An Examination of Hyperconjugative and Electrostatic Effects in the Hydride Reductions of 2-Substituted-4-*tert*-butylcyclohexanones

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To better understand electronic effects on the diastereoselectivity of nucleophilic additions to the carbonyl group, a series of 2-X-4-*tert*-butylcyclohexanones (X = H, CH_3, OCH_3, F, Cl, Br) were reacted with $LiAlH_4$. Reduction of ketones with equatorial substituents yields increasing amounts of axial alcohol in the series for X {H < CH_3 < Br < Cl < F ≪ OCH_3}. These data cannot be explained by steric or chelation effects or by the theories of Felkin−Anh or Cieplak. Instead, an electrostatic argument is introduced: due to repulsion between the nucleophile and the X group, axial approach becomes energetically less favorable with an increase in the component of the dipole moment anti to the hydride approach trajectory. The ab initio calculated diastereoselectivities were close to the experimental values but did not reproduce the relative selectivity ordering among substituents. For reduction of ketones with axial substituents, increasing amounts of axial alcohol are seen in the series for X {Cl < Br < CH_3 < OCH_3 < H < F}. After some minor adjustments are made, this ordering is consistent with both the electrostatic model and Felkin−Anh theory. Cieplak theory cannot account for these data regardless of adjustments. Ab initio calculated diastereoselectivities were reasonably accurate for the nonpolar substituents but were poor for the polar substituents.

Introduction

The diastereoselective addition of nucleophiles to carbonyl compounds is a topic of considerable importance.[1] While the first theory to address this issue was advanced by Cram,[2] most current researchers cite a hybrid theory of Felkin and Anh. Felkin proposed that bonds vicinal to the reacting center would be staggered with respect to the forming bond in order to minimize torsional interactions in the transition state (TS).[3] On the basis of ab initio calculations, Anh found that the bond vicinal to the reaction center which contained the strongest electron *withdrawing* group, C_2-X, should lie antiperiplanar to the incipient bond in order to maximize Nu···C═O σ, C_2—X σ^* orbital interactions in the TS.[4] These ideas and experimental work on the angle of nucleophilic attack[5] were incorporated into what is commonly known as the Felkin−Anh model. However, some researchers in this field subscribe to the theory of Cieplak, which states that the strongest electron *donating* group should lie antiperiplanar to the incipient bond to maximize C_2—X σ, Nu···C═O σ^* orbital interactions in the TS (Figure 1).[1c,6] In an effort to reconcile the two conflicting theories, le Noble suggested that the ideas of Felkin, Anh, and Cieplak all compete, with the dominant control element depending on the particular circumstances of the reaction.[7] Rather than examining the TS, some researchers have looked at the unequal lobes of the π orbital in the ground state of the ketone.[1a,b,d,8] These models have achieved some predictive successes, probably due to the early TS of nucleophilic addition reactions.

The particular case of hydride reduction of cyclohexanones is an important special case in the study of diastereoselective nucleophilic addition reactions to carbonyls. In these systems, there is a solid understanding of steric effects, but there is no consensus on the origin of electronic effects. A common strategy used in the study of electronic effects is to employ systems where the polar substituent, X, is far from the reaction center (Figure 2). This approach avoids the complications of competing steric effects. Houk argued for the Felkin−Anh model using data from the $NaBH_4$ reduction of 4 substituted

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(1) A thematic issue of *Chem. Rev.* was recently devoted to diastereoselection. (a) Dannenberg, J. J. *Chem. Rev.* **1999**, *99*, 1225−1241. (b) Tomoda, S. *Chem. Rev.* **1999**, *99*, 1243−1263. (c) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265−1335. (d) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337−1375. (e) Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377−1385. (f) Kaselj, M.; Chung, W.-S.; le Noble, W. J. *Chem. Rev.* **1999**, *99*, 1387−1413. (g) Adcock, W.; Trout, N. A. *Chem. Rev.* **1999**, *99*, 1415−1435. (h) Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437−1467. (i) Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469−1480.

(2) (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.

(3) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.

(4) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(5) Burgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065.

(6) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. (c) Cieplak, A. S.; Wiberg, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 9226−9227.

(7) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199−210.

(8) (a) Klein, J. *Tetrahedron Lett.* **1974**, 4307. Klein, J. *Tetrahedron* **1974**, *30*, 3349. (b) Frenking, G.; Koehler, K. F.; Reeetz, M. T. *Angew. Chem.* **1991**, *103*, 1167. (c) Huang, X. L.; Dannenberg, J. J.; Duran, M.; Bertran, J. *J. Am. Chem. Soc.* **1993**, *115*, 4024−4030. (d) Tomoda, S.; Senju, T. *Tetrahedron* **1997**, *53*, 9057. (e) Tomoda, S.; Senju, T. *Chem. Commun.* **1999**, 423.

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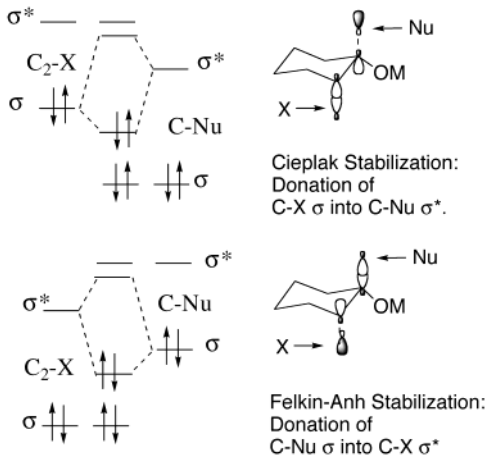

Figure 1. Molecular orbital illustration of Cieplak versus Felkin−Anh stabilization.

