FULL PAPERS

Origin of the π-Facial Stereoselectivity in the Addition of Nucleophilic Reagents to Chiral Aliphatic Ketones as Evidenced by High-Level Ab Initio Molecular-Orbital Calculations

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Abstract: Ab initio molecular-orbital (MO) calculations were carried out, at the MP2/6-311++G(d,p)//MP2/6-31G(d) level, to investigate the conformational Gibbs energy of alkyl 1-cyclohexylethyl ketones, cyclo-$C_6H_{11}CHCH_3$−CO−R (R = Me, Et, iPr, and tBu). In each case, one of the equatorial conformations was shown to be the most stable. Conformers with the axial CHCH$_3$COR group were also shown to be present in an appreciable concentration. Short C−H⋯C=O and C−H⋯O=C distances were found in each stable conformation. The result was interpreted on the grounds of C−H⋯π(C=O) and C−H⋯O hydrogen bonds, which stabilize the geometry of the molecule. The ratio of the diastereomeric secondary alcohols produced in the nucleophilic addition to cyclo-$C_6H_{11}CHCH_3$−CO−R was estimated on the basis of the conformer distribution. The calculated result was consistent with the experimental data previously reported: the gradual increase in the product ratio (major/minor) along the series was followed by a drop at R = tBu. The energy of the diastereomeric transition states in the addition of LiH to cyclo-$C_6H_{11}CHCH_3$−CO−R was also calculated for R = Me and tBu. The product ratio did not differ significantly in going from R = Me to tBu in the case of the aliphatic ketones. This is compatible with the above result calculated on the basis of the conformer distribution. Thus, the mechanism of the π-facial selection can be explained in terms of the simple premise that the geometry of the transition state resembles the ground-state conformation of the substrates and that the nucleophilic reagent approaches from the less-hindered side of the carbonyl π face.

Keywords: hydrogen bonds · conformation analysis · nucleophilic addition · transition states · pi-facial stereoselectivity
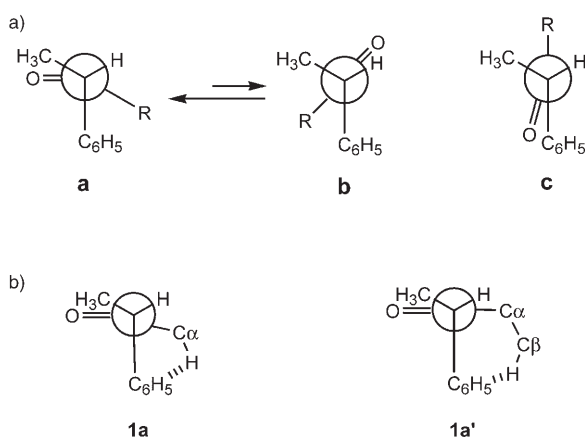
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Introduction

We recently studied, by ab initio calculations at the MP2/6-311G(d,p)//MP2/6-31G(d) level, the conformation of alkyl 1-phenylethyl ketones $C_6H_5CHCH_3$−CO−R **1** (R = Me, Et, iPr, and tBu).[1,2] In each case, the geometry whereby the benzylic CH$_3$ group is nearly eclipsed with C=O and the alkyl group R is close to C_6H_5 was found to be the most stable (Scheme 1 a, rotamer **a**; rotamer **c** does not exist). To accommodate the above finding, we suggested that the C−H⋯O[3,4,5] (forming a five-membered ring) and C−H⋯π hydrogen bonds (forming five- as well as six-membered rings)[6,7,8,9,10] control the conformation of these compounds (Scheme 1 b, **1a** and **1a′**).[2] In rotamer **a**, one of the hydrogen atoms in the benzylic methyl group is capable of interacting with the carbonyl oxygen, and one of the α- or β-H atoms in R can interact favorably with the phenyl group.

The ratio of the diastereomeric secondary alcohols produced in the nucleophilic addition of **1** was estimated on the

a)

b)

1a   **1a′**

Scheme 1. a) Stable conformers of $C_6H_5CHCH_3$–CO–R **1**. b) Rotamers **1a** (with five-membered ring from C–H···π hydrogen bond: $\phi \approx 75°$) and **1a′** (six-membered C–H···π hydrogen bond: $\phi \approx 90°$).

basis of the rotamer distribution.[2] The experimental data reported by Felkin and co-workers[11a] was satisfactorily reproduced: a gradual increase of the product ratio $r_{2/3}$ in the lower alkyl homologues was followed by an abrupt jump at R = tBu (Table 1, L = Ph). The contribution from the CH_3···O and C–H···π(C_6H_5) hydrogen bonds was suggested to be cru-

cial in stabilizing the ground- and transition-state geometries (Scheme 2).

