J. Org. Chem. **2001,** *66,* 7254−7262

A Theoretical Study of the Reaction of Lithium Aluminum Hydride with Formaldehyde and Cyclohexanone

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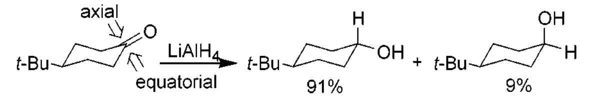
Received November 30, 2000

Geometries and energies of the reactants, complexes, and transition states for the reactions of lithium aluminum hydride with formaldehyde and cyclohexanone were obtained using ab initio and density functional (Becke3LYP/6-31G**) molecular orbital calculations. Two pathways for reaction with formaldehyde and four transition states corresponding to axial and equatorial attack at cyclohexanone were located. The transition state structures had reactant-like geometries. Predicted stereoselectivity of the reduction of cyclohexanone strongly favors axial approach of hydrogen, in agreement with experimental data. Analysis of the transition state structures suggests that electronic effects are more important than torsional effects in controlling stereoselectivity.

Introduction

The reduction of carbonyl compounds by complex metal hydride reducing agents is one of the most important reactions of organic compounds. Of particular significance is the high degree of π-facial diastereoselectivity that can be obtained in the reduction of ketones that can form more than one alcohol product. For example, in the reaction of 4-*tert*-butylcyclohexanone with lithium aluminum hydride the amount of the equatorial alcohol resulting from axial attack of hydride predominates over the isomeric alcohol by 10:1. This ratio cannot be caused by product stability, since in an equilibrium mixture the more stable equatorial alcohol predominates by only 2.4:1.[1a−c]



The determination of the factors that control the high degree of stereoselectivity in unhindered cyclic ketones has been an area of intense investigation.[2] Felkin suggested that for cyclohexanones the transition state resulting from equatorial attack by hydride has more torsional strain than the one from axial attack.[3] This is supported by ab initio calculations.[4] Anh has shown that favored transition states benefit from an antiperiplanar orientation between the incipient bond and an adjacent σ bond.[5] Cieplak has pointed out that nucleophiles tend to approach the face of the carbonyl group that is anti to the more electron rich antiperiplanar vicinal (allylic) bond,[6] and this has been confirmed by le Noble.[2f] Although Cieplak has proposed that the preferred transition state is stabilized by donation of the electrons from the nucleophile into the "vacant π^* orbital associated with the incipient bond", these observations can also be rationalized in terms of firmly established Frontier Molecular Orbital theory.[7] The HOMO of the nucleophile interacts with the LUMO of the carbonyl compound.

Of particular significance is the distortion of the extension of the orbitals of the carbonyl (π^*) LUMO caused by their interaction with vicinal bonds. Building on Klein's proposal of nonequivalence of the lobes of the LUMO,[8] Frenking, Köhler, and Reetz showed that at the carbonyl carbon in cyclohexanone the LUMO is larger on the axial than on the equatorial side.[7] A natural bond order analysis showed a stronger interaction of the LUMO with the adjacent (β) C−H bond than the (β) C−C bond. The LUMO of the carbonyl interacts better with the more electron-donating/better-overlapping vicinal bond.[2d] The resultant carbonyl LUMO (π^*) is shortened on the side of the interaction and extended on the backside.[9−11] In a reaction with an early transition state, i.e., one in which its structure resembles reactants, the hyperconjugative stabilization resulting from interaction of the carbonyl with the vicinal bond may also be present

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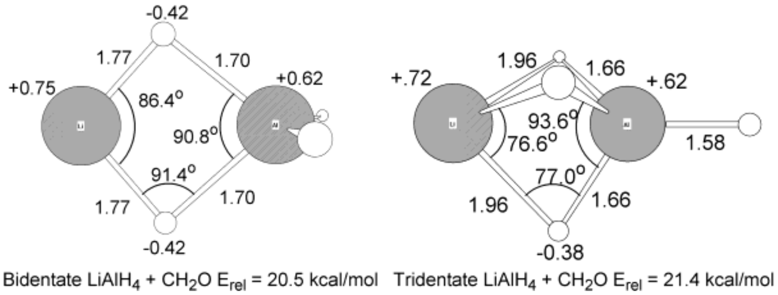

Figure 1. $LiAlH_4$ isomers, bidentate and tridentate (Becke3LYP/6-31G**).

in the transition state. If polar substituents are present, electrostatic interactions may overwhelm the effects of hyperconjugation and torsional strain.[1g,i,4,12,13]

The arguments about the origin of stereoselectivity in cyclic ketones are similar to those proposed to explain the preference for the staggered form of ethane over the eclipsed conformation. One view is that the eclipsed form of ethane is destabilized by torsional strain caused by the repulsive interaction between filled bond orbitals.[14] In an alternative approach the greater stability of the staggered form arises from a hyperconjugative interaction between a filled (σ_{C-H}) bonding orbital and a vacant (σ_{C-H}*) antibonding orbital leading to delocalization of negative charge.[15] A recent natural bond order analysis has shown that steric effects are only of secondary importance. Hyperconjugative interactions are responsible for the preference for the staggered conformation in ethane.[16]

Although the models of Felkin, Anh, and Cieplak are based on transition state effects, the uneven orbital extension models are based on the LUMO of the reactant ketone.[2a,b,d,7,8] Tomoda has been especially successful with his quantitative Exterior Frontier Orbital Extension (EFOE) model; his analysis includes an examination of steric considerations by also calculating the π-Plane Divided Accessible Space.[2b,11,17−21] In most cases the EFOE term alone predicts the correct stereoselectivity.[2b] The ground state models are effective because they are applied to reactions with early transition states.

