2: MP2/6-31G*//3-21G energy surface of **1**, relative energy values are given in kcal mol^{-1}.



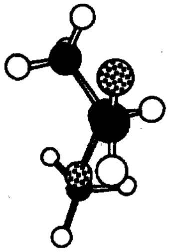
Two energetically nearly degenerate low lying structures **1a** and **1b** are theoretically predicted to be the most stable conformations of 2-methoxypropanal (Figure 3). Both conformations **1a** and **1b** have a nearly

Figure 3: Calculated potential energy minima of **1**.



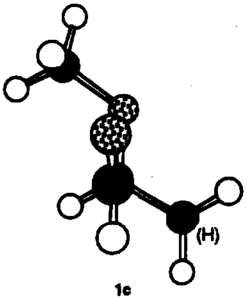
1a

α(OCCO) = 157.3°
β(CCOC) = 281.5°
E_{rel} = 0.0 kcal mol^{-1}



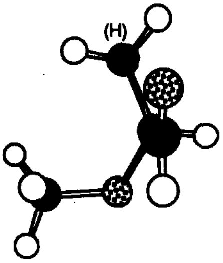
1b

α(OCCO) = 201.1°
β(CCOC) = 193.6°
E_{rel} = 0.3 kcal mol^{-1}



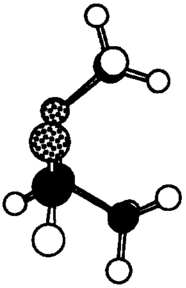
1c

α(OCCO) = 4.7°
β(CCOC) = 290.4°
E_{rel} = 0.9 kcal mol^{-1}



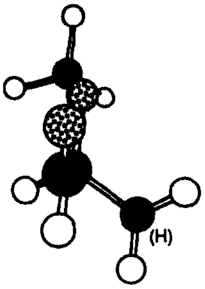
1d

α(OCCO) = 208.8°
β(CCOC) = 73.0°
E_{rel} = 1.4 kcal mol^{-1}



1e

α(OCCO) = 353.0°
β(CCOC) = 65.8°
E_{rel} = 3.1 kcal mol^{-1}



1f

α(OCCO) = 1.4°
β(CCOC) = 200.1°
E_{rel} = 3.5 kcal mol^{-1}

antiparallel arrangement of the C-OMe and C=O bonds with the torsion angle α close to 180°. This leads to favourable dipole/dipole interactions between the two bonds. The corresponding conformations have also been found theoretically as the lowest lying forms of 2-chloropropanal[1a]. In **1a**, the methoxy and methyl groups at C(α) are trans to each other, while in **1b** they are gauche. A third conformer **1d** with an antiparallel arrangement of the C-OMe and C=O bonds is higher in energy, because the methoxy and methyl groups at C(α) are cis to each other. The conformational minima **1c**, **1e**, and **1f** have the C-OMe and C=O bonds eclipsed to each other with the torsion angle α nearly 0° (Figure 3). This leads to destabilizing dipole/dipole interactions which make these conformations less favourable than **1a** and **1b**.

Figures 4 and 5 show the energy values for the HOMO and LUMO, respectively, as a function of α and β. Conformers with a high lying HOMO should be more reactive towards an attacking electrophile. Those having a low lying LUMO should be more reactive towards an attacking nucleophile. The HOMO shows a twofold barrier around the C-O bond with minima at β=0° and β=180°. The LUMO, however, shows an almost onefold barrier around the C-O bond with a minimum at β=0°. Considering the rotation around the C-C bond we find two minima at α~90° and α~270°. Conformations with α~90° (270°) are predicted by the Felkin-Anh[7] model to enhance the electronic

Figure 4. HOMO of **1**, energy values are given in kcal mol^{-1}.