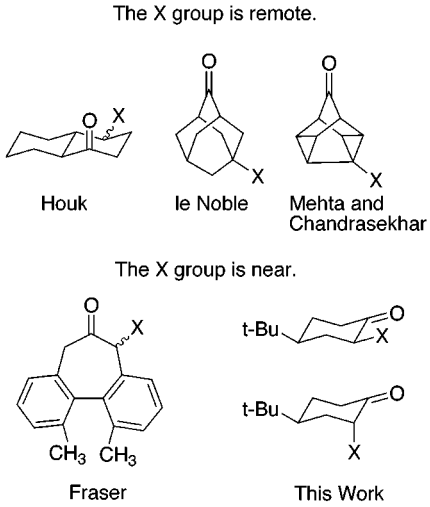

Figure 2. Examples of sterically unbiased ketones.

trans decalones.[9] le Noble found that the Cieplak model best explained the $NaBH_4$ reduction of 5-X-adamantan-2-ones.[1f,10] Adcock also looked at $NaBH_4$ reductions of 5-X-adamantan-2-ones, but asserted that electrostatic interactions were responsible for the observed product ratios.[1g,11] Using a system similar to le Noble's, Mehta and Chandrasekhar argued for both the Cieplak model and electrostatic effects.[1h,12] Unfortunately, these studies are at odds with each one another, possibly because the observed selectivities are small.

We hoped to help resolve the Felkin−Anh vs Cieplak problem by examining the $LiAlH_4$ reduction of 2-X-4-*tert*-butylcyclohexanones (**1-X**, **3-X**), where X = {H, CH_3, OCH_3, F, Cl, Br}. Our strategy is to place the X group

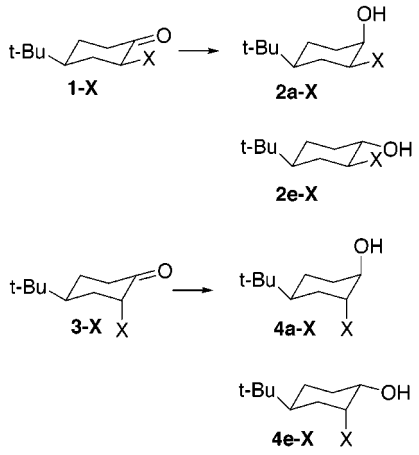

Figure 3. Reduction of **1-X** gives **2a-X** and **2e-X**. Reduction of **3-X** gives **4a-X** and **4e-X**. X = H, CH_3, OCH_3, F, Cl, Br.

vicinal to the reaction center and thus maximize electronic/orbital effects. The steric effects that result from this proximity are minimized by the small size of the nucleophile. The polar substituents X = {OCH_3, F, Cl, Br} are bracketed in size between X = H and X = CH_3, the latter providing an upper bound for steric effects. The large conformational bias of the *t*-Bu group and the well-defined geometry of the six-membered ring combine to allow the study of both axial (ax) and equatorial (eq) substituents. Unlike $NaBH_4$, $LiAlH_4$ is thought to involve a single reducing species at sufficiently high hydride-to-ketone ratios.[13]

Our approach is similar to that of Fraser who looked at the $LiAlH_4$ reduction of 2-substituted dibenzocycloheptenones.[14] Results from Fraser and us will be compared. Paquette examined the addition of allyl indium reagents to 2-alkoxy and hydroxy-4-*tert*-butylcyclohexanones, though he was concerned primarily with chelation control.[15]

Results and Discussion

1. General Considerations. The results for the reduction of ketones **1-X** and **3-X** to the alcohols **2-X** and **4-X** (Figure 3), respectively, are listed in Table 1. The eq/ax ratio of alcohols is first converted into ΔG, using the relationship $\Delta G = -RT \ln K$. K is not strictly an equilbrium constant but rather equals the following ratio: [the rate of axial attack by the hydride = amount of observed eq alcohol] divided by [the rate of eq attack by the hydride = amount of observed ax alcohol]. Then, $\Delta\Delta G$ is calculated using the relation $\Delta\Delta G_X = \Delta G_X - \Delta G_H$. For example, "$\Delta\Delta G$ **1-X** > 0.00 kcal/mol" means that less eq alcohol (alternatively, lower axial selectivity) is formed in the reduction of **1-X** than of **1-H**. It is important to note that $\Delta\Delta G$ contains contributions of the TS energies from both ax and eq approaches of the hydride.

2. Reduction of Ketones 1-X. For **1-X**, $\Delta\Delta G$ increases (axial selectivity decreases) for X in the order {H < CH_3 ≪ Br < Cl < F ≪ OCH_3}. As X is relatively close to the reaction center, both steric and chelation effects could

(9) (a) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018−5027. Other relevant papers by Houk: (b) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908−910. (c) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 10992. (d) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418−427.

(10) (a) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. (b) Lin, M.-H.; Silver, J. E.; le Noble, W. J. *J. Org. Chem.* **1988**, *53*, 5155. For recent work, see: (c) Kaselji, M.; le Noble, W. J. *J. Org. Chem.* **1998**, *63*, 2758. (d) Gonikberg, E. M.; Picart, F.; le Noble, W. J. *J. Org. Chem.* **1998**, *63*, 4885.

(11) Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867−1876.

(12) Mehta, G.; Ravikrishna, C.; Ganguly, B.; Chandrasekhar, J. *Chem. Commun.* **1997**, 75−76.

(13) Wigfield, D. C.; Gowland, F. W. *J. Org. Chem.* **1980**, *45*, 653.

(14) Fraser, R. R.; Faibish, N. C.; Kong, F.; Bednarski, K. *J. Org. Chem.* **1997**, *62*, 6164−6176.

(15) (a) Paquette, L. A.; Lobben, P. C. *J. Org. Chem.* **1998**, *63*, 5604−5616. (b) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917−1930.