One approach to determining the importance of these factors involves carrying out molecular orbital calculations for each of the competing transition states. Since the mechanism of the reaction of carbonyl compounds with $LiAlH_4$ is poorly understood and a quantum mechanical description is unavailable, several approximations have been used to estimate transition state structure. These include using LiH,[22] and AlH_3,[23,24,25] as substitutes for $LiAlH_4$. It would be helpful to know the mechanism for the reaction in question as an aid in understanding its stereoselectivity.[26,27]

Computational Methods

Geometries of reactants, complexes, and transition state structures for reaction of lithium aluminum hydride with formaldehyde and cyclohexanone were optimized using density functional theory.[28] The Becke3LYP hybrid functional was used throughout this work. It consists of the nonlocal exchange functional of Becke's three-parameter set[29] and the nonlocal correlation functional of Lee, Yang, and Parr.[30] All the functionals are applied to the self-consistent-field HF densities. The 6-31G** basis set was used in all calculations. Stationary points were fully optimized and characterized by vibrational frequency calculations that also provided zero-point vibrational energies (ZPE); all transition states were characterized by having only one imaginary frequency. Restricted Becke3LYP calculations were performed on all structures using the TITAN electronic structure determination program.[31] Reported electrostatic charges are determined by a fitting of the electrostatic potential.

Computational Results

We now report results of density functional calculations that provide the energies and structures for the complexes and the transition states of the reactions of $LiAlH_4$ with formaldehyde and cyclohexanone.

$LiAlH_4$ Reduction of Formaldehyde. Two ground-state geometries of $LiAlH_4$ were located on the potential energy surface. The bidentate structure of $LiAlH_4$ (lithium is coordinated to two hydrogens) is lower in energy than the tridentate structure (lithium is coordinated to three hydrogens) by 0.9 kcal/mol (ZPE corrected Becke3LYP/6-31G**) (Figure 1, Table 1). Zyubin and co-workers reported similar energies for isomers of $LiAlH_4$.[32]

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[26] Although $LiAlH_4$ reactions are carried out in solution, remarkably similar stereochemical outcomes have been observed from gas-phase hydride reductions of cyclohexanones by pentacoordinate silicon hydride ions. The similarity between the condensed-phase and gas-phase behavior implies that environmental effects are either unimportant or cancel out and that the reduction diastereoselectivity can be attributed to the intrinsic nature of the isolated reactants.[27]

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Table 1. Becke3LP/6-31G Relative Energies[a] and Entropies of Stationary Points on the Formaldehyde Plus $LiAlH_4$ Potential Energy Surface**

molecule	E_{rel} (kcal/mol)	S_{rel} (eu)
$LiAlH_4$ bidentate[b]+ formaldehyde	20.5	29.6
$LiAlH_4$ tridentate[b]+ formaldehyde	21.4	30.3
bidentate complex[c]	0.0	4.2
tridentate complex[c]	0.0	0.0
bidentate TS[d]	4.1	0.3
tridentate TS[d]	2.1	−6.5
tridentate TS2	0.5	−6.4
excited product[e]	−1.3	−2.0
product $CH_3OLiAlH_3$	−40.0	−5.1

[a] Relative energies include zero-point corrections. [b]Figure 1. [c]Figure 2. [d]Figure 3. [e]Figure 4.

The importance of the association of the lithium ion with the carbonyl oxygen atom during the course of reduction by LiAlH4 was recognized very early.[33] The calculated energy profile indicates that complex formation occurs in a step prior to transfer of the hydride to the carbonyl carbon.

Two stable isomers of the $CH_2O{-}LiAlH_4$ complex (Figure 2) with energies within 0.2 kcal/mol were located. After ZPE correction the complexes are equal in energy (Becke3LYP/6-31G**). Because of the similarity to the $LiAlH_4$ structures,[32] the complexes are referred to as bidentate and tridentate. Although the tridentate complex has neighboring hydrogens (C−H and Al−H) separated by only 2.3 Å, there is greater charge separation in the bidentate complex. The dipole moments of the tridentate and bidentate complexes are calculated at 6.1 and 8.2 D, respectively. Complex formation is highly exothermic. The calculated heat of complexation equals −20.5 kcal/mol for the bidentate isomer, and −21.4 kcal/mol for the tridentate (ZPE corrected Becke3LYP/6-31G**)(Table 1).

Two six-center transition states (TS) (Figure 3) were located, corresponding to bidentate and tridentate structures. The tridentate TS structure is more stable by 2.0 kcal/mol. Both can be described as cyclic TS structures with reactant-like geometries; the C−H bond is much longer than the bond length of the first encountered product (1.23 Å vide infra). The forming C−H bond length of the tridentate TS structure is 1.87 Å; the corresponding value of the bidentate TS structure is 2.46 Å. For both TSs, normal mode vibration analysis shows a vibration corresponding to shortening of the $C{-}H_{Nu}$ bond. The bidentate TS is considerably earlier and also shows a rotational component around the C−O bond. Dipole moments for the bidentate and tridentate TSs are 6.1 and 3.3 D, respectively. The incipient $C{-}H_{Nu}$ bond length observed for the bidentate structure (2.46 Å) was unique among the transition states reported in this work. Bidentate $LiAlH_4$ TS structures with less reactive acetaldehyde and acetone (Becke3LYP/6-31G**) show much shorter incipient $C{-}H_{Nu}$ bond lengths of 1.74 and 1.66 Å, respectively, and their normal mode vibrations do not have the rotational component around the C−O bond. Because of the low barrier for C−H bond formation, the very early nature of the unique $LiAlH_4$−formaldehyde bidentate TS may be related to the energy required to separate the negatively charged nucleophilic hydrogen from the lithium cation to which it was complexed. In less reactive aldehydes and ketones, forming the new C−H bond provides a barrier greater than the separation of charge, and the TS occurs later.

Both pathways lead to a common bidentate intermediate (Figure 4a, excited product) whose energy is 1.3 kcal/mol below the energy of the complexes (Table 1). The favored tridentate pathway has a second transition state (TS2) that corresponds to flipping from a tridentate structure to the bidentate intermediate (Figure 4a, excited product). The energy gradient becomes very steep as the reaction proceeds to the structure of the lithium trihydromethoxyaluminate product. During this final step the aluminum atom migrates toward the oxygen, and the lithium becomes complexed to both of these atoms.