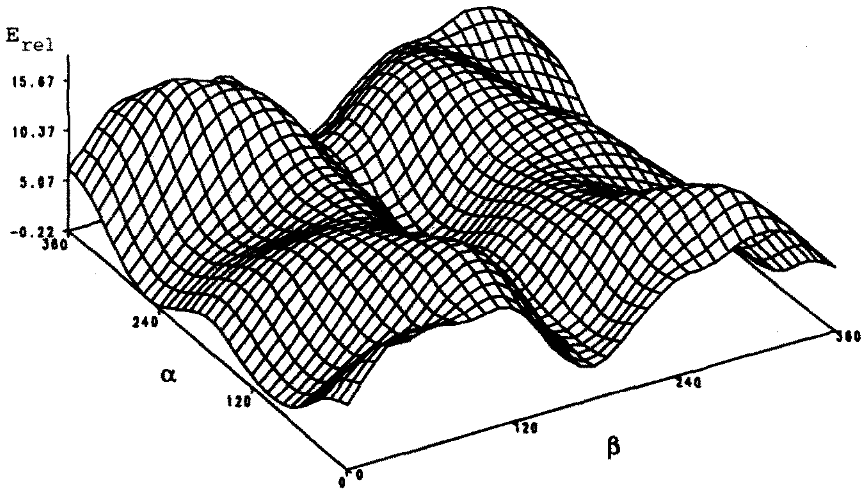
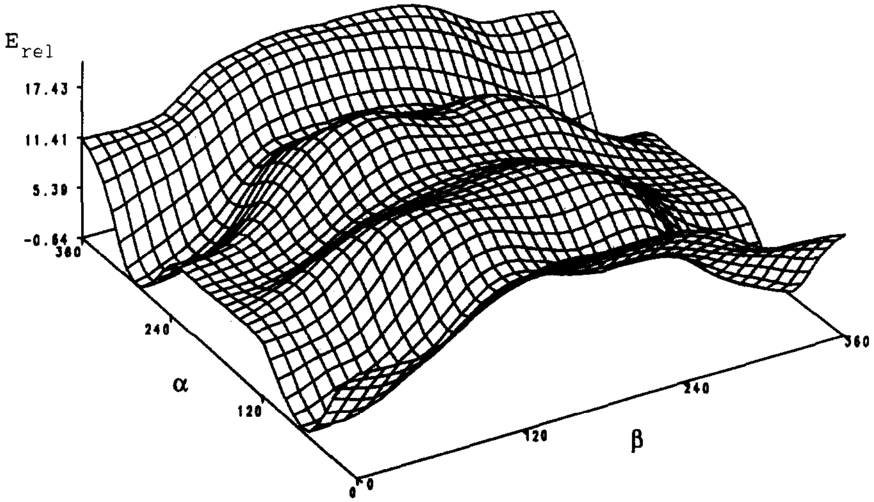


Figure 5. LUMO of **1**, energy values are given in kcal mol^{-1}.

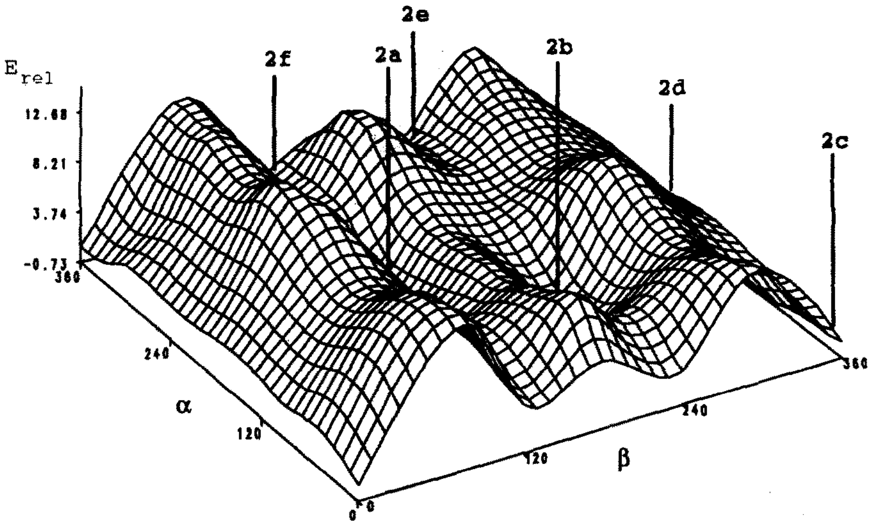


interaction with a nucleophile because of an energy lowering of the LUMO due to negative hyperconjugation. Figure 5 shows that the Felkin-Anh prediction is correct. However, the energy level of the LUMO is also strongly affected by the rotation around β and thus, may influence electronic interactions. In particular, conformations with β between 120-240° show a high lying LUMO irrespective of the value for α.