Table 1. Reductions of 1 and 3 with $LiAlH_4$ in THF at 0 °C

	1			3		
X	% **2a**[a]	$\Delta\Delta G$[b]	Fraser[c]	% **4a**[a]	$\Delta\Delta G$[b]	Fraser[c]
H	9(0.6,4)[d]	0.00	0.00	9	0.00	0.00
CH_3	11(1)[d]	0.12	0.82	5(1)[d]	−0.35	−1.35
OCH_3	67(1.7,3)[e]	1.64	>1.61	8(4.0,3)[e]	−0.08	<−1.61
F	40(4.8,6)	1.04	1.11	9(1.4,6)	0.00	
Cl	34(0.8,5)[f]	0.90	1.15	0.9(0.0,2)[g]	−1.30	<−1.61
Br	29(1.9,4)	0.77		1.4(0.04,2)[g]	−1.05	

[a] Data are reported in the form $m(s,n)$, where m is the mean value of n trials and s is the standard deviation. [b] In kcal/mol. $\Delta\Delta G$ is defined in the text. [c] Reproduced from ref 14. [d] In accord with ref 30. [e] Battioni reports 64% of **2a-OCH_3** and 15% of **4a-OCH_3** (ref 28). The discrepancy of our data with the latter value is probably due to spectral congestion in the 3.3−3.9 δ region of the 60 MHz ^{1}H NMR signals for the product mixture. [f] Cherest reports significantly higher axial selectivity (19%) with ether as a solvent (ref 30). [g] The value listed is from integration of a very weak ^{1}H NMR resonance and thus is an upper limit for the amount of minor product present.

potentially contribute to the observed selectivity. Steric repulsion between the substituent and the reagent would hinder axial but not equatorial attack and therefore lead to higher values of $\Delta\Delta G$. The CH_3 group serves as a control for steric effects, since it is both the largest substituent used in this study {as judged by van der Waals radii (CH_3 2.0 Å, Br 1.85 Å) or by A values (in kcal/mol, CH_3 1.8, OCH_3 0.60, Br 0.48)}[16] and it is unlikely to have significant chelation or electronic effects. Steric effects are seen to be minor as judged by the $\Delta\Delta G$ of **1-CH_3** which is only 0.12 kcal/mol, a value which is significantly smaller than the $\Delta\Delta G$'s of 0.77−1.64 kcal/mol seen for the polar substituents. Another argument against steric control is the fact that $\Delta\Delta G$ increases as the halogen atom size decreases ($\Delta\Delta G$ for **1-Br** is 0.77 kcal/mol, while **1-F** has a $\Delta\Delta G$ of 1.04 kcal/mol). Increased chelation of the reagent by X would direct the hydride to the axial face of the ketone and lead to lower values of $\Delta\Delta G$. Chelation would be more important in X in the progression {OCH_3 > F > Cl > Br ≫ H = CH_3}, resulting in an ordering in $\Delta\Delta G$ of {OCH_3 < F < Cl < Br ≪ H = CH_3}. This prediction for $\Delta\Delta G$ is exactly the opposite of what is observed. While not excluded as a factor, chelation control is clearly not the dominant control element. Thus, the selectivity seen in the reduction of **1-X** must be governed by torsional strain and/or electronic effects. The latter includes the diverse ideas of transition state hyperconjugation and electrostatics.

The torsional strain component of the Felkin−Anh model (the other component is hyperconjugation, discussed next) has often been used to explain diastereoselectivity in hydride reductions of cyclohexanones.[3,4,9ab] In this theory, the large amount of equatorial alcohol seen in the hydride reduction of **1-H** is explained by a TS which is perfectly staggered during ax attack but has partial eclipsing interactions during eq attack. Furthermore, Anh has suggested that as the ketone gets flatter, ax attack becomes even more favored.[4,9b] The flatness of the ketones **1-X** will be compared to **1-H** to see if there are significant geometric distortions in the former which may account for the observed selectivities. Here, flatness is defined as the sum of the three angles made between the bonds C_3-C_2, C_5-C_6, and $O-C_1$ and the plane formed by $C_6-C_1-C_2$. Geometric data for all ketones are presented in Table 2 and are obtained from MP2/6-31G* ab initio calculations, a level of theory well-known for giving highly accurate structural information.[17]

Table 2. Ab Initio Calculated Values of Selected Angles for Ketones 1 and 3[a]

X		$\angle C_3-C_2$[b]	$\angle C_5-C_6$[b]	$\angle O-C_1$[b]	sum of deviations
H	**1**	47.6	47.6	1.1	0.0
CH_3	**1**	2.2	2.2	0.6	5.0
OCH_3	**1**	1.5	0.9	−0.4	2.0
F	**1**	3.2	2.7	1.0	6.9
Cl	**1**	3.9	3.3	0.7	7.9
CH_3	**3**	−3.3	−1.7	−0.9	−5.9
OCH_3	**3**	2.0	1.3	0.2	3.5
F	**3**	6.9	5.8	3.7	16.4
Cl	**3**	−0.5	1.0	2.3	2.8

[a] In degrees using MP2/6-31G* optimized geometries. [b] For **1-H**, the value shown is the angle made by the designated bond with the plane defined by $C_6-C_1-C_2$. For X ≠ H, the value given equals the angle made by the bond in **1 (or 3)-X** minus the angle made by **1-H**.

For **1-X**, the carbonyl becomes more puckered in X in the order {H < OCH_3 < CH_3 < F < Cl}. According to the torsional strain model, the most puckered ketones should have the least amount of axial selectivity and the largest values of $\Delta\Delta G$. The $\Delta\Delta G$ for **1-OCH_3** is the highest in the **1-X** series, yet it is just 2° less flat than **1-H**, the ketone with the lowest value of $\Delta\Delta G$. In contrast, the two ketones **1-H** and **1-CH_3** have very similar $\Delta\Delta G$'s yet differ in flatness by 5°. From these and other examples, one can conclude that the small variations in flatness for the ketones **1-X** do not correlate well with their $\Delta\Delta G$'s of reduction.