The calculated ZPE corrected activation energies are 2.1 and 4.1 kcal/mol for tridentate and bidentate pathways, respectively (Figure 4b, Table 1), which compares with the experimental data obtained with less reactive ketones (10.5 kcal/mol[34]). The heat of reaction (Becke3LYP/6-31G**) is calculated at −40.0 kcal/mol, in agreement with the experimentally derived value for the metal hydride reductions of carbonyl compounds (−45 kcal/mol per one hydride transfer[35]).

$LiAlH_4$ Reduction of Cyclohexanone. The potential energy surface (Becke3LYP/6-31G**) of the gas-phase addition of $LiAlH_4$ to cyclohexanone (Table 2) has been examined in this research. The reaction proceeds via initial complex formation, followed by nucleophilic attack of the lithium aluminum hydride moiety. Two complexes of approximately equal energy corresponding to bidentate and tridentate structures are formed. Consistent with the cation complexation model[36] proposed by Yadav, the increase in charge on the carbonyl carbon caused by complex formation causes increased hyperconjugative delocalization of the p orbital of the carbonyl carbon with the better electron-donating allylic bond, C−H in this case. The ring flattens, increasing the preference for axial approach by the nucleophile. The dihedral angle $C_3{-}C_2{-}C_1{-}C_6$ decreases from 51.6° in cyclohexanone to 47.4° and 48.0° in the bidentate and tridentate complexes, respectively. The angle formed by the intersection of ring planes $C_2{-}C_3{-}C_5{-}C_6$ and $C_2{-}C_1{-}C_6$ increases from 133.0° in cyclohexanone to 136.9° and 136.3° in the bidentate and tridentate complexes. The association of flattening of the cyclohexanone ring with increased axial attack has often been noted.[4,5,25,35] In each of the complexes the LUMO shows an even greater extension toward the axial face than is found in cyclohexanone at the same level of theory.

The bidentate and tridentate six-center transition states for axial and equatorial attack of hydride are shown in Figure 5. The ZPE corrected (B3LYP/6-31G**) enthalpy of complexation for cyclohexanone and $LiAlH_4$ is calculated at −27.1 kcal/mol. The ZPE corrected activation energy leading to the bidentate axial transition state is 11.7 kcal/mol (Table 2), compared to experimental data with other ketones (10.5 kcal/mol[34]).

The six-membered ring transition states allow the angle of approaching H_{Nu} (bidentate 106°, tridentate

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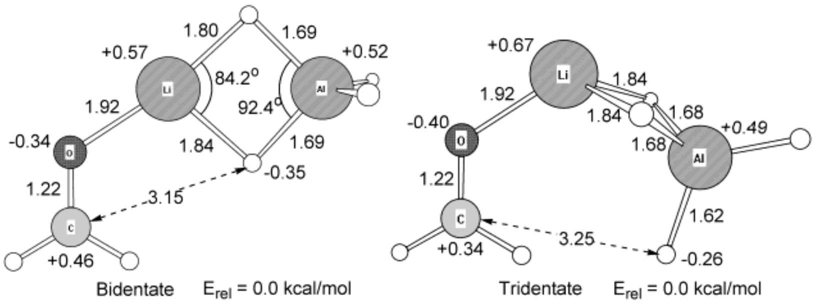

Figure 2. $LiAlH_4$−formaldehyde complexes (Becke3LYP/6-31G**).

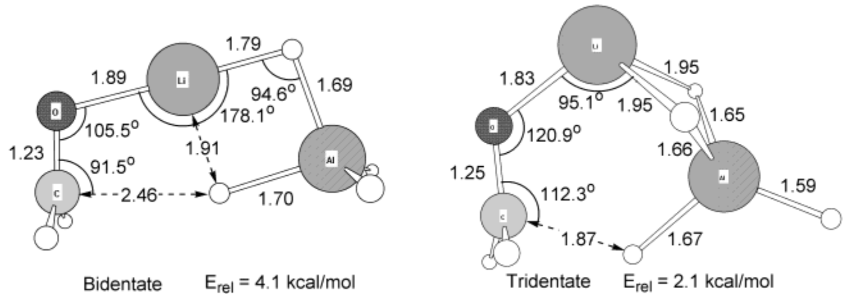

Figure 3. $LiAlH_4$−formaldehyde transition states (Becke3LYP/6-31G**).

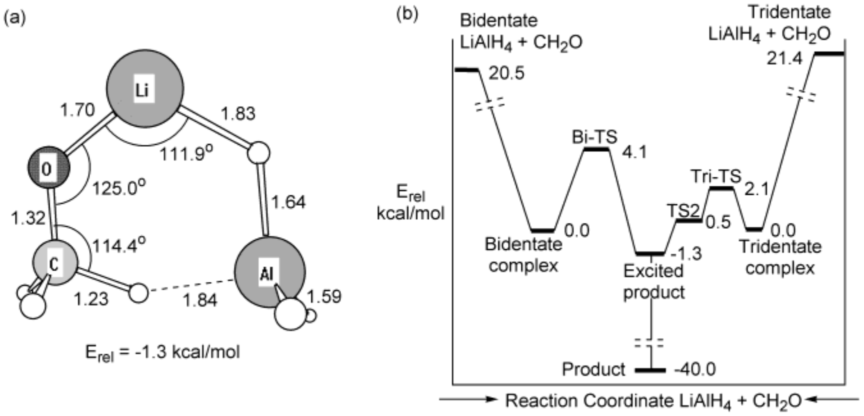

Figure 4. (a) $LiAlH_4$−formaldehyde excited product. (b) Relative energies of stationary points (kcal/mol) (Becke3LYP/6-31G**).

Table 2. Becke3LYP /6-31G Relative Energies[a] and Entropies for Complexes and Transition States on the Cyclohexanone Plus $LiAlH_4$ Potential Energy Surface**

molecule	E_{rel} (kcal/mol)	S_{rel} (eu)
$LiAlH_4$ bidentate[b] + cyclohexanone	27.1	33.2
$LiAlH_4$ tridentate[b] + cyclohexanone	28.0	33.9
bidentate complex	0.0	0.0
tridentate complex	0.0	−1.4
bidentate-axial TS[c]	11.7	−4.4
bidentate-equatorial TS[c]	13.3	−3.9
tridentate-axial[c]	12.3	−7.1
tridentate-equatorial TS[c]	13.6	−7.0

[a] Relative energies include zero-point corrections. [b] Figure 1. [c] Figure 5.