When L is an aliphatic group such as in alkyl 1-cyclohex-

major product **2**   **1**   minor product **3**

Scheme 2. Suggested stereochemical mechanism for the π-facial selectivity in the nucleophilic addition of **1**.

ylethyl ketones, however, Felkin and co-workers reported that the ratio of the product alcohols ($r_{5/6}$) did not obey this pattern (Table 1, L = c-C_6H_{11}): the gradual increase in the product ratio was followed by a drop at R = tBu. To explore the reason for the remarkable contrast in these two cases, herein we calculated the conformational Gibbs energy of the cyclo-$C_6H_{11}CHCH_3$–CO–R compounds **4** (R = Me, Et, iPr, and tBu), all of which bear a nonaromatic group at the terminus (Scheme 3).

Table 1. Diastereomeric ratios of secondary alcohols (major/minor) produced by reduction of ketones LCHCH₃–CO–R **1** and **4** with LiAlH₄ in diethyl ether.
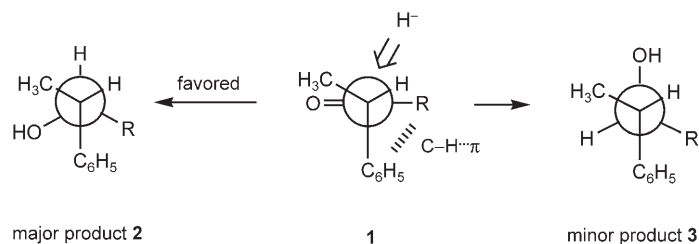
R	**1** (L = C_6H_5): $r_{2/3}$		**4** (L = c-C_6H_{11}): $r_{5/6}$		
	35 °C	Calcd[2]	35 °C	−11.5 °C	−43 °C
Me	2.8	3.7	1.6	2.1	2.7
Et	3.2	3.9	2.0	2.8	3.8
iPr	5.0	4.4	4.1	6.6	9.7
tBu	49	49	1.6	1.55	1.5

Abstract in Japanese:

アルキル 1-シクロヘキシルエチルケトン cyclo-C₆H₁₁CHCH₃-CO-R (R = Me, Et, iPr, tBu の配座自由エネルギーを研究するため、非経験的分子軌道計算を MP2/6-311++G(d,p)//MP2/6-31G(d)レベルで行った。全ての場合において、エクアトリアル配座の１つが最も安定となった。アキシアル配座はやや不安定となることが示された。すべての安定配座でCH/C=O と CH/O=C の距離が短くなっている事が明らかになった。これらの得られた結果はCH/π (C=O) や CH/O 水素結合による分子構造の安定化として解釈される。cyclo-C₆H₁₁CHCH₃-CO-R への求核付加により生成される 2 級アルコールジアステレオマーの比率を配座分布を基に評価した。計算結果はFelkinらによって報告された実験データ(生成比(主生成物/副生成物)が徐々に増加するが、R=t-C₄H₉の時に小さくなる)と一致した。cyclo-C₆H₁₁CHCH₃-CO-R へLiHが付加する時のジアステレオマー生成経路における遷移状態のエネルギーをR = Me and tBuの場合に算出した。これらの生成物には顕著な差が認められなかった。これは上述の配座分布を基にした計算結果と対応している。よって、π 面選択性の機構は遷移状態の構造が基質の基底状態における配座と類似しており、さらに求核試薬はカルボニル π 面のより立体障害の少ない側から近づく、という単純な前提によって説明することができる。
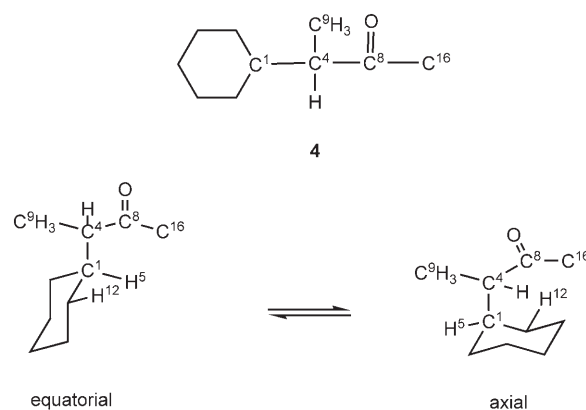
4

equatorial   axial

Scheme 3. Atom assignments of the equatorial and axial conformers of **4**.