Hyperconjugation in the TS is used to explain diastereoselectivity by both the Cieplak and Felkin−Anh models. In both theories, stereocontrol arises from the relative stabilization provided by the orbitals on the carbon-substituent bond adjacent to the reaction center which are anti to each of the two approaches of the reagent. For Felkin−Anh, maximum stabilization occurs when the σ^* orbital is low in energy, while for Cieplak, maximum stabilization is achieved when the σ orbital is high in energy. In the case of **1-X**, the antiperiplanar orbitals for ax attack are in the C_2-H bond and those for eq attack are in the C_2-C_3 bond. Analysis of the Felkin−Anh and Cieplak models is now reduced to determining what effect an equatorial and polar X group has on the *relative* energies of the C_2-H and C_2-C_3 orbitals. Determining this effect may be quite difficult given that a seemingly simpler problem, the relative donor/acceptor abilities of unperturbed C−H vs C−C bonds, is still being actively debated.[18] Even if the relative orbital perturbations of an X group could be determined, it is unlikely that subtle differences in the energies of the C_2-H vs C_2-C_3 orbitals could lead to the sizable $\Delta\Delta G$'s seen in the **1-X** series regardless of which model is used.[19] Another difficulty faced by the orbital theories is that the $\Delta\Delta G$ for **1-OCH_3** is significantly higher than for **1-F**, yet fluorine has a larger effect on orbital energies

(16) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A*; Plenum Press: New York, 1990; p 135 (A values) and p 120 (van der Waals radii).

(17) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(18) For recent work arguing that C−C is the better donor, see refs 1a and 9a. For recent work claiming that C−H is the better donor, see refs 1c and 1g.

than methoxy. Thus, the major theories used to describe electronic effects on nucleophilic additions are incomplete. At the very least, they are not applicable to the important case of equatorial substituents which are adjacent to the reaction center in cyclohexanones. In a broader sense, the effect of substituents which do not access a geometry anti to the approach of a nucleophile are poorly described by the Felkin−Anh and Cieplak models.

Another model used to explain diastereoselective hydride reductions of polar ketones is electrostatic effects. Wu, Tucker, and Houk invoked electrostatic repulsion between the hydride and the substituent to account for the high selectivity for axial attack in the $NaBH_4$ reduction of axial 4-fluoro *trans* decalone.[9a] They also used ab initio studies to show that when the substituent was OH or NH_2, the selectivity was strongly dependent on the orientation of the lone pairs. Paddon-Row, Wu, and Houk found electrostatic interactions between the substituent and the nucleophile to be the exclusive control element in a computational study of the addition of LiH to 2,3-disubstituted 7-norbornanones.[20] Adcock argued that electrostatic interactions could account for the selectivity seen in the $NaBH_4$ reduction of 5-X-adamantan-2-ones but did not rule out participation of Felkin−Anh orbital effects.[1g,11] Wipf and Kim invoked electrostatic effects in explaining the stereoselectivity of methyl Grignard addition to 4,4-disubstituted cyclohexadienones, though no selectivity was seen in these systems when hydride reducing agents were used.[1i,21]

With this background, it is proposed that axial attack by the hydride is electrostatically repelled by the partial negative charge on the X group. This repulsion is lower for eq attack due to the larger distance between the hydride and the X group. Thus, as X becomes more electronegative in the series {Br < Cl < F}, ax attack becomes more unfavorable relative to eq attack and the $\Delta\Delta G$ will increase as is observed. An explanation of the very high $\Delta\Delta G$ seen for **1-OCH$_3$** requires a slightly more elaborate model. Since dipole-charge interactions are proportional to the cosine of the angle, cos θ, made between the C−X dipole and the incoming nucleophile (treated here as a point charge),[22] repulsion of axial attack is greatest when the C−X dipole is anti to the nucleophile's trajectory. Ab initio calculated values of cos θ for the C−X dipole in both the ground state and TS are listed in Table 3. In **1-F** and **1-Cl**, only a small percentage of the C−X dipole lies perpendicular to the carbonyl group. However, this value increases significantly in the TS to 43 and 28%, respectively. For **1-OCH$_3$**, most of the group dipole moment lies perpendicular to the carbonyl group and this value increases to 97% in the TS. Taken with the roughly equal values of the C−F, C−Cl, and C−OCH_3 dipole moments, the cos θ values predict that **1-OCH$_3$** should have significantly greater electrostatic repulsion of the nucleophile than **1-F** and **1-Cl**. This prediction is consistent with the experimental data (Figure 4).

Table 3. Ab Initio Calculated Values of the Anti Component for the C−X Dipole[a]

X		ground state[b] θ	ground state[b] cosθ	transition state[c] θ	transition state[c] cos θ	group moment for C−X[d]
F	**1**	86	0.08	64	0.43	1.41
Cl	**1**	89	0.02	74	0.28	1.46
OCH_3	**1**	144	0.81	15	0.97	1.3
F	**3**	−147	0.84	−170	0.98	1.41
Cl	**3**	−156	0.91	−164	0.97	1.46
OCH_3	**3**	−92	0.03	−119	0.49	1.3

[a] For the ground-state compounds **1-X** and **3-X**, the HF/6-31G* optimized geometries for 2-X-cyclohexanone were used. For transition states, the HF/6-31G* optimized geometries of the transition state for LiH addition to 2-X-cyclohexanone were used. [b] θ = the angle made between the C−X bond vector and the vector perpendicular to the plane defined by $C_2-C_1-C_6$. For X = OCH_3, the C−X bond vector is taken as the vector sum of the C_2−O and O−CH_3 bonds. [c] θ = the angle made between the C−X bond vector and C_1−H bond vector. For X = OCH_3, the C−X bond vector is defined as in footnote *b*. [d] Values are in es units × 10^{18}. Taken from ref 16, p 16.

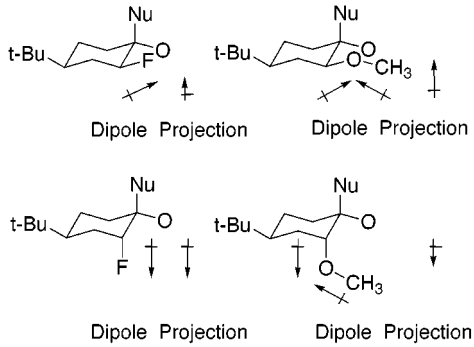

Figure 4. Vector illustration of both the bond dipole(s) from the C−X bond and of the projection of the resultant dipole onto the *y* axis.

