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Conformational Analysis of 2-Chloro-2-fluoroacetaldehyde and Calculated Transition State Structures of Nucleophilic Addition Reactions.

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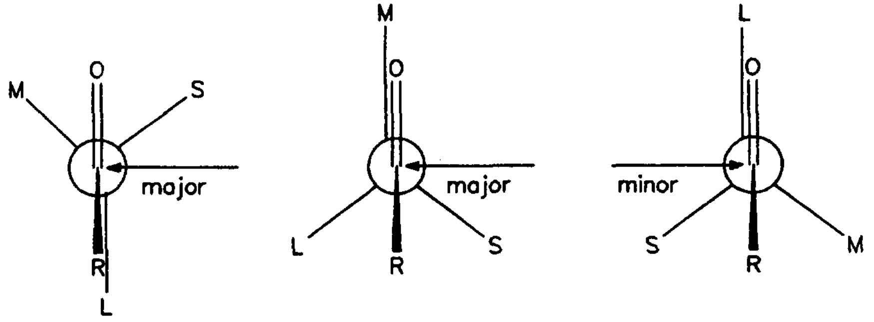
Summary: The rotational profiles and conformational minima of 2-chloro-2-fluoroacetaldehyde have been calculated using ab initio methods at the MP2/6-31G(d)//HF/6-31G(d) level of theory. Two minima could be located on the potential energy hypersurface. The transition state structures for the addition of CN^- to 2-chloro-2-fluoroacetaldehyde have been calculated to predict theoretically the π-facial stereoselection.

Introduction

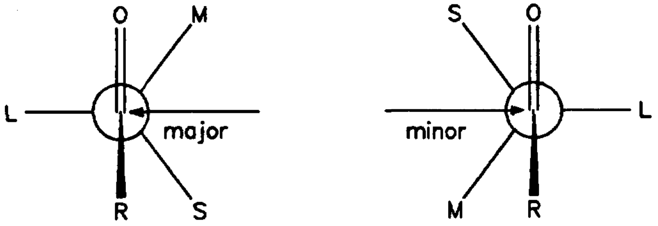
In the previous four papers of our series on the origin of π-facial diastereoselectivity in nucleophilic additions to chiral carbonyl compounds we presented theoretical results of the conformational profiles for propanal, chloroacetaldehyde, 2-chloropropanal, 2-methoxypropanal, 2-N,N-dimethylaminopropanal, and the transition states for the addition of nucleophiles to the substituted aldehydes.[1] We compared the calculated structures with the predictions of the Felkin-Anh model.[2] It was concluded that the π-facial diastereoseletivity in the nucleophilic reactions can be determined by several factors, such as steric, electronic, conformational and electrostatic effects. Particularly the role of the lowest energy conformation of the educt was emphasized.[1b] In contrast to all other models, ground state conformational effects were shown to correlate directly with the geometry of the transition state.[1]

A crucial feature of the models suggested by Cram,[3] Karabatsos,[4] and Felkin-Anh[2] is that the substituents in the α position to the carbonyl group are classified as small (s), medium (m) and large (l, see Figure 1). It has been recognized by Cornforth[5] that strong electron withdrawing substituents may take the position of the large substituent. But what is the position of the substituents if two strongly polar atoms such as fluorine and chlorine are present? In this paper we report calculated results for the rotational profile of 2-chloro-2-fluoroacetaldehyde **1** and the transition states for addition of the nucleophilic agents CN^-.

Figure 1. Schematic representation of the Cram, Karabatsos and Felkin models.



Cram model Karabatsos model



Felkin model

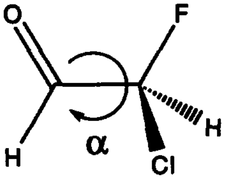
Theoretical Details

The calculations were carried out using the GAUSSIAN 92 series of programs on CONVEX, Siemens/Nixdorf and Silicon Graphics computers[6]. The highest level of theory is denoted MP2/6-31G(d)//HF/6-31G(d). Unless otherwise noted, energy values are given at that level of theory. Details about the theoretical procedure are given in the previous papers.[1]

Results and Discussion

The following definition of the torsion angle α will be used throughout this paper: 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 2). A value of $\alpha = 0°$ corresponds to an eclipsed conformation of the C=O and the C-F groups.

Figure 2. Definition of the torsion angle α.