2-N,N-Dimethylaminopropanal (2)

The three-dimensional potential energy surface of **2** is shown in Figure 6. Six minima **2a**-**2f** could be found, which are shown in Figure 7. Calculated energies are given in Table 2. The results are similar to those obtained for **1**, i.e. the energetically lowest lying conformers **2a** and **2b** are favoured because of stabilizing dipole/dipole interactions between the C=O and the C-NMe_2 bonds. The most favourable conformation **2a** has the dimethylamino group anti to the carbonyl group and the α-methyl-substituent eclipsed to the oxygen atom which corresponds to the results for 2-chloropropanal[1]. The theoretically lowest lying conformer **2a** is in agreement with the experimentally determined structure of a phenyl

Figure 6: MP2/6-31G*//3-21G energy surface of **2**, energy values are given in kcal mol^{-1}.



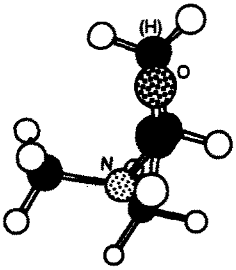
derivative of **2**, i.e. N,N-dibenzylphenylalaninal, found by X-ray analysis[3c].

The conformations **2a** and **2d** also have an antiparallel arrangement of the C=O and C-NMe$_2$ bonds. In **2d**, the steric interaction of the NMe$_2$ group with the carbonyl moiety is stronger than in **2a**, while in **2b** the attractive dipole/dipole interaction between the C=O and the C-Me bonds is absent. The conformations **2c**, **2e**, and **2f** have destabilizing dipole/dipole

Table 2. Calculated total energies E_{tot} (hartrees), relative energies E_{rel} (kcal mol^{-1}) and zero-point vibrational energies ZPE (kcal mol^{-1}) scaled by 0.89.

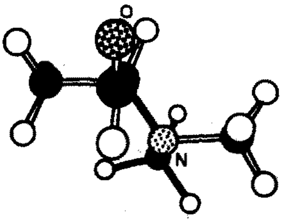
	HF/6-31G(d)//3-21G			MP2/6-31G(d)//3-21G	
	E_{tot}	E_{rel}	ZPE	E_{tot}	E_{rel}
2a	-325.02473	0.0	94.8	-326.01343	0.0
2b	-325.02254	1.4	94.9	-326.01196	0.9
2c	-325.02138	2.1	94.9	-326.01119	1.4
2d	-325.02081	2.5	94.6	-326.00939	2.5
2e	-325.01805	4.2	95.1	-326.00894	2.8
2f	-325.01938	3.4	94.8	-326.00886	2.9

Figure 7: Potential energy minima of **2**.