It is worthwhile to compare and contrast our results with those of Fraser, who looked at the $LiAlH_4$ reduction of 2-substituted dibenzocycoheptadienones.[14] Fraser's data is reproduced in Table 1. A common feature of both studies is a diminished nucleophilic attack on the face of the carbonyl that is syn to the electronegative atom, with the largest effect seen for OCH_3. As here, Fraser argued that his reduction data are best explained by a combination of electrostatic/dipole forces and argued against the hyperconjugative theories of the Felkin−Anh and Cieplak models.

Our system has two minor advantages over Fraser's. First, Mehta and Chandrasekhar have suggested that steric effects of the 2-substituent swamp out the hyperconjugative contributions that are present in Fraser's system.[1h] This argument cannot be applied to our system as the steric effect has been shown to be almost negligible (0.12 kcal/mol for **1-CH$_3$**). In a second example, le Noble has suggested that complexation of lithium ion to aromatic rings could effect stereoselectivity.[10b] Again, this concern is not relevant to our system.

The reduction of **1-X** was studied by ab initio calculations in an attempt at gaining a deeper understanding of the reaction mechanism. Calculated selectivities for the reduction of **1-X** by LiH, NaH, BH_3, and AlH_3 are listed in Table 4. For reduction of **1-X**, the agreement

(19) This intuitive statement is derived from the following reasoning. Assume that differential orbital perturbation can explain the $\Delta\Delta G$ values for reduction of **1-X**. If so, then the effects for the reduction of **3-X** must be much larger than for **1-X**, as replacement of X for H (**3-X)** affects orbital energies substantially more than the perturbation that X (in **1-X**) causes in the energy of the C_2-H orbital. Yet the $\Delta\Delta G$'s for **3-X** are comparable in magnitude to those seen for **1-X**. Therefore, the hypothesis is invalid.

(20) Paddon-Row; M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638−10639.

(21) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.

(22) Halliday, D.; Resnick, R.; Walker, J. *Fundamentals of Physics, Vol. 2*; John Wiley and Sons: New York, 1997; p 570.

Table 4. Ab Initio Calculated Diastereoselectivity for the Reduction of 1 and 3[a]

X		LiH	NaH	BH_3	AlH_3	expt[b]
H	**1**	−1.12	−0.80	−1.25	−1.18	−1.26
CH_3	**1**	−0.61	−0.27	−0.58	−0.53	−1.14
OCH_3	**1**	0.40	−0.95	−2.18[c]	−1.85	0.38
F	**1**	−1.15	0.28	−0.09	−0.07	−0.22
Cl	**1**	−0.44	0.19	−0.24	−0.25	−0.36
H	**3**	−1.12	−0.80	−1.25	−1.18	−1.26
CH_3	**3**	−1.88	−1.78	−1.68	−1.46	−1.61
OCH_3	**3**	−2.54	−2.77	−1.52[c]	−1.28	−1.34
F	**3**	−2.84	−2.84	0.79	0.54	−1.26
Cl	**3**	−5.16	−4.97	−1.43	−1.82	−2.56

[a] In kcal/mol using MP2/6-311+G**//HF/6-31G*. Entries = ΔH(TS for eq alcohol) − ΔH(TS for ax alcohol). [b] From Table 1. [c] The HF/3-21G geometry is used.

with experiment by all four reagents is excellent, with only the value for the reduction of **1-OCH₃** by BH_3 or AlH_3 deviating from experiment by significantly more than 1 kcal/mol. While LiH is the reagent that best reproduces the experimental data, both AlH_3 and BH_3 would be significantly better than LiH if not for **1-OCH₃**.

Opposite to expectations, the reasonably accurate ΔG's of the reaction did not translate into good predictions of relative reduction ratios for the various **1-X**'s. Experimental reduction of **1-X** gives less negative ΔG's (more axial alcohol) in X in the order {H, CH_3 < F, Cl < OCH_3}. LiH correctly predicts that **1-OCH₃** will yield the least amount of equatorial alcohol but fails to order the remaining substituents correctly. The other three reagents all model the H, CH_3 < F, Cl trend well but fail badly (NaH) to very badly (BH_3, AlH_3) for **1-OCH₃**. This unexpectedly poor ordering of the energetics of this reaction does not allow one to reliably draw subtle mechanistic insights on the basis of the ab initio calculated transition states.

3. Reduction of Ketones 3-X. For the reduction of **3-X**, $\Delta\Delta G$ decreases (axial selectivity increases) for X in the order {F = H > OCH_3 > CH_3 ≫ Br > Cl}. Unlike **1-X**, steric and chelation effects cannot be ignored in the reduction of **3-X**. Steric repulsion of the nucleophile by X retards eq but not ax approach and leads to more negative values of $\Delta\Delta G$. Analogous to **1-CH₃**, the $\Delta\Delta G$ for the reduction of **3-CH₃** (−0.35 kcal/mol) provides an upper bound for the *magnitude* of the steric effect in this system. Though significant, steric effects can account for only a fraction of the large negative $\Delta\Delta G$'s seen in the reduction of **3-Cl** (−1.30 kcal/mol) and **3-Br** (−1.05 kcal/mol). Chelation of the nucleophile by the X group would direct attack to the equatorial face and lead to less negative values of $\Delta\Delta G$ with the effect decreasing in X as follows: {OCH_3 > F > Cl > Br > H = CH_3}. This reasoning may help explain the lower axial selectivity seen for the reduction of OCH_3, F as compared to Cl, Br. Against this, it is not clear why chelation would be important in the reduction of **3-X** but not in **1-X**. Importantly, the high axial selectivity seen in the reduction of **3-Cl** and **3-Br** is clearly not due to chelation, which lowers axial selectivity. Instead, there must be an additional effect(s). As with **1-X**, torsional effects, transition state hyperconjugation, and electrostatics will be discussed.