110°) to be closer to the average angle (107°) observed in crystalline ketones;[37] these values are larger than those found in four-center AlH_3 transition states (Becke3LYP/6-31G**) by 11° (axial) and 15° (equatorial).

Bidentate Cyclohexanone−$LiAlH_4$ Transition State Structures. Projections down the C_1−C_2 bond show dihedral angles O−C−C−H_{eq} in the bidentate axial and equatorial transition states of 44.5° and 36.1°, respectively (Figure 6a,b). This is consistent with greater torsional strain in the equatorial, compared to the axial transition state. The ring $C_6C_1C_2C_3$ dihedral angles distort from 51.3° in cyclohexanone to 40.3° for axial attack and 60.8° for equatorial attack. The ring distortion is measured by the angle of the $C_1C_2C_6$−$C_2C_3C_5$ planes (Figure 6c,d). This angle indicates that compared with a value of 133.0° in cyclohexanone (Becke3LYP/6-31G**), the ring is flattened to 144.0° at the transition state for axial attack and puckered to 123.7° for equatorial attack.

The dihedral angles of the adjacent C−H and C−C bonds with the forming C−H_{Nu} bonds provide a measure of the ability of these bonds to participate in hyperconjugation and minimize torsional strain. For axial attack the H_{Nu}−C−C−H_{ax} dihedral angle is 178.8° and the H_{Nu}-C−C−C dihedral for equatorial attack is 161.9° (Figure 6c,d). The ring distortion provides a balance between minimizing torsional strain and maximizing orbital interactions with the adjacent σ-bonds (C−H for axial and C−C for equatorial attack).[25]

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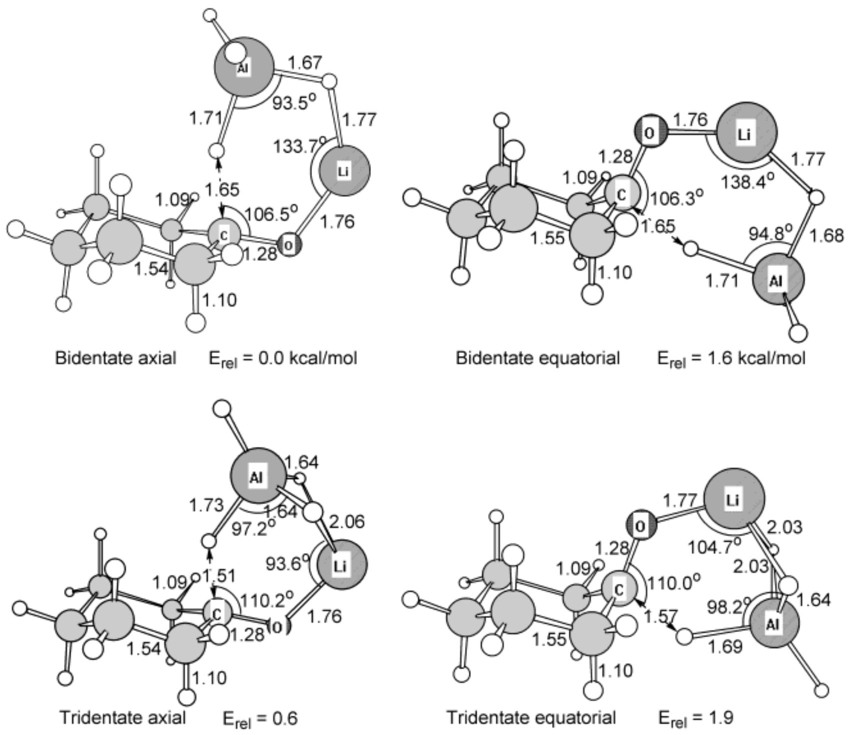

Figure 5. $LiAlH_4$–cyclohexanone transition states (Becke3LYP/6-31G**).

