Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2955–2959

TETRAHEDRON:
ASYMMETRY

Asymmetric transition states of allylation reaction: an ab initio molecular orbital study

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Received 12 September 2001; accepted 11 November 2001

Abstract—An ab initio MO study of the allylation of α-methoxypropanal by allylboronic acid has been carried out. The calculated most stable transition state arrangement was found to be similar to that proposed by Cornforth. The Felkin–Anh orientation was found to be less stable than the Cornforth-like arrangement at the B3LYP/6-31G* level of theory in the six-membered cyclic transition state. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

One of the most useful tools that organic chemists employ in the planning of syntheses is the stereochemical models predicting diastereoselection.[1] According to the depiction of Cram's original model for nucleophilic addition to α-chiral carbonyl compounds, the largest of the three α-substituents is antiperiplanar to the carbonyl oxygen, with the nucleophile attacking from the less hindered side.[2] For carbonyl compounds with an α-polar substituent, Cornforth proposed an electrostatic model in which the electronegative group assumes the role of the large group pointing away from the polar carbonyl function.[3] The rationale for the Cornforth model is the minimization of the dipole moment of the system. The prediction for facial selection in the additions is often, but not always, the same for the two transition state models.

Felkin modified Cram's model based on the concept of torsional strains.[4,5] The principle of this modification is the minimization of non-bonded interactions between the nucleophile and the substituents α to the carbonyl group in the transition state. The attacking nucleophile is antiperiplanar to the largest α-substituent. Early theoretical studies by Anh support the Felkin modification of the Cram model and provide a theoretical basis for the antiperiplanar arrangement of an α-polar substituent (not necessarily the 'larger' substituent).[6] The improved model is now widely known as the Felkin–Anh model.[6]

Hoffmann has suggested that Cornforth transition states play a significant role in the reactions of α-benzyloxypropanal and pinacol (*E*)- and (*Z*)-(methoxyallyl)-boronates.[7,8] Roush et al. also reported a study on the stereochemistry of allylation of chiral aldehydes by allylboronates in 1986.[9] In their analysis of the factors that influence aldehyde diastereofacial selectivity, the Cornforth transition state was proposed to be more favorable than the Felkin–Anh arrangement. Since the allylation of carbonyl compounds is an important reaction in organic syntheses,[10,11] our interest in this area have prompted us to carry out an ab initio MO study of the allylation of α-methoxypropanal by allylboronic acid.[12–14]

Several more recent theoretical studies of carbonyl additions using a metal hydride or a metal cyanide as the nucleophile have been reported.[15–19] In general, the Felkin–Anh arrangement was found most stable when the nucleophile was CN^- or H^-. The chelated transition state was most favorable when the nucleophile was a metal hydride. Houk studied the transition state for the allylation of formaldehyde at the HF/3-21G level of theory.[20] The cyclic chair transition state was preferred over the twist boat conformation.

To our knowledge, no study involving cyclic transition states for the allylation of an α-oxygenated chiral aldehyde has been reported in which entirely ab initio molecular orbital methods were employed.[21] There is a study of an allylation reaction using molecular mechanics methods incorporating ab initio parameters.[22] How-

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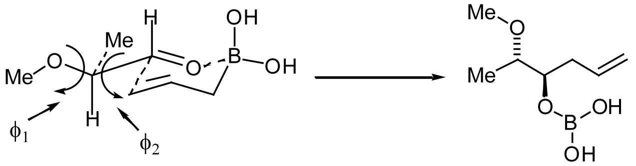
PII: S0957-4166(01)00533-X

ever, the authors used ab initio parameters from the previous calculations where CN$^-$ was the nucleophile.[22]

We have now found that the Cornforth-like transition state is more stable than the Felkin–Anh arrangement at a much higher level of theory than previously reported. Although both Cornforth and Felkin–Anh models predict the same product, our results suggest that an electrostatic effect, rather than orbital overlap, is more important in the transition states of nucleophilic additions to carbonyl compounds.

2. Computational methods

The computations of transition states using ab initio molecular orbital methods are in general more time-consuming than the corresponding task on a ground state structure. We found that in general we spend less time 'coaxing' in locating the transition structures using the command OPT = QST3 in the Gaussian 94 program than using the command OPT = TS. This means one must first calculate the equilibrium structures of the starting materials and the products for the elementary reaction involved. Our calculations start from the core cyclic transition state structure and the substituents were added subsequently. The calculations were carried out using the Gaussian 94 program[23] on the CRAY T90 computer at the Ohio Supercomputer Center. Initial molecular structures were generated using the Chem3D graphical program. The starting complexes of 2-methoxypropanal and allylboronic acid were determined by a conformational search in which the torsional angles, ϕ_1 and ϕ_2, were varied as shown in Eq. (1).