Similar to **1-X**, the torsional strain component of the Felkin−Anh model predicts that increased puckering by the ketones **3-X** will lead to decreasing amounts of ax attack and thus less negative values of $\Delta\Delta G$. Geometric data for ketones **3-X** are listed in Table 2, with "flatness" defined the same as for **1-X**. For **3-X**, the carbonyl becomes more puckered in X in the order {CH_3 < H < Cl < OCH_3 ≪ F}. For most of these ketones, puckering and $\Delta\Delta G$ are not well correlated. For example, while **3-Cl** is just slightly more puckered than **1-H**, its $\Delta\Delta G$ is large and negative. Similarly, **3-Cl** and **3-OCH₃** have very similar geometries but significantly different $\Delta\Delta G$'s. However, for **3-F** there is a very large increase in puckering and a relatively high amount of eq attack in accordance with the Felkin−Anh model. The resulting $\Delta\Delta G$ for **3-F** is not easily explained by other factors, vide infra. These data lead to the observation that the torsional strain contribution to selectivity will not vary much unless the geometric perturbation between molecules is relatively large.

Unlike that for the reduction of **1-X**, the hyperconjugation theories of Felkin−Anh and Cieplak have unambiguous and opposite predictions for the reduction of **3-X**. Felkin−Anh states that an electron-withdrawing group anti to the nucleophile will accelerate axial attack leading to $\Delta\Delta G$'s with an ordering in X of {CH_3 ≈ H > Br > Cl > OCH_3 > F}. Cieplak predicts a maximum acceleration when the group lying anti to the nucleophile is electron donating, leading to an exact reversal from the ordering above. Neither theory fully accounts for the experimental data. Felkin−Anh correctly predicts lower $\Delta\Delta G$'s (higher axial selectivity) for the polar versus nonpolar X's. However, this theory incorrectly predicts that the $\Delta\Delta G$'s for **3-F** and **3-OCH₃** should be lower than for **3-Cl** and **3-Br**, an energy difference between theory and experiment of more than 1 kcal/mol. This discrepancy could be due to a combination of three factors: (1) the $\Delta\Delta G$ lowering steric component of X = Cl, Br, CH_3 is larger than for when X = F, OCH_3, though this factor can account for at most 0.35 kcal/mol (−ΔΔG of **3-CH₃**), (2) the $\Delta\Delta G$ for X = F, OCH_3 could be raised by chelation relative to X = Cl, Br, though there was no evidence for effects of similar magnitude in the reduction of **1-X**, and (3) **3-F** has a relatively large geometric distortion which leads to a higher than expected $\Delta\Delta G$. The Cieplak model correctly orders the $\Delta\Delta G$ for the polar substituents, F > OCH_3 > Cl > Br. However, this model incorrectly theorizes that reduction of **3-CH₃** should have a more negative $\Delta\Delta G$ than **3-Br**, **3-Cl**, an error of over 0.7 kcal/mol. Unlike the Felkin−Anh model, this discrepancy cannot be explained by adding steric and chelation considerations. The 0.7 kcal/mol error mentioned above is only made larger when one considers the greater steric bulk of CH_3 versus either Cl or Br. Also, any chelation seen in **3-Br**, **3-Cl** would raise $\Delta\Delta G$ relative to **3-CH₃**, further worsening this already poor prediction.

The electrostatic repulsion argument used for **1-X** can be applied to the reduction of **3-X**. In eq attack of **3-X**, there is unfavorable electrostatic repulsion between two partially negative groups, the hydride and the electronegative X group. For ax attack, there is a favorable electrostatic interaction as the partially negative hydride approaches from the positive end of the C−X dipole. As for **1-X**, calculated values of cos θ for the C−X dipole in both the ground state and TS are listed in Table 3. For **3-F** and **3-Cl**, over 80% of the C−X dipole lies perpendicular to the carbonyl group. This stabilizing dipole becomes even more optimally aligned in the TS. In contrast, the group dipole moment in **3-OCH₃** has only a small component perpendicular to the carbonyl group.

This value increases to about 50% in the calculated TS. The predictions of the electrostatic model would give decreasing $\Delta\Delta G$'s with an ordering in X of {H ≈ CH_3 > OCH_3 > Br > Cl > F}. Experimentally, the $\Delta\Delta G$ for **3-CH$_3$** is more negative than for both **3-H** and **3-OCH$_3$**, a result that can be attributed to steric effects. With this adjustment, only the value for the reduction of **3-F** is anomalous. As discussed above, there is a severe geometric distortion in **3-F** which leads to a higher than expected amount of eq attack.

While the data of Fraser[14] are very similar to ours in the **1-X** series, the corresponding data for ax substituents are very different. While both studies see large negative $\Delta\Delta G$'s for Cl, Fraser sees a much more negative $\Delta\Delta G$ for OCH_3 than we do (< −1.61 kcal/mol for OCH_3 versus −0.08 kcal/mol for **3-OCH$_3$**). The larger steric effect in Fraser's system ($\Delta\Delta G$ of −1.35 kcal/mol for CH_3 versus −0.35 kcal/mol for **3-CH$_3$**) may contribute to some of this difference. Another factor could be that the orientation of the OCH_3 group, and hence the direction of the dipole moment, is different in the two studies.

Unfortunately, the reduction results for **3-X** cannot be explained unambiguously. The electrostatic model is effective in describing all compounds after a correction for torsional effects is applied to **3-F**. The Felkin−Anh model is effective after a torsional correction for **3-F** and chelation adjustments to both **3-F** and **3-OCH$_3$** are applied. We prefer the electrostatic model as it is not dependent on chelation effects for **3-OCH$_3$** and **3-F**, effects not seen in the reduction of **1-X**. Finally, the Cieplak model fails to explain the high axial selectivity seen in the reduction of **3-Cl** and **3-Br** relative to **3-CH$_3$**. This failure cannot be corrected by adjustments made for steric or chelation effects.