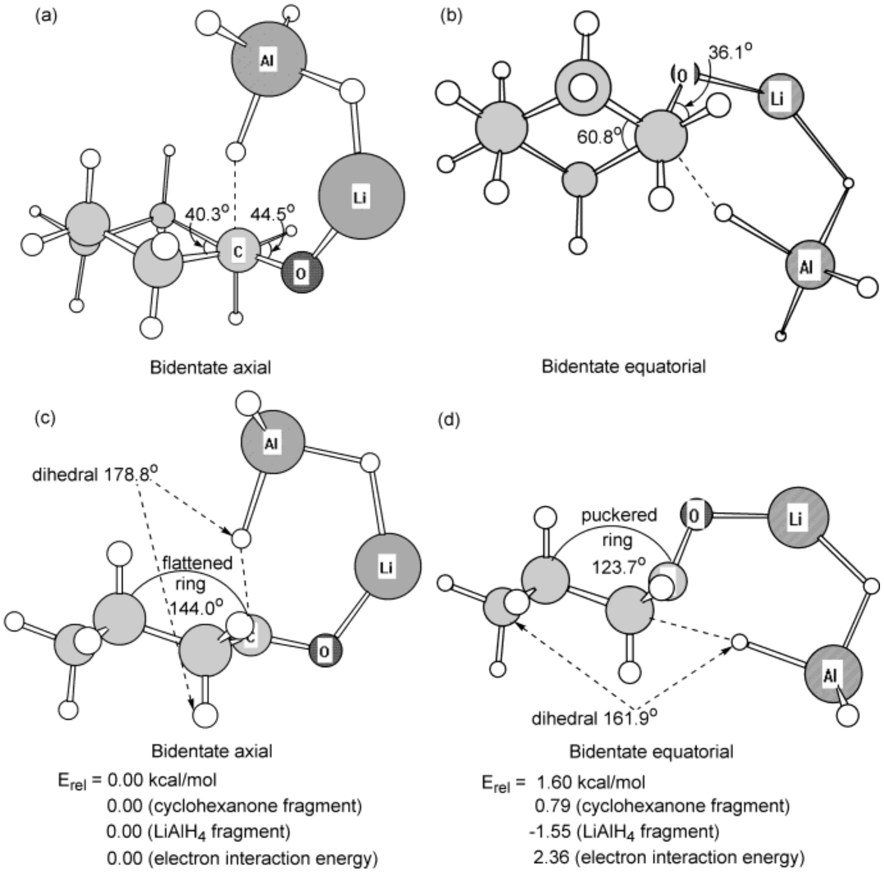

Figure 6. Dihedral angles in the bidentate transition states for axial (a,c) and equatorial (c,d) attack (Becke3LYP/6-31G**).

Tridentate Cyclohexanone–LiAlH4 Transition State Structures. Just as in the bidentate transition states, the tridentate-equatorial transition state shows greater torsional strain than the tridentate-axial transition state. Dihedral angles in the nonplanar transition state structures for axial and equatorial attacks are shown in Figure 7. Projections down the C_1-C_2 bond (Figure 7a,b) show dihedral angles $O-C-C-H_{eq}$ in the

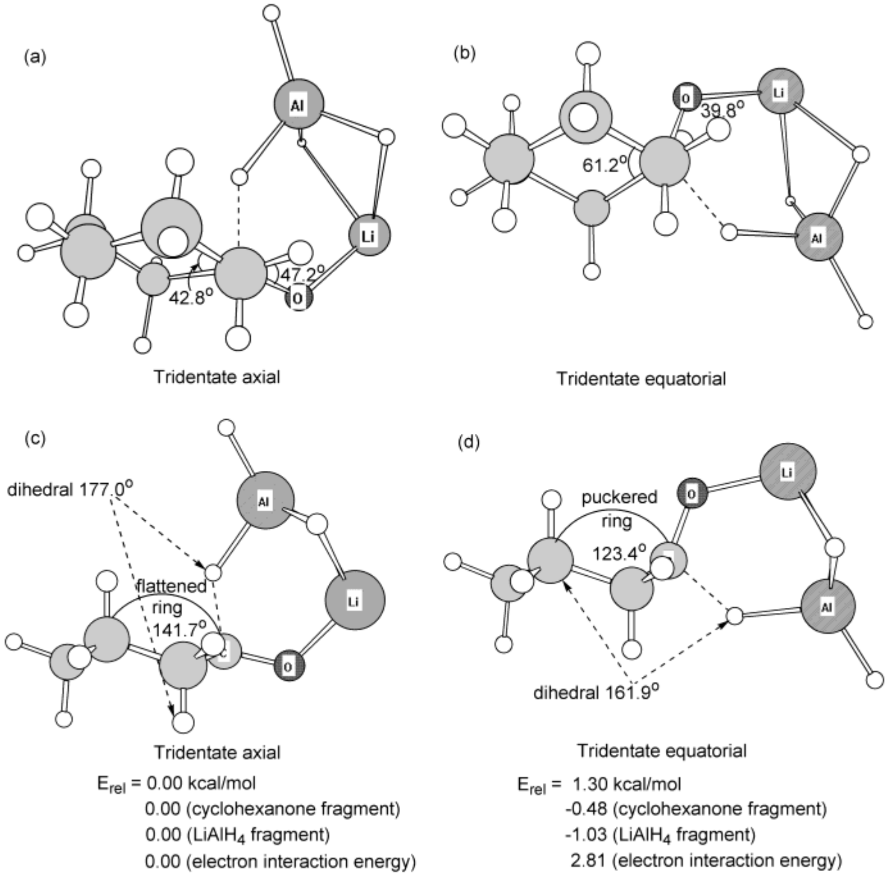

Figure 7. Dihedral angles in the tridentate transition states for axial (a,c) and equatorial (c,d) attack (Becke3LYP/6-31G**).

tridentate-axial and equatorial transition states of 47.2° and 39.8°, respectively. The ring $C_6C_1C_2C_3$ dihedral angles distort from 51.3° in cyclohexanone (Becke3LYP/6-31G**) to 42.8° for axial attack and 61.2° for equatorial attack (Figure 7a,b).

The ring distortion is measured by the angle of the $C_1C_2C_6-C_2C_3C_5$ planes (Figure 7c,d). As indicated by this angle, the ring is flattened to 141.7° for axial attack and puckered to 123.4° for equatorial attack (cyclohexanone value 133.0°). The dihedral angle $H_{Nu}-C-C-H_{ax}$ for axial attack is 177.0° and angle $H_{Nu}-C-C-C$ for equatorial attack is 161.9°. These values are similar to those observed in the bidentate transition state structures. The shorter incipient $C-H_{Nu}$ bond in the axial TS may indicate a stronger bond than in the equatorial structure.

Relative Becke3LYP/6-31G** ZPE corrected energies (kcal/mol) of the four transition states increase in the order: bidentate-axial (0.00), tridentate-axial (0.59), bidentate-equatorial (1.60), tridentate-equatorial (1.89). In the tridentate pathway axial attack is favored over equatorial by 1.60 kcal/mol; the tridentate pathway favors axial attack by 1.30 kcal/mol. The calculated product ratio (93% equatorial alcohol from axial attack, 7% axial alcohol from equatorial attack) is in good agreement with the experimental values (91%: 9%) obtained from $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone.[13]

The interaction energies in the transition state structures were evaluated by separating each transition state structure into component fragments. The energy difference between the transition state structure itself and combined energies of its components, at infinite separation, is a measure of the interaction energy at the transition state. The interaction energy should be a measure of the attraction (or repulsion) between the fragments, which could be caused by electronic/electrostatic and/or steric interactions by these fragments. Single point calculations were carried out on the “cyclohexanone” and the “$LiAlH_4$” parts of each transition state. To estimate their relative contributions, the enthalpy of each component, “frozen” at the transition state geometry, was calculated. The bidentate-axial cyclohexanone fragment is more stable than the bidentate-equatorial cyclohexanone fragment by 0.8 kcal/mol. The bidentate $LiAlH_4$ fragment shows an enthalpy difference favoring equatorial attack (1.6 kcal/mol). For tridentate transition states, the cyclohexanone fragment and the $LiAlH_4$ fragment favor the equatorial attack by 0.5 and 1.0 kcal/mol, respectively. These energies are summarized in Figures 6 and 7.