The rotational profile of **1** was calculated by optimizing the geometry of **1** in intervals of α = 30° with complete optimization of the remaining geometry parameters. The rotational profile of **1** is shown in Figure 3. Two conformational minima **1a** and **1b** could be located on the potential energy hypersurface. They are shown in Figure 4. The calculated conformational minima of fluoro-[7] (**2**) and chloroacetaldehyde[1a] (**3**) are also shown for comparison. The energy values of **1a** and **1b** are given in Table 1.

Figure 3. Calculated (MP2/6-31G(d)//HF/6-31G(d)) rotational profile for the rotation around the C-C bond.

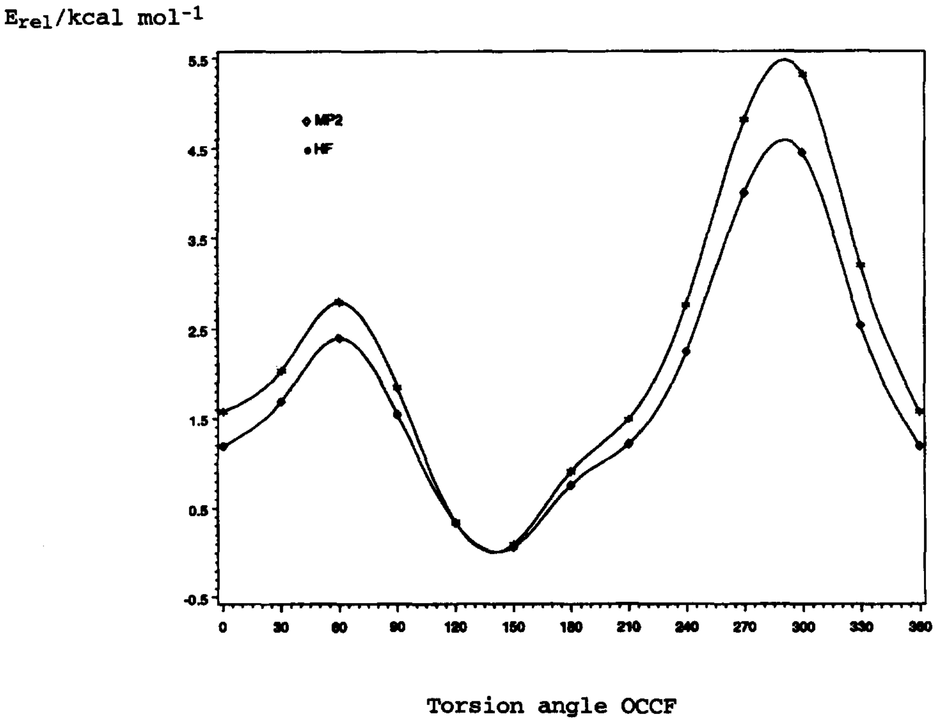
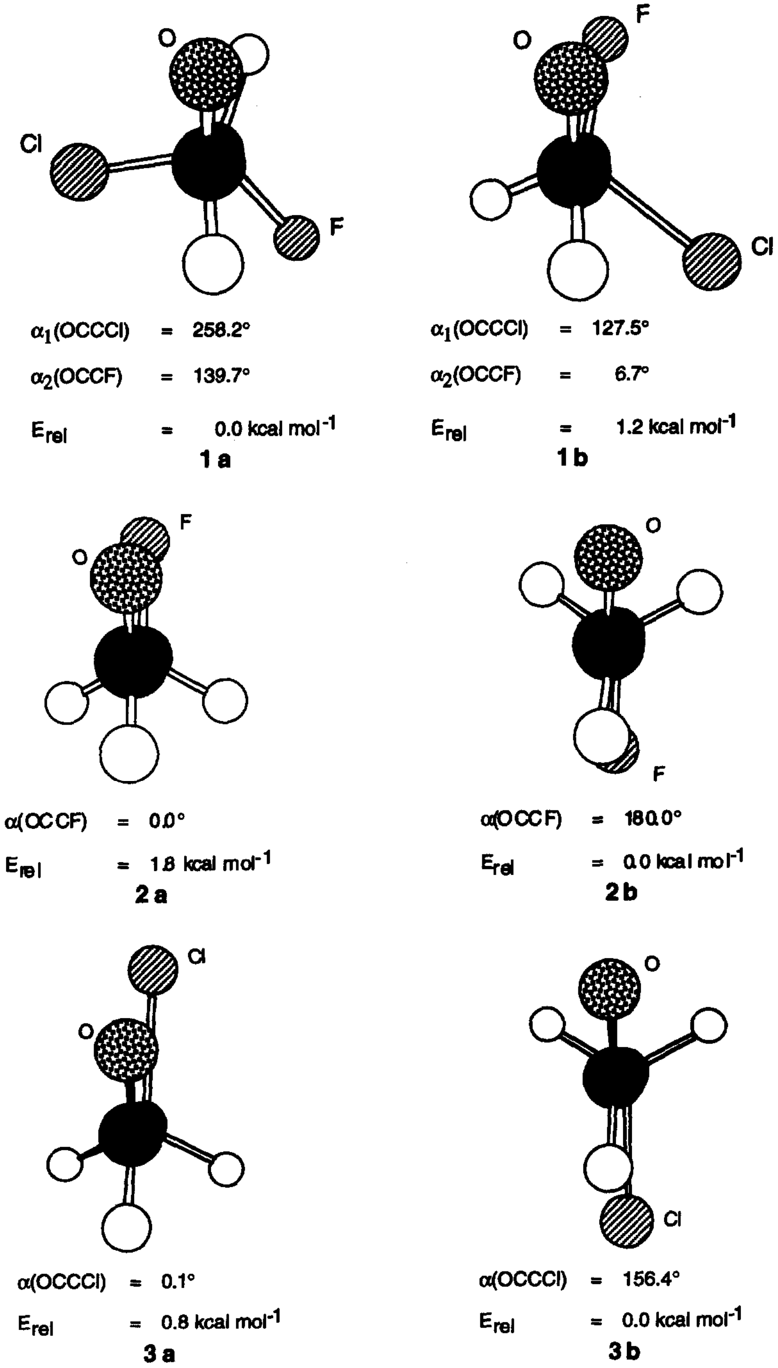