The reduction of **3-X** was studied by ab initio calculations. Specifically, calculated selectivities for reduction of **3-X** by LiH, NaH, BH_3, and AlH_3 are listed in Table 4. While all four models correctly reproduced the experimental selectivities for **3-H** and **3-CH$_3$**, they performed significantly worse for the polar ketones. In particular, calculations using LiH and NaH overestimated the magnitude of the ΔG's for **3-OCH$_3$**, **3-F**, and **3-Cl** by a range of 1.20−2.60 kcal/mol. Use of BH_3 and AlH_3 was somewhat more successful, correctly modeling **3-OCH$_3$** and **3-Cl** but performing very badly in the case of **3-F**. For **3-F**, not only was the calculated ΔG off by over 1.5 kcal/mol but the calculated sign of ΔG was also incorrect.

Not surprisingly, the calculated qualitative ordering for the reduction of **3-X** did not mirror the experimental data. Experimental reduction of **3-X** gives less negative ΔG's in X = Cl ≪ CH_3, OCH_3 < H, F. Both LiH and NaH adequately describe the relative selectivities of **3-Cl**, **3-CH$_3$**, and **3-H** but are not close in ordering **3-F** and **3-OCH$_3$**. Both BH_3 and AlH_3 do considerably better, with AlH_3 correctly ordering the whole series. Against this, the problems of the calculated selectivity of **3-F** by AlH_3 are quite severe, as described above.

Conclusions

Selectivity in the reduction of *cis* 2-X-*tert*-butylcyclohexanones (**1-X**) is controlled by electrostatic interactions between the nucleophile and substituent and not by steric or chelation effects or hyperconjugation as described by the theories of Felkin−Anh or Cieplak. For reduction of *trans* 2-X-*tert*-butylcyclohexanones (**3-X**), either the electrostatic model or the Felkin−Anh theory is consistent with the data. The Cieplak model fails to describe this system. Ab initio calculations reproduced experimental data fairly well, especially with the *cis* ketones, though experimental trends across substituents were modeled less satisfactorily.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. Reagents were used without further purification unless otherwise indicated. THF was freshly distilled from potassium. Solutions were evaporated under reduced pressure with a rotary evaporator. Column chromatography was performed on a silica gel column using an ethyl acetate−hexanes mixture as the eluent.

Synthesis of Ketones. Ketone **1-H** was obtained commercially. Other ketones, **1-CH$_3$** and **3-CH$_3$**,[23] **1-F** and **3-F**,[24] **1-Cl** and **3-Cl**,[25] **1-Br** and **3-Br**,[26] and **1-OCH$_3$** and **3-OCH$_3$**[15b] were synthesized as mixtures of diastereomers using literature procedures. Purification into eq and ax isomers was accomplished by either preparatory gas chromatography (**1-CH$_3$**, **3-CH$_3$** and **1-F**, **3-F**) or flash chromatography (**1-Br**, **3-Br 1-Cl**, **3-Cl**, and **1-OCH$_3$**, **3-OCH$_3$**). Structural assignments for the purified ketones were based on comparisons with literature spectral data (for X = F, Cl, and Br, see Moreau et al.,[27] for X = OCH_3, see Battioni et al.[28]).

General Procedure for Reaction of Ketones with LiAlH$_4$. To a 0.1 M solution of $LiAlH_4$ in THF (prepared from either a commercial 1.0 M solution of $LiAlH_4$ in THF or from solid $LiAlH_4$) at 0 °C was added dropwise an equal volume of a 0.1 M solution of ketone in THF. Assuming that all the hydrides in $LiAlH_4$ react, there are 4 equiv of hydride per equivalent of ketone. The solution was stirred for 30 min at 0 °C, and then an excess of H_2O was added cautiously. After effervescence ceased, an excess of 10% H_2SO_4 was added in one portion, followed by extraction with ether. The organic layer was washed successively with 10% $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was then subjected to analysis by either ^{1}H NMR or gas chromatography.

Determination of Product Ratios. Reduction ratios for **1-H** **1-CH$_3$**, and **3-CH$_3$** were obtained by gas chromatography using data from the literature to assign peaks (**1-H**[29] and **1-CH$_3$**, **3-CH$_3$**[30]).

Reduction products for other alcohols were identified and quantified by ^{1}H NMR. Peak assignments from Moreau et al.[27] were used for **2-X** and **4-X** when X = F, Cl, Br. For **2-OCH$_3$** and **4-OCH$_3$**, initial assignments were taken from Battioni et al.[28]

The above NMR peak assignments were confirmed by isolation of the appropriate alcohols. Thus, reduction of **1-X**, where X = F, Cl, Br, OCH_3, gave a mixture of the alcohols **2a-X** and **2e-X**. The resulting mixture was separated into two pure components by column chromatography. Similarly, **4a-F**, **4e-F**, **4e-Cl**, **4e-Br**, and **4e-OCH$_3$** were synthesized by

(23) (a) Allinger, N. L.; Blatter, H. M.; Freiberg, L. A.; Karkowski, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 3002. (b) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935.
(24) Umemoto, T.; Tomita, K.; Kawada, K. In *Org. Synth.* **1990**, *69*, 129.
(25) Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. In *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 162.
(26) (a) Allinger, J.; Allinger, N. L. *Tetrahedron* **1958**, *2*, 64−74. (b) Allinger, N. L.; Allinger, J. *J. Am. Chem. Soc.* **1958**, *80*, 5476−5480.
(27) Moreau, P.; Casadevall, A.; Casadevall, E. *Bull. Soc. Chim. Fr.* **1969**, 2013−2020.
(28) Battioni, J.-P.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1977**, 320−328.
(29) Hajos, A. *Complex Hydrides*; Elsevier: New York, 1979.
(30) Cherest, M. *Tetrahedron* **1980**, *36*, 1593−1598.

reduction of the appropriate ketone **3-X**, followed by purification by column chromatography. Alcohol **4a-Cl** was synthesized using the method of le Bel and Czaja.[31] Alcohol **4a-Br** was prepared using the procedure of Palumbo et al.[32] Alcohol **4a-OCH$_3$** was synthesized by the addition of H_2SO_4/MeOH[33] to *cis*-4-*tert*-butylcyclohexene oxide.[27] The spectra for **2-OCH$_3$** and **4-OCH$_3$** differed from the literature and are reported below.