The magnitude of the interaction energies provides a measure of the attraction (or repulsion) of the reactants at the transition state. The attraction of the reactants is considerably greater for axial than equatorial attack for both pathways. The interaction energies are 2.4 kcal/mol favoring axial attack for bidentate transition states and 2.8 kcal/mol favoring axial attack for tridentate transition states. Although the distance from H_{Nu} to axial hydrogens 3 and 5 is smaller in the tridentate-axial TS (2.43 Å vs 2.46 Å in bidentate-axial), the distance from the 3 and 5 axial hydrogens to the Al atom is smaller in the bidentate-axial TS (3.46 Å vs 3.65 Å in tridentate-axial). The interaction energy favors axial approach by removal of the slight steric axial encumbrances and by any electronic attractions that favor axial attack.

Table 3. Structural Parameters for Transition States with Cyclohexanone (Becke3LYP/6-31G)**

	LiH		BH_3		AlH_3		bi-$LiAlH_4$[a]		tri-$LiAlH_4$[a]	
	ax	eq	ax	eq	ax	eq	ax	eq	ax	eq
$C-H_{Nu}$ (Å)	2.57	2.42	2.20	2.10	2.00	1.99	1.65	1.65	1.51	1.57
$O-C-C-H_{eq}$[b]	25.0	16.7	24.0	15.5	34.7	27.3	44.5	36.1	47.2	39.8
$C_6C_1C_2C_3$[c]	41.2	57.3	39.1	58.5	38.6	61.1	40.3	60.8	42.8	61.2
$C_1C_2C_6-C_2C_3C_5$[d]	143.0	127.2	144.7	125.9	145.4	123.1	144.0	123.7	141.7	123.4
bond extension[e]	0.18	0.26	0.18	0.39	0.18	0.52	0.09	0.06	0.00	−0.06

[a] Figure 4. [b] Dihedral angle (deg). [c] Dihedral angle compared to cyclohexanone value 51.3°. [d] Angle of planes compared to cyclohexanone value 133.0°. [e] Percent bond extension: C_2-H_{ax} for axial, C_2-C_3 for equatorial.

Table 4. Relative Energies (kcal/mol) of Cyclohexanane Transition States (Becke3LYP/6-31G)[a]**

	LiH		BH_3		AlH_3		bi-$LiAlH_4$[b]		tri-$LiAlH_4$[b]	
	ax	eq	ax	eq	ax	eq	ax	eq	ax	eq
transition state	0.00	2.07	0.00	1.74	0.00	1.95	0.00	1.60	0.00	1.30
$C_6H_{10}O$ fragment	0.00	1.39	0.00	1.32	0.00	1.32	0.00	0.79	0.00	−0.48
other fragment	0.00	0.00	0.00	1.25	0.00	−0.37	0.00	−1.55	0.00	−1.03
interaction energy	0.00	0.68	0.00	−0.83	0.00	1.00	0.00	2.36	0.00	2.81

[a] ZPE-Corrected energy of the equatorial transition state or component relative to axial, same reactant. Figure 4.

Discussion

π-Facial Selectivity in the Reduction of Cyclohexanone. In this study we have examined the factors that control π-facial selection in the reduction of cyclohexanones by lithium aluminum hydride. The preference for axial approach of the nucleophile by 1.6 kcal/mol for the bidentate reaction pathway, and 1.3 kcal/mol for the tridentate pathway (Becke3LYP/6-31G**), indicates that there is some additional stabilization at the axial transition state relative to the equatorial. A calculated combined enthalpy of activation difference for the axial−equatorial diastereoselectivity is 1.5 kcal/mol, compared to the experimental value of 0.8 kcal/mol.[38] The measured free energy difference is 1.3 kcal/mol.

Torsional Strain. The $O-C-C-H_{eq}$ dihedral angle provides a measure of the torsional strain in the axial and equatorial transition states. For all cyclohexanone − $LiAlH_4$ TS structures the $O-C-C-H_{eq}$ dihedral angle is greater in the axial transition state than in the equatorial TS, which is consistent with greater torsional strain in the equatorial TS. This trend has been observed in transition states calculated for cyclohexanone with LiH,[4,7] AlH_3,[24] and BH_3.[39] Table 3 shows the dihedral angle $O-C-C-H_{eq}$ in the TS structures of cyclohexanone with $LiAlH_4$, AlH_3, LiH, and BH_3.

Torsional strain is less important in the six-center transition states ($LiAlH_4$) than in the four-center transition states (AlH_3, LiH, and BH_3). Comparing the same dihedral angle at the same level of theory (Becke3LYP/6-31G**) for several transition states, the $O-C-C-H_{eq}$ dihedral angle of the bidentate and tridentate-equatorial $LiAlH_4$ TSs (36.1° and 39.8°, respectively) is relatively large, indicative of much less torsional strain than in the equatorial BH_3 (15.5°) and LiH (16.7°) transition states which have relatively small four-membered rings. Because aluminum has an atomic radius larger than boron and lithium, AlH_3 forms an even larger four-ring TS; the corresponding dihedral angle of the equatorial AlH_3 TS (27.3°) is also larger. As the reagent changes from AlH_3 to $LiAlH_4$ the transition state torsional strain decreases with an increase in the ring size. Although transition state calculations of cyclohexanone with LiH led to the conclusion that torsional strain is the most important factor in determining stereoselectivity in that example,[4] calculations with AlH_3[24] suggested that both torsional strain and hyperconjugative stabilization are significant. Based on the dihedral angles, torsional strain appears to be less important in determining stereoselectivity in the cyclohexanone−$LiAlH_4$ reaction.