Results and Discussion

Figure 1 shows the rotational-energy profile, at the MP2/6-31G(d) level of approximation, plotted against the C^1–C^4–C^8–C^{16} torsion angle ϕ for **4** (R = Me, equatorial). The distance and angle parameters other than ϕ were relaxed. Two energy minima were observed at $\phi = −110$ and $100°$.

Figure 2 shows the energy profile of **4** plotted against the H^5–C^1–C^4–C^8 torsion angle α (R = Me, equatorial). Here, the value of ϕ reported in Figure 1 was used as the initial input, and the parameters other than α (including ϕ) were relaxed. The most-stable conformations of **4** for R = Me are illustrated in Figure 3.
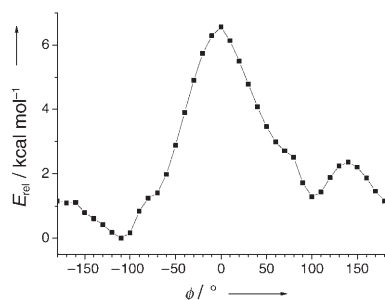
Figure 1. Rotational-energy profile, at the MP2/6-31G(d) level of approximation, plotted against ϕ for **4** (R = Me, equatorial). The angle and distance parameters other than ϕ were relaxed.
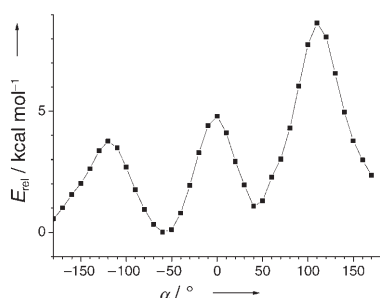

Figure 2. Rotational-energy profile of **4** (R = Me, equatorial) plotted against α. The other angle and distance parameters were relaxed.
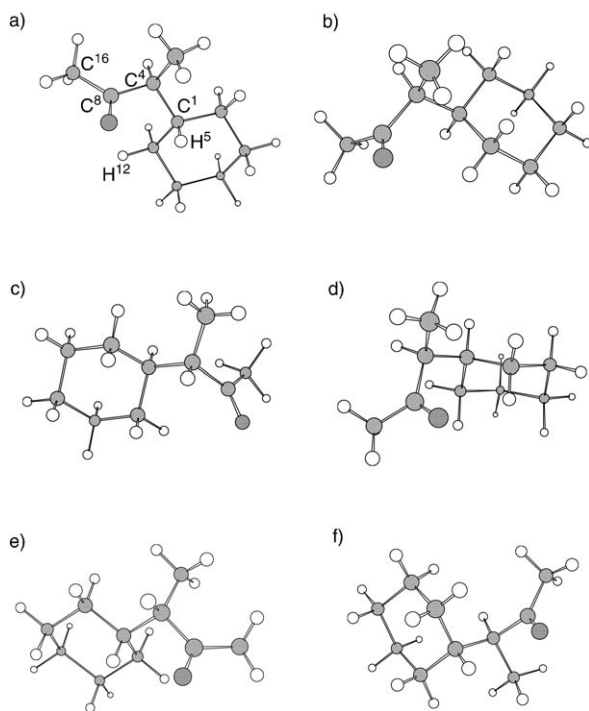

Figure 3. Stable conformers of **4** (R = Me): a) eq1, b) eq2, c) eq3, d) eq4, e) eq5, and f) ax1.

Table 2 summarizes the relative energies, proportions, and geometric parameters of the stable conformers of **4** (see

Table S1 for the coordinates). Only conformations with ΔG less than 4 kcal mol^{-1} are listed for each compound.