The ketones **3-Cl** and **3-Br** are reported to be thermally unstable toward equilibration with the eq isomers at room temperature, though indefinitely stable at dry ice temperatures.[34] We found that storage of these compounds at −20 °C for periods of several weeks gave only a small percentage of eq ketone as judged by ^{1}H NMR. Fortunately, the undesired ^{1}H NMR shifts that resulted from reduction of the eq ketone at 0 °C did not interfere with the peaks that came from reduction of the ax ketone.

NMR Data. *trans*-4-*tert*-Butyl-*trans*-2-methoxycyclohexanol (2e-OCH$_3$): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.40 (s, 3), 3.35 (m, 1), 2.93 (m, 1), 2.61 (broad s, 1), 2.12 (m, 1), 2.00 (m, 1), 1.71 (m, 1), 1.24 (m, 2), 1.05 (m, 2), 0.86 (s, 9); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 85.9, 74.6, 57.0, 46.7, 32.9, 32.0, 29.9, 28.1, 25.4.

***cis*-4-*tert*-Butyl-*cis*-2-methoxycyclohexanol (2a-OCH$_3$):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.07 (m, 1), 3.38 (s, 3), 3.13 (m, 1), 2.15 (broad s, 1), 2.05 (m, 1), 2.00 (m, 1), 1.76 (m, 1), 1.31 (m, 3), 0.99 (m, 1), 0.85 (s, 9); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 82.2, 65.7, 56.3, 46.9, 32.9, 30.6, 28.0, 27.2, 20.4.

***trans*-4-*tert*-Butyl-*cis*-2-methoxycyclohexanol (4e-OCH$_3$):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.52 (m, 1), 3.44 (m, 1), 3.34 (s, 3), 2.24 (broad s, 1), 2.12 (m, 1), 1.74 (m, 2), 1.49 (m, 1), 1.24 (m, 1), 0.97 (m, 2), 0.83 (s, 9); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 79.7, 72.1, 56.7, 40.3, 32.2, 30.9, 28.3, 27.9, 25.6.

***cis*-4-*tert*-Butyl-*trans*-2-methoxycyclohexanol (4a-OCH$_3$):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (m, 1), 3.38 (m, 1), 3.32 (s, 3), 1.74 (m, 4.3), 1.47 (m, 2), 1.30 (m, 4.2), 0.83 (s, 9); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 80.0, 67.3, 56.8, 41.0, 32.5, 29.1, 27.7, 25.4, 20.7.

Computational Methodology. Calculations were performed using the Gaussian 94 program suite.[35] In short, geometries are optimized using the 3-21G and 6-31G* basis sets.[36] For ketones, second-order Moeller−Plesset perturbation theory (MP2)[37] optimizations were performed, while TS calculations were done at the Hartree−Fock level. All stationary points were confirmed with analytical second derivatives. Single point calculations that employed MP2 theory with the 6-31++G** basis set were used to correct for electron correlation and basis set deficiencies, respectively. Thus, ΔE(MP2/6-31G*) + ΔE(HF/6-311+G**) − ΔE(HF/6-31G*) is used as an approximation for a single point calculation at the MP2/6-311+G** level of theory.

The computational modeling of $LiAlH_4$ reductions of ketones is complicated because "$LiAlH_4$" itself does not give an acceptable TS.[38−40] Instead, reagents such as LiH,[9ab,41] NaH,[9b] BH_3, and AlH_3[9d,42] are used to model diastereoselectivity. Diastereoselectivities were calculated by subtracting the energy of the TS that leads to the ax alcohol from the energy of the TS that leads to the eq alcohol.

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(31) le Bel, N. A.; Czaja, R. F. *J. Org. Chem.* **1961**, *26*, 4768−4770.
(32) Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* **1983**, *24*, 1307−1310.
(33) Winstein, S.; Ingraham, L. L. *J. Am. Chem. Soc.* **1952**, *74*, 1160.
(34) For **ax 2-Br**: Allinger, N. L.; Allinger, J. *J. Am. Chem. Soc.* **1958**, *80*, 5476−5480. For **ax 2-Cl**: Allinger, N. L.; Allinger, J.; Freiberg, L. A.; Czaja, R. F.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 5876.
(35) Gaussian 94 (Revision B. 3). Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Ragavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Repogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc. Pittsburgh, Pa 1995.
(36) For a complete description of the basis sets, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986.
(37) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.
(38) Bonaccorsi, R.; Cimiraglia, R.; Tomasi, J.; Miertus, S. *J. Mol. Struct.* **1983**, *94*, 11. Bonaccorsi, R.; Palla, P.; Tomasi, J. *J. Mol. Struct.* **1982**, *87*, 181.
(39) Eisenstein, O.; Schlegel, H. B.; Kayser, M. M. *J. Org. Chem.* **1982**, *47*, 2886.
(40) Recently, Tomoda (ref 8e) showed that "$LiAlH_4$" did give an acceptable TS for cyclohexanone itself. However, our preliminary computational data for 2-substituted cyclohexanones using this method gave no improvement over the data reported.
(41) (a) Kaufman, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560−5562. (b) Shi, Z.; Boyd, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 9614−9619. (c) Wong, S. S.; Paddon-Row; M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327−330.
(42) Coxon, J. M.; Luibrand, R. T. *Tetrahedron Lett.* **1993**, *34*, 7097−7100.