Figure 4. Calculated (MP2/6-31G(d)//HF/6-31G(d)) rotational minima.



α_1(OCCCl) = 258.2°
α_2(OCCF) = 139.7°
E_{rel} = 0.0 kcal mol^{-1}
1 a

α_1(OCCCl) = 127.5°
α_2(OCCF) = 6.7°
E_{rel} = 1.2 kcal mol^{-1}
1 b

α(OCCF) = 0.0°
E_{rel} = 1.8 kcal mol^{-1}
2 a

α(OCCF) = 180.0°
E_{rel} = 0.0 kcal mol^{-1}
2 b

α(OCCCl) = 0.1°
E_{rel} = 0.8 kcal mol^{-1}
3 a

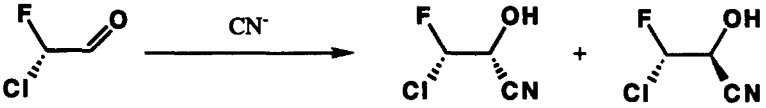
α(OCCCl) = 156.4°
E_{rel} = 0.0 kcal mol^{-1}
3 b

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)//HF/6-31G(d)			MP2/6-31G(d)//HF/6-31G(d)	
	E_{tot}	E_{rel}	ZPE	E_{tot}	E_{rel}
1a	-710.65503	0.0	24.4	-711.37906	0.0
1b	-710.65261	1.5	25.5	-711.37721	1.2

Structure **1a** is predicted to be 1.2 kcal mol^{-1} lower in energy than **1b**. The inclusion of ZPE corrections increases the energy difference by 1.1 kcal mol^{-1}. Thus, the calculations predict that **1a** is 2.3 kcal mol^{-1} more stable than **1b**. The conformation of **1a** looks like the vector product of the energetically lowest lying forms of **2** and **3**, i.e. **2a** and **3a**. Structure **1b** can be considered as the combination of **2b** and **3a**. It seems that the position of the chlorine atom dominates the rotational profile of **1** and that the position of the fluorine atom is less important.

The addition of a nucleophile to aldehyde **1** may lead to two products, the threo and the erythro adducts:



1 erythro threo

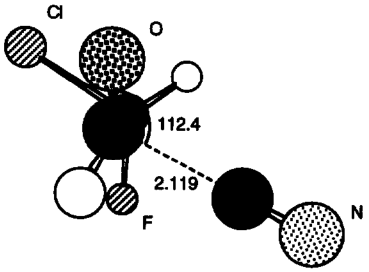
We calculated the transition states for the nucleophilic addition of CN$^-$ to **1**. Six transition state structures **1*****a** - **1*****f** could be located on the potential energy surface (Figure 5). The energy values are given in Table 2.