The equatorial conformers are generally more stable than the axial ones; this was expected. However, the difference in energy between the most-stable equatorial and axial conformers, $\Delta G_{ax1-eq1}$, is not necessarily very large: 1.43, 1.49, 1.53, and 1.35 kcal mol^{-1} for R = Me, Et, iPr, and tBu, respectively. Of interest is the relative stability of the axial conformers of **4** in contrast to the values reported for alkyl cyclohexane derivatives (A value: 1.74, 1.79, 2.21, 4.7 kcal mol^{-1} for methyl, ethyl, isopropyl, and $tert$-butyl cyclohexane, respectively).[13] This suggests that the presence of a carbonyl group is important in stabilizing the axial conformation. Consequently, the axial conformers exist in a not-negligible proportion: 6.6, 6.1, 4.5, and 7.6% for R = Me, Et, iPr, and tBu, respectively.

Interestingly, the geometrical parameters of several conformers fall into a narrow range. For instance, ϕ −117 to −143°, α −55 to −61°, $d(H^{12}-C^8)$ 2.52–2.84 Å, $d(H^{12}-O)$ 2.46–2.91 Å, $d(H^5-O)$ 2.54–2.67 Å, for the type A conformer. Table 2 shows that the other conformers are grouped into four types, in which the geometries also fall into a narrow range: B (ϕ −81 to −88°, α 47–50°), C (ϕ 71–73°, α −59 to −74°), D (ϕ −106 to −141°, α 172–175°), and E (ϕ −118 to −147°, α −51 to −58°).

The distance $d(H^{12}-C^8)$ is short (2.50–2.96 Å) in each conformer. This shows that C−H···π interactions, which occur between a cyclohexyl H atom (H^{12}) and the carbonyl π group, play a key role in stabilizing the conformation of **4**. We suggest that C−H···π(C=O) hydrogen bonds[14] are important in controlling the conformation of carbonyl compounds. There is ample evidence that C−H···π hydrogen bonds determine the conformation of various compounds, organic[15,16,17] as well as organometallic.[18]

Also of note is the observation that $d(H^{12}-O)$ is short (2.40–3.14 Å) in each conformer, suggesting the importance of C−H···O hydrogen bonds. The distance $d(H^5-O)$ is short in every A (2.54–2.67 Å) and E (2.44–2.67 Å) conformer, for which such an interaction is stereochemically possible. This seems to be a cause of the stability of these conformers. Hence, we suggest that C−H···O hydrogen bonds[3,4] also play a considerable part in determining the conformation of **4**. Such hydrogen bonds are known to be important in determining the crystal,[19] solution,[20] and gas-phase[21] conformation of various organic compounds.

The diastereomeric ratio of the secondary alcohols produced in the nucleophilic addition of **4** was estimated on the basis of the rotamer distribution. Scheme 4 shows that Re-face attack gives **5**, whereas Si-face attack gives **6**.

Inspection of molecular models suggests that, in type A, B, D, and E conformers, approach of the nucleophile to the substrate takes place more easily from the Re face than from the Si face of the C=O group. On the contrary, in type C conformers, the nucleophilic attack may take place more easily from the si face. The product ratios $r_{5/6}$ were calculated as reported in Table 3,[22] based on the somewhat arbitrary assumption that the ratio of the nucleophile attack

Table 2. Stable conformations of alkyl 1-cyclohexylethyl ketones $cyclo$-$C_6H_{11}CHCH_3$-CO-R **4** (R=Me, Et, iPr, and tBu), relative Gibbs energy, abundance, and geometrical parameters calculated at the MP2/6-311++G(d,p)//MP2/6-31G(d) level of approximation.