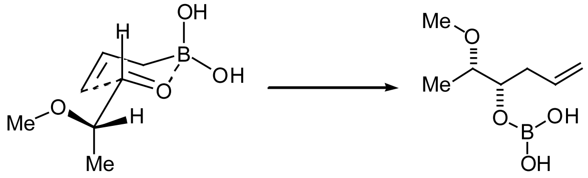


(1)

The corresponding conformations of the products were likewise generated by rotating the torsional angles, ϕ_1 and ϕ_2. Structural optimizations for the starting materials and products were initially determined by means of the 3-21G split-valence basis set. Calculations were progressively continued at the HF/6-31G* level. The transition structures were fully optimized without any constraint and characterized by vibrational frequency calculations. Only one negative frequency was found for each structure. Single point calculations using Moller–Plesset perturbation theory were performed at second and third order. Attempted MP4/6-31G* calculation failed due to prohibitive cost in CPU time and disk space. However, the optimization of the transition structures using density functional theory[24,25] (B3LYP/6-31G*) was successfully completed at the cost of 10–20 h of CPU time for each structure. The relative energies shown in Fig. 1 are calculated at the B3LYP/6-31G* level of theory.

3. Results and discussion

A total of six transition structures were located for each π-face attack. Shown in Fig. 1 are the most stable structures for rotational minima around ϕ_2. Structures **1a–c** are derived from Eq. (1), i.e. Cram selectivity, while structures **2a–c** represents transition structures from Eq. (2), the anti-Cram attack.



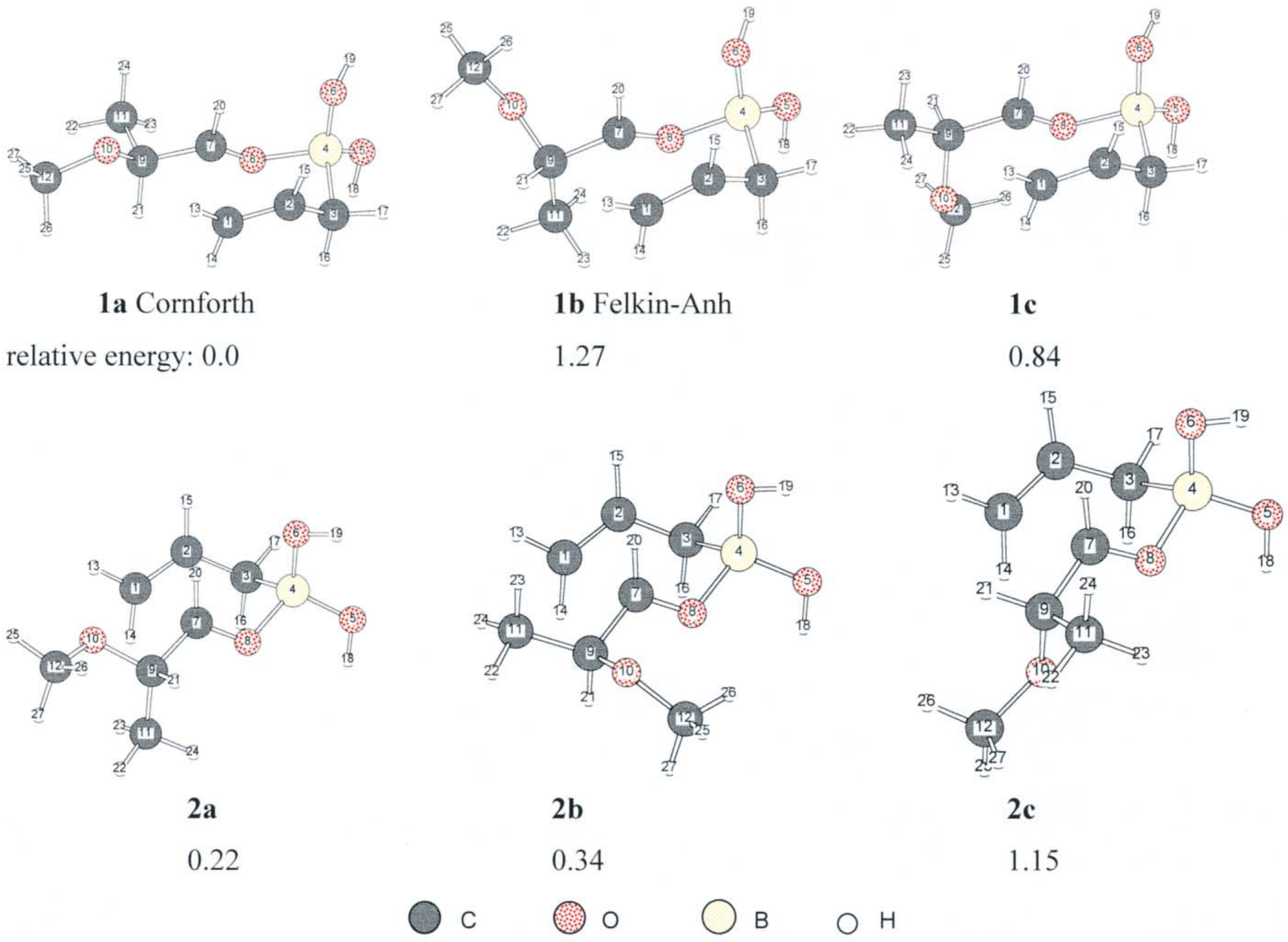
(2)