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)//HF/3-21+G			MP2/6-31G(d)//HF/3-21+G	
	E_{tot}	E_{rel}	ZPE	E_{tot}	E_{rel}
1*a	-802.95769	0.0	27.9	-803.97965	0.0
1*b	-802.95472	1.9	27.9	-803.97862	0.7
1*c	-802.95339	2.7	27.9	-803.97788	1.1
1*d	-802.95463	1.9	27.9	-803.97771	1.2
1*e	-802.95044	4.6	27.6	-803.96671	8.1
1*f	-802.94815	6.0	27.3	-803.96108	11.7

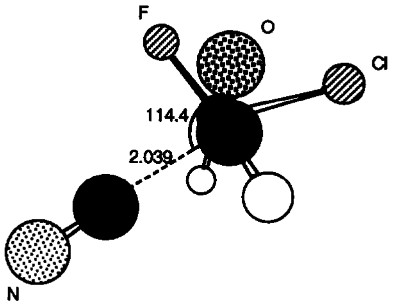
The energetically lowest lying forms, **1*a**, which leads to the erythro isomer, and **1*b**, which leads to the threo isomer, have the chlorine atom trans to the attacking nucleophile. It follows that chlorine takes the position of the large substituent in the nucleophilic addition reaction to **1**. Structure **1*b** is 0.7 kcal mol^{-1} less stable than **1*a**. The transition states **1*c** and **1*d** with the fluorine atom trans to the attacking nucleophile are slightly higher in energy (Figure 5). Transition state **1*c**, which leads to the erythro form, is 1.1 kcal mol^{-1} higher in energy than **1*a**. Transition state **1*d**, which leads to the threo form, is 1.2 kcal mol^{-1} higher in energy than **1*a**. The transition states with the hydrogen atoms in the trans position **1*e** and **1*f** are much less stable than **1*a**. **1*e** and **1*f** are "early" transition states with

Figure 5. Optimized transition state structures of the addition of CN$^-$ to **1**.



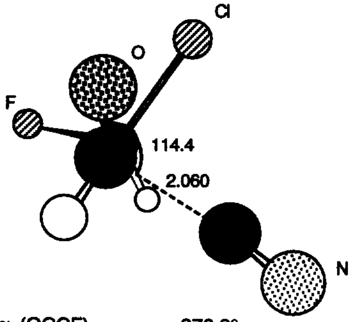
α_1(OCCF) = 183.3°
α_2(OCCCl) = 297.0°
E_{rel} = 0.0 kcal mol^{-1}
E_{rel} (-CN$^-$) = 5.0 kcal mol^{-1}
ε_{LUMO} (-CN$^-$) = 1.44 eV

1*a



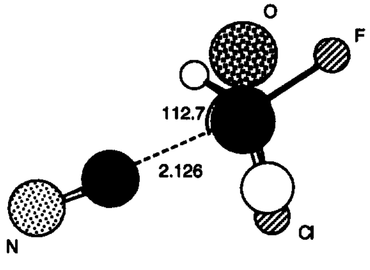
α_1(OCCF) = 322.7°
α_2(OCCCl) = 79.4°
E_{rel} = 0.7 kcal mol^{-1}
E_{rel} (-CN$^-$) = 8.8 kcal mol^{-1}
ε_{LUMO} (-CN$^-$) = 1.27 eV

1*b



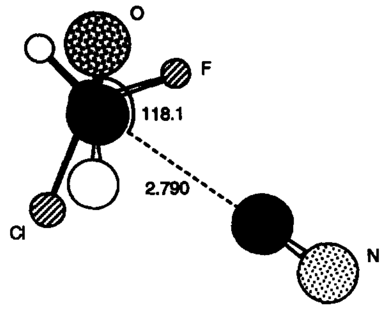
α_1(OCCF) = 276.2°
α_2(OCCCl) = 33.3°
E_{rel} = 1.1 kcal mol^{-1}
E_{rel} (-CN$^-$) = 8.0 kcal mol^{-1}
ε_{LUMO} (-CN$^-$) = 1.90 eV