R	Conformer	ΔG[a] [kcal mol^{-1}]	Ratio[b] [%]	ϕ [°]	α [°]	d(H^{12}-C^8) [Å]	d(H^{12}-O) [Å]	d(H^5-O) [Å]	Type[c]
Me	eq1	0.00	56.6	-133	−57	2.58	2.78	2.57	A
	eq2	0.69	17.7	71	−68	2.53	2.83	3.87	C
	eq3	0.92	12.0	−86	48	2.74	2.61	3.46	B
	eq4	1.41	5.2	−109	174	2.84	2.47	4.10	D
	eq5	2.23	1.3	118	53	2.65	3.10	2.52	
	eq6	2.66	0.6	102	−172	2.82	2.48	4.11	
	ax1	1.43	5.1	-132	−56	2.59	2.84	2.54	E
	ax2	2.14	1.5	73	−72	2.51	2.80	3.88	C
Et	eq1	0.00	52.7	−129	−58	2.56	2.82	2.59	A
	eq2	1.07	8.6	71	−70	2.52	2.82	3.88	C
	eq3	1.11	8.1	−88	47	2.75	2.58	3.42	B
	eq4	1.22	6.7	−143	-55	2.84	2.46	2.54	A
	eq5	1.32	5.7	−109	174	2.66	3.14	4.10	D
	eq6	1.36	5.3	−120	-60	2.71	2.67	2.65	A
	eq7	1.58	3.7	−83	48	2.73	2.66	3.49	B
	eq8	2.22	1.2	−107	175	2.81	2.49	4.11	D
	eq9	2.60	0.7	116	54	2.64	3.10	2.54	
	eq10	2.72	0.5	177	43	2.86	2.60	2.43	
	eq11	2.84	0.4	102	−172	2.82	2.47	4.11	
	eq12	2.99	0.3	−141	172	2.71	2.67	4.01	D
	ax1	1.49	4.3	−128	−57	2.57	2.87	2.56	A
	ax2	2.51	0.8	73	−74	2.50	2.80	3.89	C
	ax3	2.76	0.5	−146	−52	2.66	2.74	2.47	E
	ax4	2.79	0.5	−120	−58	2.56	2.96	2.60	E
iPr	eq1	0.00	30.0	−82	48	2.72	2.66	3.50	B
	eq2	0.09	25.7	−117	−61	2.52	2.91	2.67	A
	eq3	0.11	24.8	−143	−55	2.63	2.69	2.54	A
	eq4	0.84	7.2	−106	175	2.81	2.49	4.11	D
	eq5	1.26	3.6	69	−59	2.57	2.79	3.77	C
	eq6	1.72	1.6	−133	−59	2.59	2.75	2.57	A
	eq7	1.90	1.2	−142	172	2.96	2.40	4.01	
	eq8	2.18	0.8	−167	40	2.92	2.52	2.53	
	eq9	2.59	0.4	−103	45	2.81	2.47	3.28	
	eq10	3.41	0.1	−128	172	2.54	2.98	2.61	D
	ax1	1.53	2.3	−118	−58	2.66	2.75	2.46	E
	ax2	1.62	1.9	−147	−51	2.66	2.75	2.46	E
	ax3	2.57	0.4	72	−62	2.56	2.75	3.76	C
	ax4	3.41	0.1	−136	−51	2.66	2.90	2.44	E
tBu	eq1	0.00	73.8	−133	−59	2.59	2.75	2.56	A
	eq2	1.03	13.0	−81	50	2.71	2.62	2.40	B
	eq3	1.53	5.5	−128	172	2.70	2.89	4.01	D
	ax1	1.35	7.6	−139	−56	2.61	2.73	2.49	E

[a] Relative conformational energy. [b] Proportion of conformers. [c] Type of conformer.

x: Re-face attack
y: Si-face attack
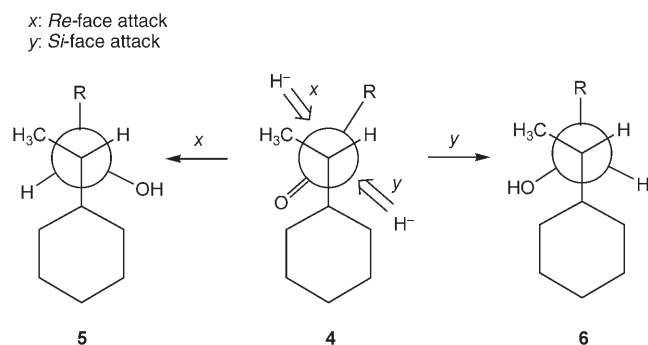
Scheme 4. Plausible mechanism of the π-facial selectivity in the nucleophilic addition to alkyl 1-cyclohexylethyl ketones **4**.

Table 3. Calculated ratios of secondary alcohols produced in the nucleophilic addition of $cyclo$-$C_6H_{11}CHCH_3$-CO-R **4** (R=Me, Et, iPr, and tBu).

R	A+E[a] [%]	B [%]	C [%]	D [%]	**5**[b] [%]	**6**[c] [%]	$r_{5/6}$
Me	61.7	12.0	19.2	5.2	54.4	43.7	1.25
Et	70.0	11.8	9.4	6.9	59.8	38.3	1.56
iPr	56.4	30.0	4.0	7.3	67.8	29.9	2.27
tBu	81.4	13.0	0.0	5.5	65.5	34.4	1.90

[a] Proportion of conformers. Contributions from other conformers of higher energies (1.9, 1.9, 2.3, and 0.1 % for R=Me, Et, iPr, and tBu, respectively) were neglected. [b] From (A+E)×0.6+(B+D)×0.9+C×0.1. [c] From (A+E)×0.4+(B+D)×0.1+C×0.9.