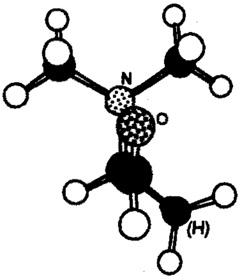
2a

α(OCCN) = 216.8°
β(CCNDu) = 137.5°
E_{rel} = 0.0 kcal mol^{-1}



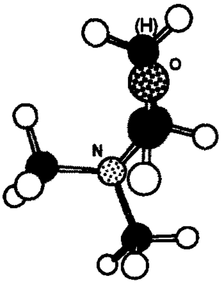
2b

α(OCCN) = 146.3°
β(CCNDu) = 224.6°
E_{rel} = 0.9 kcal mol^{-1}



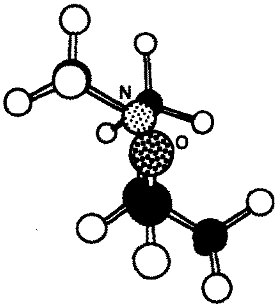
2c

α(OCCN) = 0.7°
β(CCNDu) = 358.1°
E_{rel} = 1.4 kcal mol^{-1}



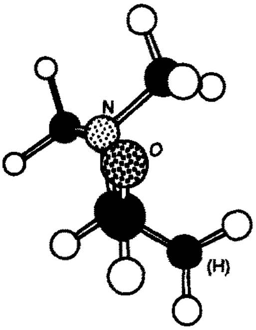
2d

α(OCCN) = 218.7°
β(CCNDu) = 348.3°
E_{rel} = 2.5 kcal mol^{-1}



2e

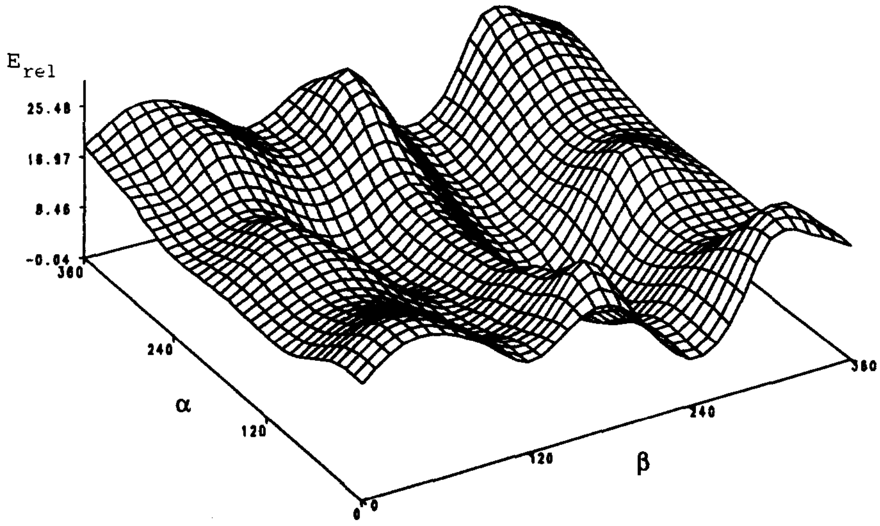
α(OCCN) = 358.6°
β(CCNDu) = 230.8°
E_{rel} = 2.8 kcal mol^{-1}



2f

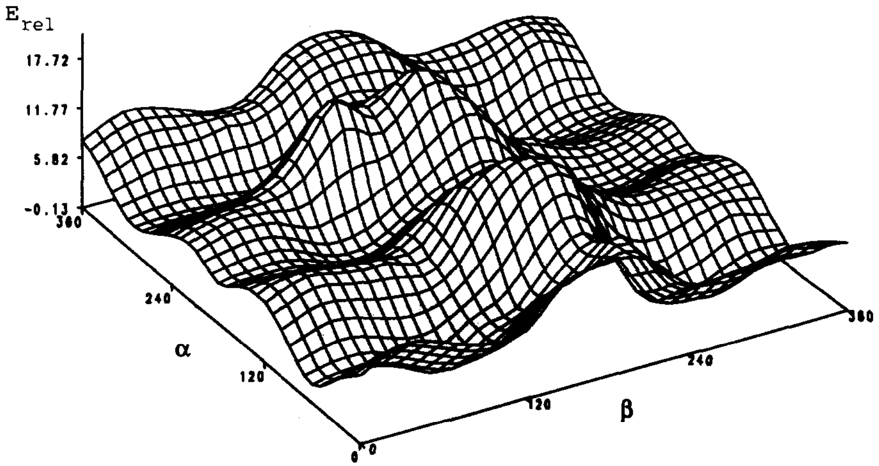
α(OCCN) = 352.3°
β(CCNDu) = 133.9°
E_{rel} = 2.9 kcal mol^{-1}

Figure 8: HOMO of **2**, energy values are given in kcal mol^{-1}.



interactions between the C=O and $C-NMe_2$ bonds and, therefore, are higher in energy. A comparison of the calculated potential energy surfaces for **1** and **2** shown in Figures 2 and 6 indicates that the rotation around β has higher barriers for **2** than for **1**.

Figure 9: LUMO of **2**, energy values are given in kcal mol^{-1}.