A comparison of the energies of the cyclohexanone fragments for the axial and equatorial transition states provides another measure of torsional strain (Figures 6, 7 and Table 4). The axial LiH, BH_3, AlH_3, and $LiAlH_4$ transition states generally have less energy in their cyclohexanone fragments. The exception occurs in the $LiAlH_4$ tridentate-equatorial transition state. The decreased stability of the cyclohexanone fragment in the $LiAlH_4$ tridentate-axial TS may be caused by closer approach (2.43 Å) of the nucleophilic hydrogen to axial H_3 and H_5 than is found in the bidentate-axial TS (2.46 Å), and the ring deformation that would relieve strain from this interaction. The ZPE corrected enthalpy of the tridentate-axial cyclohexanone fragment is 3.34 kcal/mol higher than in the bidentate axial TS. Although torsional strain appears to be relatively unimportant in the $LiAlH_4$ tridentate-equatorial cyclohexanone fragment based on comparison with the tridentate-axial TS, the $LiAlH_4$ bidentate-equatorial transition state shows significant torsional strain in the cyclohexanone fragment, up to one-half (0.8 kcal/mol) of the total energy difference (1.6 kcal/mol) calculated for this pathway. Considering the contribution of both pathways, torsional strain in the cyclohexanone component makes a minor contribution to the diastereoselectivity of reduction with $LiAlH_4$.

Deformation of the Ring. The distortion of the ring, which is measured by the angle of the $C_1-C_2-C_6$ and $C_2-C_3-C_5$ planes, shows that in the cyclohexanone transition state structures with LiH, BH_3, AlH_3, and $LiAlH_4$ the ring is flattened for axial attack and puckered for equatorial attack (Table 3, Figures 6c,d and 7c,d). Anh first noted this effect as a consequence of the stabilization that results when the nucleophile and a σ bond adjacent to the carbonyl can achieve an antiperiplanar orientation.[5b]

The dihedral angles of the adjacent C−H and C−C bonds with the forming $C-H_{Nu}$ bond in $LiAlH_4$ TSs provide a measure of the ability of these bonds to participate in hyperconjugation. For axial attacks an

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[38] Rosenberg, R. E.; Vilardo, J. S. *Tetrahedron Lett.* **1996**, *37*, 2185−2188.

[39] Yamataka, H. *J. Phys. Org. Chem.* **1995**, *8*, 445−451.

almost perfect antiperiplanar relationship is calculated (e.g., bidentate-axial TS H_{Nu}−C−C−H_{ax} is 178.8°; bidentate-equatorial TS H_{Nu}−C−C−C is 161.9°, Figure 6c,d). Ring distortion provides a balance between minimizing torsional strain and maximizing orbital interactions with the adjacent π-bonds (C−H for axial and C−C for equatorial attack).[25]

Stabilization by Antiperiplanar Allylic Bonds. In cyclohexanone an uneven orbital distribution occurs in the LUMO (π*) orbital of the carbonyl, caused by an interaction with the allylic C−H bond. As suggested by Klein,[8] and later clarified by Frenking[7] and Houk,[9] the interaction of the carbonyl (π*) with the most eclipsed allylic bond occurs in an antibonding fashion, resulting in an extension of the LUMO in the direction trans to the allylic bond. In cyclohexanone, the C−H bond is more eclipsed with the π orbitals resulting in orbital distortion in the axial direction. The electrons of the attacking nucleophile (HOMO) will be attracted to the more available LUMO surface of the carbonyl (axial approach).

An examination of the direction of the extension of the LUMO orbital of the carbonyl compound should predict the direction of nucleophilic attack at carbonyl groups. The phenomenon of uneven orbital distribution is inseparable from Cieplak's prediction that nucleophiles tend to approach the face of the carbonyl group that is anti to the more electron rich antiperiplanar vicinal bond in cyclic ketones. If two allylic bonds have similar overlap, the favored interaction should be the more electron-rich bond with the carbonyl π*. The more electron-rich σ bond will have higher energy and will be more similar in energy to the (antibonding) carbonyl π* orbital, resulting in greater stabilization. The direction of the extension of the LUMO orbital of the carbonyl compound should be a reliable predictor of the direction of nucleophilic attack at carbonyl groups. This method should be valid for unhindered cyclic carbonyl compounds and nucleophiles and reactions with early transition states. The presence of remote polar substituents may introduce electrostatic effects that can also influence the outcome.[4]

The use of LUMO uneven orbital extension of a carbonyl compound as a predictor of the direction of π-facial diastereoselection can be valid only if the energy advantage of this interaction is present in the transition state of the nucleophilic attack. This phenomenon is related to the antiperiplanar effect described by Anh and can be described as a hyperconjugation, or molecular orbital interaction between the incoming nucleophile and an allylic bond.

Evidence for hyperconjugative stabilization has been found in the reactions of cyclohexanone with reagents whose transition states occur earlier than those in $LiAlH_4$ reductions.[24] For example in transition states corresponding to reduction by AlH_3 the bonds that are antiperiplanar to the forming C−H_{Nu} bond are elongated; this corresponds to axial (β) C−H bonds for axial attack and (β) C−C bonds for equatorial attack (Table 3). Using the calculated bond length of the adjacent axial C−H bond for cyclohexanone as a reference (1.101 Å at Becke3LYP/6-31G**) there is a further lengthening[40] to 1.103 Å (0.18%) in the axial TS with no extension of the C_α−C_β bonds. The equatorial transition state for AlH_3 shows C_α−C_β bonds extended to 1.555 Å (0.52%) compared to the calculated bond length of cyclohexanone (1.547 Å). No extension of the C_α−H_{ax} bond is observed. The C_1−C_2 bond is shortened from 1.522 Å in cyclohexanone to 1.510 Å (0.79%) and 1.509 Å (0.85%) in the axial and equatorial TS structures. These changes are consistent with those anticipated from hyperconjugation. The bond extensions in the $LiAlH_4$ TSs are much smaller than those observed in the AlH_3 calculations. In the bidentate-axial TS the axial Cα-H_{ax} bonds are longer than in cyclohexanone by only 0.09%. In the bidentate-equatorial TS Cα-C_β bonds are 0.06% longer. At the Becke3LYP/6-31G** level the bond extensions are absent in the tridentate transition states, although small extensions are observed with the Becke3LYP/6-31+G* basis set.[2b] There is no evidence of shortening of the C_1−C_2 bond in the $LiAlH_4$ transition states.