R/S is 60:40 (CH₃ vs. cyclohexyl) for type A and E conformers, 90:10 (H vs. cyclohexyl) for B and D, and 10:90 (cyclohexyl vs. H) for C.

The above result is consistent with the experimental data reported by Felkin and co-workers (Table 1). The gradual increase of the product ratio from R = Me to *i*Pr and the decline in the *tert*-butyl case has been reproduced. Here, we do not discuss in more detail the steric course of the reactions of every possible conformer, as changes in the experimental conditions easily modify the stereochemical outcome (Table 1). The present result is in sharp contrast to the data previously reported for the nucleophilic addition of the aromatic analogues **1**.[2] There, the gradual increase in the product ratios $r_{2/3}$ (Table 1, column 3) was followed by an abrupt jump at R = *t*Bu; the experimental data (Table 1, column 2) were satisfactorily reproduced by calculations.

Ab initio calculations were also carried out for the transition-state structures of a model reaction. Thus, activation free energies of the diastereomeric transition states (**4** + LiH) were calculated at the same level of approximation, starting from every stable equatorial conformation of **4** (eq1–6 for R = Me and eq1–3 for R = *t*Bu). The difference in the activation Gibbs energies leading to **5** and **6**, $\Delta G^{\ddagger}_{TS1-TS2} = \Delta G^{\ddagger}_{TS1} - \Delta G^{\ddagger}_{TS2}$, was calculated to be 1.562 (from eq1 of R = Me) and 1.559 kcal mol^{-1} (from eq1 of R = *t*Bu). These values correspond to a product ratio $r_{5/6}$ of around 10. Although this does not agree very well with the experimental data (Table 1; 1.6–2.7 for R = Me, 1.5–1.6 for *t*Bu), we think the result is reasonable as there are many other conformers to be considered. The effect of solvent and temperature is not included in the calculations. The difference in $\Delta G^{\ddagger}_{TS1-TS2}$ for the reaction of aromatic analogues (L = Ph) **1** to give **2** and **3** was calculated to be 1.37 and 4.13 kcal mol^{-1} for R = methyl and *t*-butyl, respectively.[2]

The geometry of TS1 (R = Me) is shown in Figure 4. The geometrical parameters of the ground state (eq1, R = Me, *t*Bu) and the transition state leading to the major product **5**
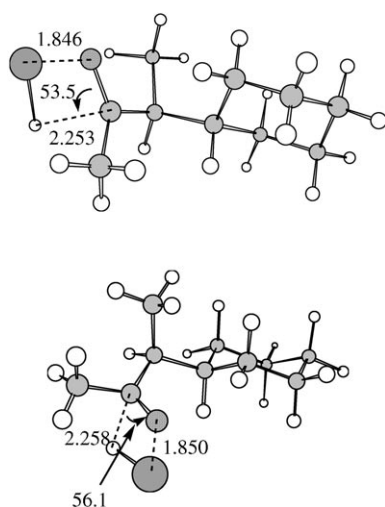
(TS1) are compared in Table 4. The torsion angles ϕ and α in TS1 were considerably twisted relative to the ground-state geometry. Notably, however, the distances between H^{12}

Table 4. Geometrical parameters, calculated at the MP2/6-311++G-(d,p)//MP2/6-31G(d) level of approximation, of ground-state (GS) and transition-state (TS1) structures of **4**, leading to the preferred product **5**.