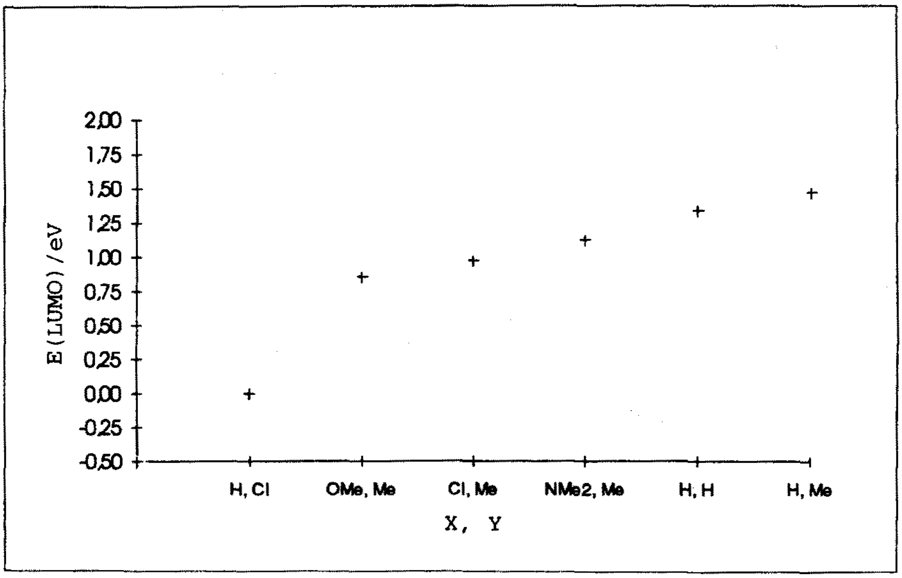


Figures 8 and 9 show the energy level of the HOMO and LUMO as a function of α and β. Unlike in methoxypropanal, the HOMO follows the total energy. The LUMO shows three minima for the rotation around the C-C bond.

The effect of rotating around the C-N bond on the LUMO is not as large as the effect of the C-O bond. The lowest lying energy values for the LUMO are found for β=90° and β=270° and for α=60°, 180°, and 300°. From the shape of the LUMO it follows that the Felkin-Anh[7] conformers with α~90° or 270° may not be as important for electronic interactions of **2** with a nucleophile than for **1** or 2-chloropropanal[1a,3c].

Figure 10 shows the relative values of the lowest lying LUMO of chloroacetaldehyde, 2-methoxypropanal, 2-chloropropanal, 2-N,N-dimethylaminopropanal, acetaldehyde, and propanal. Substitution of hydrogen in propanal by the electronegative substituents lowers the LUMO, as expected. The calculated ε_{LUMO} values for substituted propanals show the sequence OMe < Cl < NMe_2 < Me. The energy lowering by the electronegative substituents, however, is very small. A much stronger energy lowering of the LUMO is calculated for Lewis-acid-complexed aldehydes.[8]

Fig. 10. Relative values in eV of the LUMO of disubstituted acetaldehydes XYH-CHO.



Conclusions

The most stable conformations of 2-methoxypropanal (**1**) and 2-N,N-dimethylaminopropanal (**2**) are theoretically predicted to have an antiparallel orientation of the C=O bond and the C-OMe (**1**)or C-NMe_2 (**2**) bond. The conformational profiles of **1** and **2** are determined not only by rotation around the C-C bond, but also around the C-R (R=OMe, NMe_2) bond. Two energetically nearly degenerate conformations **1a** and **1b** are calculated as the most stable forms of **1**. The methyl and methoxy groups at C(α) are trans in **1a** and gauche in **1b**. The most stable conformation of 2-N,N-dimethylaminopropanal **2a** has favourable dipole/dipole interactions between C=O and the methyl and NMe_2 groups at C(α). The energy levels of the HOMO and LUMO show a strong dependency upon the torsion angles α and β. The "Felkin-Anh conformations" with $\alpha \sim 90°$ (270°) show the predicted low lying LUMO. However, the effect is very small in the case of the amino substituted aldehyde **2**. The methoxy substituent has a larger "Felkin-Anh-effect" than the dimethylamino substituent in **2**, but is nevertheless smaller than in the system that Felkin and Anh[7] used as a model compound (2-chloropropanal[1a]). This trend is also observed in substituted acetaldehydes[3c].

In the following paper, we discuss the calculated transition states for addition of LiH to **1** and **2**.

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