The overall computational results are consistent with experimental studies of the allylation reactions of 2-alkoxypropanal with allylboronates.[9,26,27] The observed selectivity in these additions involving allylboronate was low. The most surprising result is that the Felkin–Anh arrangement is less stable than any of the rotamers including the anti-Cram transition states (Fig. 1 and Table 1).

The calculated transition state **1a** varies slightly from the original Cornforth model. The Burgi–Dunitz trajectory of attack is found to be $\angle$C–C–O = 102.3°. This trajectory is between that previously calculated for cyanide ($\angle$NC$^-$–C–O = 115°),[28] and LiH addition to a carbonyl ($\angle$H–C–O = 97°).[17,19] Secondly, the α C–O bond of the aldehyde is not completely eclipsed with the aldehydic C–H bond ($\angle$OCCH = 34.8°). An attractive interaction between the α oxygen atom and the aldehyde hydrogen atom is present in the Cornforth arrangement but not in the Felkin–Anh orientation. This type of electrostatic attraction between an oxygen atom and an aldehyde hydrogen atom has been identified as a force in carbohydrate conformations and also in Lewis acid promoted additions to aldehyde.[29,30]

Several features of the Felkin–Anh arrangement **1b** account for its high energy. The most obvious deviation from previous ab initio structures of carbonyl addition reactions is the incomplete antiperiplanarity of the α C–O bond with respect to the attacking nucleophile. The dihedral angle between the incipient bond and the α C–O bond (C(1)C(7)C(9)O(10)) is 153.7°. The origin of the deviation appears to be the steric repulsion between the α-methyl substituent of the aldehyde and the vinyl protons of the allyl moiety. The vinyl hydrogen atom H(14) and H(23) of the methyl group are only 2.39 Å apart (see Fig. 1 and Table 2). It would be necessary to move these two hydrogen atoms into even closer contact if the α C–O bond were to rotate to complete antiplanarity. The incomplete antiplanarity of the α C–O bond would presumably prevent overlap between the σ^*_{C-O} with the HOMO of the nucleophile, which raises the energy of the transition state.

To further explore why the Cornforth transition state **1a** is lower in energy than the Felkin–Anh transition



1a Cornforth
relative energy: 0.0

1b Felkin-Anh
1.27

1c
0.84

2a
0.22

2b
0.34

2c
1.15

Figure 1. Optimized transition state structures (B3LYP/6-31G*) for the allylation of 2-methoxypropanal and allylboronic acid. Relative energies (kcal/mol) are calculated at B3LYP/6-31G* level of theory.

Table 1. Relative energies (kcal/mol) for transition states **1** and **2**, absolute energies in parenthesis

Structure	HF/6-31G*	MP2/6-31G*[a]	MP3/6-31G*[a] (Hartrees)	B3LYP/6-31G*
1a	0.0	0.0	0.0 (−599.7326462)	0.0 (−601.5582092)
1b	2.86	1.52	1.98 (−599.7294956)	1.27 (−601.5561793)
1c	1.73	0.93	1.06 (−599.7309525)	0.84 (−601.5568707)
2a	0.71	0.42	0.39 (−599.7320186)	0.22 (−601.5578569)
2b	2.34	0.97	1.45 (−599.7303428)	0.34 (−601.5576684)
2c	2.12	1.23	1.50 (−599.7302558)	1.15 (−601.55637)