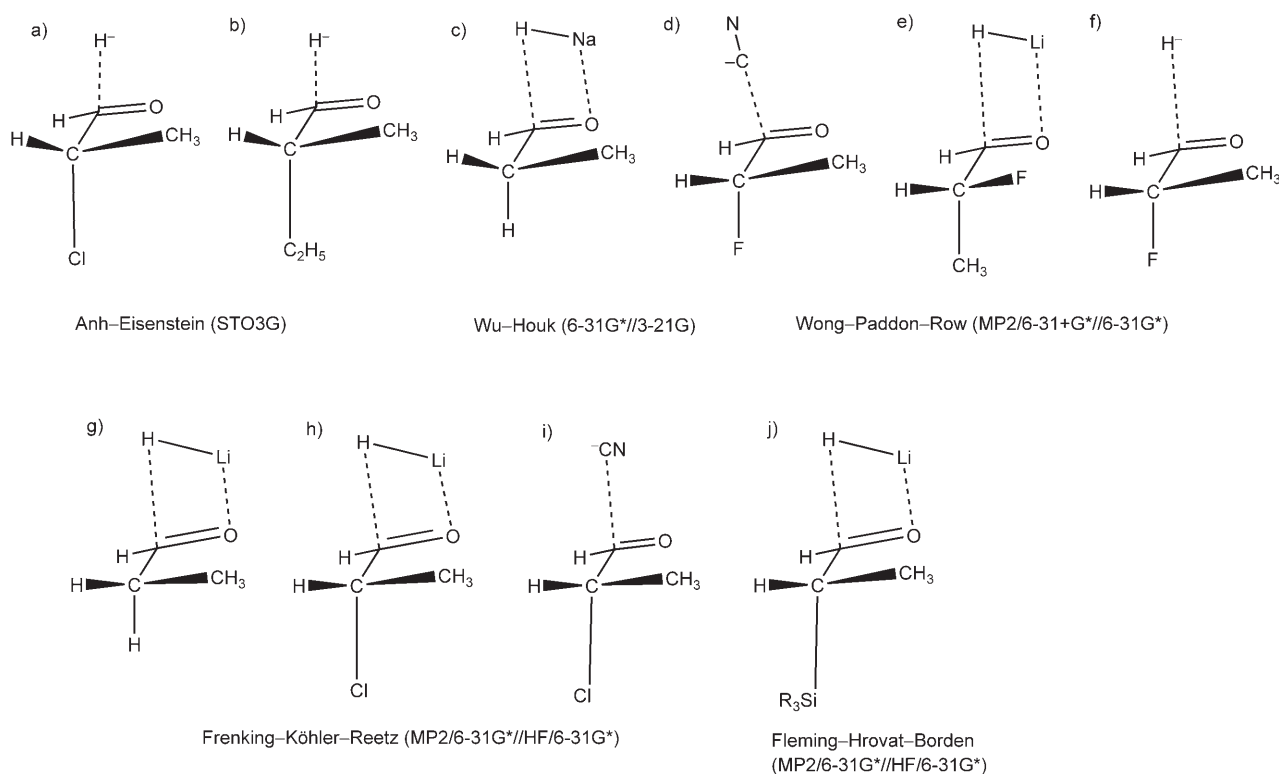| | R = Me | | R = *t*Bu | |
	GS (eq1)	TS1	GS (eq1)	TS1
ϕ [°]	−133	−63	−133	−68
α [°]	−57	56	−59	56
$d(H^{12}–C^8)$ [Å]	2.58	2.67	2.59	2.71
$d(H^{12}–O)$ [Å]	2.78	2.68	2.75	2.68
$d(H^5–O)$ [Å]	2.57	3.64	2.56	3.66
$d(CH_3–O)^{[a]}$ [Å]	2.85	2.61	2.80	2.57

[a] Distance between one of the methyl hydrogen atoms and O=C.

and C^8 and O remain short. This shows that the C−H···π(C= O) and C−H···O hydrogen bonds are both important in stabilizing the TS geometry, leading to the preferred product. Furthermore, one of the methyl hydrogen atoms is close to the carbonyl oxygen, suggesting the importance of the five-membered ring formed by the C−H···O hydrogen bond.

The importance of CH₃···O hydrogen bonds has been suggested in the structures of the transition states for the nucleophilic reactions of propanal (Scheme 5c and g),[23,25a] 2-fluoropropanal (Scheme 5d–f),[24] 2-chloropropanal, 2-methoxypropanal (Scheme 5h and i),[25] 2-*N*,*N*-dimethylpropanal, 2-silylpropanal, and 2-trimethylsilylpropanal (Scheme 5j).[26]

With regard to the methyl and carbonyl groups in the substituted propanal, the eclipsed or gauche conformation was reported in the transition states leading to the predominant product (which includes the results of Anh and Eisenstein;[11c] Scheme 5a and b) with an exception (Scheme 5e), for which the importance of the Li$^+$···F interaction was suggested; however, the CH₃/C=O eclipsed geometry was reported to be close in energy to the most-stable. The above observations suggest the importance of the five-membered rings formed by C−H···O hydrogen bonds in stabilizing the geometry of the transition states.