The $LiAlH_4$ transition states have shorter incipient C−H_{Nu} bonds (1.51−1.65 Å) than those of AlH_3 (1.99−2.00 Å). Since the $LiAlH_4$ TS structures resemble the reactants more than products (C−H 1.10 Å), they are early, but later than those of AlH_3.[41] The hyperconjugation should be maximized when an electron-donating bond can delocalize into an electron deficient p orbital of an sp^2-hybridized atom, such as a carbonyl π* orbital. As rehybridization of the atom to sp^3 occurs the C_1−C_2 bond must get longer, in opposition to the bond shortening from hyperconjugation. Consequently, in reactions with later transition states the bond length changes associated with the antiperiplanar effect may be absent.[2b]

Electronic Effects. The energies of the transition states provide the ultimate prediction for diastereoselectivity in ketone reductions. Analysis of the energy differences of the components for axial and equatorial attack suggests that only a portion is due to torsional strain in the cyclohexanone fragment (Table 4). In the series LiH, AlH_3, and $LiAlH_4$ there is greater attraction of the reagents in the axial than equatorial transition states.[42]

The higher electronic interaction energy of the axial TS may be a measure of the more effective orbital overlap in the axial compared to the equatorial TS. The interaction energies of cyclohexanone−$LiAlH_4$ transition states are greater than the corresponding energies in the previously studied cyclohexanone−AlH_3 transition states[24] (1.0 kcal/mol Becke3LYP/6-31G**). The six-center cyclohexanone−$LiAlH_4$ transition states have polar lithium ions in their structures that cause stronger interactions between the fragments.[44] Axial attack is favored over equatorial attack in each of these reactions.

The origin of the electronic effect that favors axial attack can be observed in the carbonyl LUMO of cyclohexanone and the complex that it forms with the reducing reagents. The LUMO coefficient is larger on the axial lobe, resulting in an extension of the orbital that extends

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[40] In cyclohexanone Cα−H_{ax} bonds are somewhat extended due to their interaction with the carbonyl.

[41] Yamataka, H.; Hanafusa T. *J. Org. Chem.* **1988**, *53*, 772−776.

[42] The BH_3 transition states are an exception. This may be related to orbital symmetry considerations.[43] Unlike AlH_3, BH_3 does not have additional orbitals to avoid these constraints.

[43] [43] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Verlag Chemie, Academic Press: Weinheim, 1970.

[44] The interactions between the fragments may be analyzed as interactions between the O and Li and C and H_{Nu} in cyclohexanone−$LiAlH_4$ transition states, and O and Al and C and H_{Nu} in cyclohexanone−AlH_3 transition states. The C−H_{Nu} forming bonds (1.51 Å to 1.65 Å) and O−Li bonds (1.76 Å to 1.77 Å) are much shorter in the bidentate and tridentate six-center transition states of $LiAlH_4$−cyclohexanone, compared to C−H_{Nu} forming bonds (1.99 and 2.00 Å) and O−Al bonds (1.92 Å) of four-center AlH_3−cyclohexanone transition states (Becke3LYP/6-31G**).

beyond the van der Waals radius. On the equatorial face the LUMO coefficient is smaller. Attraction of the nucleophile (HOMO) to that face must compete with steric repulsion that accompanies collision of the reagents, since there is less protrusion of the lobe beyond the van der Waals surface. The differences in the magnitudes of the coefficients result in variations in orbital overlap in the transition states. These overlap differences result in energies of the competing transition states that are predicted by quantum mechanical calculations,[2a,b,d] and are based on frontier molecular orbital theory.[45] These observations are consistent with Tomoda's EFOE model[2d] for prediction of stereoselectivity.

Conclusions

Energies and geometries of the complexes and transition states for the reactions of formaldehyde and cyclohexanone with $LiAlH_4$ have been determined by Becke3LYP/6-31G** calculations. For the reaction of $LiAlH_4$ with cyclohexanone, four transition states were located—two for axial and two for equatorial attack. The bidentate-axial transition state provides the lowest energy pathway. Predicted stereoselectivity of the reduction of cyclohexanone by lithium aluminum hydride correlates well with experimental results. From the magnitude of the O−C−C−H_{eq} dihedral angle in each transition state, it appears that torsional strain in the equatorial TS is less important in the reaction of cyclohexanone with $LiAlH_4$ but increases with AlH_3, LiH, and BH_3. Only minimal evidence of bond extensions due to hyperconjugation was observed in the $LiAlH_4$ transition state structures. The electronic preference for axial approach may be related to differences in the magnitudes of the coefficients in the cyclohexanone LUMO that results in different degree of orbital overlap in the transition states. Hyperconjugation of antiperiplanar allylic bonds which exists in cyclohexanone, resulting in uneven orbital extension of the π* LUMO, also is present in the complexes of this reaction. The direction of the LUMO extension can be predicted from consideration of the electron-donating ability and degree of overlap of the vicinal bonding atom. The transition state in which the nucleophile approaches the carbonyl group from the face that is anti to the more electron-donating/better overlapping vicinal bond receives greater electronic stabilization. For unhindered cyclic carbonyl compounds without polar substituents and reactions with an early transition state, observation of the direction of uneven orbital extension of the carbonyl LUMO should be a good indicator of the preferred approach of nucleophilic attack.

Supporting Information Available: Energies and coordinates of all structures reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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[45] (a) Fukui, K. *Theory of Orientation and Stereoselection*; Springer-Verlag: Heidelberg, 1979. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: New York, 1976.