[a] Single point calculations using structures optimized at the HF/6-31G* level of theory.

state **1b** the interacting fragments were calculated separately with frozen geometry (Table 3). The energy differences between the fragments using the frozen geometry and the transition state would presumably show the strengths of the interaction energies; the differences between the frozen fragments and the fragments in the equilibrium conformation would show the deformation energies. Similar methods to explore the origin of transition state preferences have been previously employed.[17,19] As shown in Table 3, the reactants are less deformed in transition state **1a** while they appear to better interact in transition state **1b**. However, the excess in conformational deformation seems to raise the transition state energy and overwhelm the slightly favored interaction in **1b**.

4. Conclusions

In summary, ab initio calculations suggest that the lower energy orientations are of the Cornforth-type in cyclic transition states of allylmetal additions to α-oxygenated aldehydes. This preference appears to be mainly conformational in origin, i.e. the preferential *anti*-arrangement of the α-CO bond and the carbonyl C=O bond. The perceived repulsion between the nucle-

Table 2. Comparison of important structural parameters (B3LYP/6-31G*) for the six transition states (the numbering is for convenience, not according to conventional rules)

	Structure					
	1a	**1b**	**1c**	**2a**	**2b**	**2c**
Bond length (Å)						
C(1)–C(7) (incipient bond)	2.334	2.321	2.338	2.33	2.334	2.334
C(7)–O(8) (C=O)	1.269	1.27	1.269	1.27	1.273	1.265
H(13),H(21) (repulsion)	3.316	2.616	4.285	4.157	3.61	2.709
H(13),H(24) (repulsion)	4.931	4.858	**2.298**	4.520	**2.313**	4.760
H(14),H(21) (repulsion)	2.457	2.721	3.853	4.0	2.682	2.852
H(14),H(23) (repulsion)	4.546	**2.398**	3.905	**2.19**	3.886	4.642
Bond angle (°) (attack trajectory)						
C(1),C(7)–O(8)	102.3	102.0	101.5	102.8	101.0	102.2
Torsional angle (°) (antiperiplanarity is shown in bold face)						
C(1),C(7)–C(9)–O(10)	61.7	**153.7**	−62.3	−53.8	**−172.5**	68
C(1),C(7)–C(9)–C(11)	**−176.9**	−88.3	62.4	74	−56	**−169.8**
C(1),C(7)–C(9)–H(21)	−58.2	36	**179.2**	**−168.5**	69.5	−52

Table 3. Total energies (Hartrees) calculated separately (B3LYP/6-31G*) for each reactant in transition state **1a** and **1b** with frozen geometry, conformational deformation energy are in parenthesis (kcal/mol)[a]

	Transition state **1a**	Transition state **1b**
2-Methoxypropanal	−307.6452066 (7.92)[b]	−307.6423981 (9.93)[c]
Allylboronic acid	−293.8673637 (31.27)[d]	−293.863216 (33.87)[d]
Interaction energy[e]	−28.64 kcal/mol	−31.73 kcal/mol

[a] Conformational energy (ΔE_{conf}) is defined as the difference in energy between the ground state conformation and the corresponding fragment in transition state with frozen geometries.

[b] The most similar ground state conformation has a total energy of −307.657827 Hartrees.

[c] The most similar ground state conformation has a total energy of −307.6582302 Hartrees.

[d] The ground state conformation has a total energy of −293.917194 Hartrees.

[e] Interaction energy is defined as $\Delta E_{\text{int}}=E_{\text{TS}}-E_{\text{ald}}-E_{\text{all}}$ where E_{TS} is the transition state energy, E_{ald} and E_{all} are the energies of the aldehyde and the allylboronic acid with frozen geometry, respectively.

ophile and the α-oxygen atom is absent in the transition state of this reaction. Conversely, an important feature of the Felkin–Anh model, i.e. the orientation of an electronegative α-substituent *anti* to the attacking nucleophile is not perfectly achieved in the cyclic transition state. This favorable Cornforth-like structural feature might be applicable to other related additions that proceed by way of cyclic transition states. Studies along this line are currently under way in our laboratories.

Acknowledgements

Acknowledgement is made to the donors of the Petroleum Research Fund (PRF No. 36841-AC4) administered by the American Chemical Society, for support of this research. The authors wish to express appreciation for inspirational discussions with James A. Marshall. We thank the Ohio Supercomputer Center and the Department of Chemistry and Biochemistry of Miami University for computational resources.

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