As mentioned earlier, the present result is in sharp contrast to the data previously reported for the nucleophilic addition of aromatic analogues **1**. There, the gradual increase in the product ratios $r_{2/3}$ (Table 1, column 2) was followed by an abrupt jump at R = *t*Bu; the experimental data were satisfactorily reproduced by calculations (Table 1, column 3).[2] In the oxidation of structurally related alkyl 1-phenylethyl sulfides C₆H₅CHCH₃−S−R **7**, which give rise to diastereomeric sulfoxides **8** and **9** (Scheme 6), the gradual increase of the product ratio $r_{8/9}$ (3.1, 3.2, and 3.6 for R = Me, Et, and *i*Pr, respectively) was also followed by an abrupt jump at R = *t*Bu (49:1).[27] This, again, was reproduced by calculations.[28] In the most-stable rotamers of **1**[2] and **7**,[27] the alkyl group was shown to be close to C₆H₅ in every case. In these geometries, R is capable of interacting favorably with the phenyl group by C−H···π(C₆H₅) hydrogen bonds. The discrepancy observed between **1** (and **7**) and **4** is attributable,
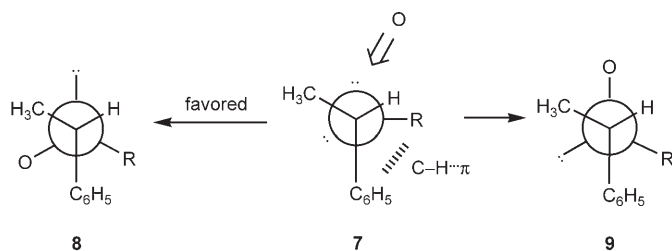

Figure 4. Transition-states geometries in the addition of LiH to alkyl 1-cyclohexylethyl ketones **4** (R = Me). Top: TS1; bottom: TS2.

Scheme 5. Most-stable transition geometries reported for nucleophilic additions to various propanal derivatives.

Scheme 6. Plausible mechanism of the diastereofacial selectivity in the oxidation of alkyl 1-phenylethyl sulfides $C_6H_5CHCH_3$–S–R **7**.

therefore, to the presence (in **1** and **7**) or absence (in **4**) of C–H···C_6H_5 interactions.

We conclude that the mechanism of the π-facial selection can be rationalized on the basis of the simple premise that the geometry of the ground-state conformation of the substrates is the most important. Frenking, Köhler, and Reetz[29] have already reached the same conclusion by calculating, at the MP2/6-31G(d)//HF/6-31G(d) level, the transition-state structures of nucleophilic-addition reactions of various substituted acetaldehydes. We concur with Frenking et al., but this argument extends to the mechanisms of other diastereoselective reactions, irrespective of the type of reaction (nucleophilic or electrophilic), the reaction medium (polar or nonpolar), or the nature of the substituent (aliphatic or aromatic).

Conclusions

Ab initio MO calculations were carried out at the MP2/6-311++G(d,p)//MP2/6-31G(d) level to investigate the conformational Gibbs energy of alkyl 1-cyclohexylethyl ketones **4**. The C–H···π(C=O) and C–H···O hydrogen bonds have been shown to be important in controlling the conformation of these compounds. Activation free energies of the diastereomeric transition states (**4**+LiH) were also calculated at the same level of approximation for R=Me and *t*Bu. The activation Gibbs energies leading to **5** and **6**, $\Delta G^{\ddagger}_{TS1-TS2}$, have been estimated to be not much different; the result is consistent with the experimental data. We conclude that the mechanism of the π-facial selection can be rationalized on the basis of the simple premise that the geometry of the ground-state conformation of the substrates is the most important.

Computational Methods

The Gaussian 03 program[12] was used. Electron correlation energies were calculated by applying the second-order Møller–Plesset (MP2) perturbation theory. The geometry of **4** was optimized at the MP2/6-31G(d) level of approximation. By using these geometries, single-point calculations were performed at the MP2/6-311++G(d,p) level to estimate the Gibbs energies of the conformers and the transition states of the model reaction **4**+LiH. Vibrational frequencies were calculated by using the analytical second derivatives at the same level of the geometry optimization for each conformer. We verified that there is only one imaginary frequency

for each transition state. With these results, the thermal-energy corrections were added to the total Gibbs energy at 298.15 K and 1 atm.

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