1*c



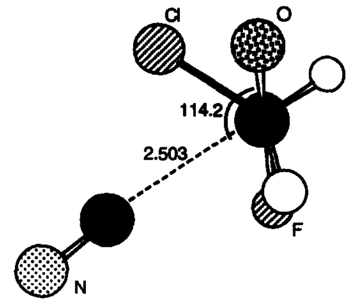
α_1(OCCF) = 54.5°
α_2(OCCCl) = 170.0°
E_{rel} = 1.2 kcal mol^{-1}
E_{rel} (-CN$^-$) = 5.8 kcal mol^{-1}
ε_{LUMO} (-CN$^-$) = 1.94 eV

1*d



α_1(OCCF) = 78.2°
α_2(OCCCl) = 201.0°
E_{rel} = 11.7 kcal mol^{-1}
E_{rel} ($-CN^-$) = 0.3 kcal mol^{-1}
ε_{LUMO} ($-CN^-$) = 2.31 eV

1*e



α_1(OCCF) = 176.7°
α_2(OCCCl) = 302.0°
E_{rel} = 8.1 kcal mol^{-1}
E_{rel} ($-CN^-$) = 0.0 kcal mol^{-1}
ε_{LUMO} ($-CN^-$) = 2.13 eV

1*f

rather long NC-$C_{Carbonyl}$ distances, while **1*a** - **1*d** are "late" transition states with significantly shorter NC-$C_{Carbonyl}$ distances (Figure 5).

A closer examination of the transition states **1*a** and **1*b** shows that the calculations predict anti-Felkin-Anh selectivity for the π-facial addition reaction! This is opposite to theoretical results for the nucleophilic addition reaction to 2-chloropropanal[1b] and 2-fluoropropanal[8], for which the validity of the Felkin-Anh model[2] has previously been determined. The lowest lying transition state **1*a** has the small substituent hydrogen staggered between the carbonyl group and the attacking nucleophile, while the medium substituent fluorine is trans to the carbonyl group. The Felkin-Anh model[2] predicts that this transition state should lead to the minor isomer, and that **1*b** should lead to the major isomer, opposite to the calculated energies of the transition states. The difference can be explained when the energy of **1** is calculated using the geometry of the transition states **1*a** and **1*b**. Structure **1*a** without the nucleophile CN^- is 3.8 kcal mol^{-1} lower in energy than **1*b** calculated without CN^-. This means that the deformation of the substrate **1** costs 3.8 kcal mol^{-1} more energy in **1*b** than in **1*a**. This can not fully be compensated by the interaction energy in the transition state. The interaction between CN^- and the substrate **1** in the geometry of the transition state is 3.1 kcal mol^{-1} more favorable in **1*b** than in **1*a**. The calculations show that the LUMO of **1*a** is higher lying than in **1*b** (Figure 5).

The transition states **1*e** and **1*f** have substrate geometries which are energetically even more favorable than those of **1*a** and **1*b** (Figure 5). This is, because the substrate geometries are less deformed in the "early" transition states **1*e** and **1*f** than in the "late" transition stats **1*a** - **1*d**. However, the interaction with the attacking nucleophile in the transition state is much more favourably in **1*a** - **1*d** than in **1*e** and **1*f**. Thus, the

Felkin-Anh model predicts correctly that the interactions between the attacking nucleophile and the substrate are more favorable when the small substituent is in the outside position as in **1*b**. However, this energy gain can be smaller than the deformation energy of the substrate, which nakes **1*a** lower in energy than **1*b**. We come to the same conclusion as in our previous study[1b], namely that the ground state conformation of the substrate molecule may become the dominating factor for the π-facial diastereoselectivity in nucleophilic addition reactions.

Conclusions:

The most important result of this study is the theoretical prediction that the addition of a nucleophilic agent to 2-chloro-2-fluoroacetaldehyde **1** should show anti-Felkin-Anh selectivity. The energetically lowest lying transition states **1*a** and **1*b** yielding the erythro and threo products have the chlorine atom trans to the attacking nucleophile. **1*a** is lower in energy than **1*b** because of the more favorable conformation of the substrate in the former transition state, although the interactions between **1** and the nitrile anion are very important for the relative energies of the transition states. This shows clearly that conformational effects of the substrate are very important for the π-facial diastereoselectivity.

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