Stereoselectivities of Nucleophilic Additions to Cyclohexanones Substituted by Polar Groups. Experimental Investigation of Reductions of *trans*-Decalones and Theoretical Studies of Cyclohexanone Reductions. The Influence of Remote Electrostatic Effects

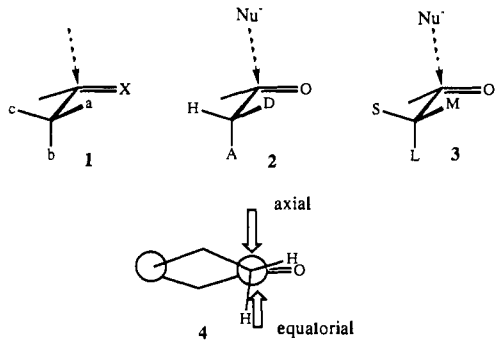
Yun-Dong Wu, John A. Tucker, and K. N. Houk*

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90024. *Received December 21, 1990*

Abstract: A series of nine 4-substituted *trans*-decalones have been synthesized and submitted to hydride reduction by $NaBH_4$. Equatorial electron-withdrawing substituents have very little effect on the stereoselectivity, while axial substituents have a large effect. Ab initio molecular orbital calculations on the reaction of cyclohexanone with lithium hydride gave a 1.8-kcal/mol preference for the axial transition state at the RHF/6-31G* level. Substituent effects were studied by calculations with substituents at the C_4 position in the transition structure. The effects of OH and NH_2 substitutions on the stereoselectivity are strongly dependent upon group orientation, indicating the importance of long-range electrostatic effects on stereoselectivity. Cyclohexanone, 4-*ax*-, 4-*eq*-, and 3-*eq*-fluorocyclohexanones, and 5-fluoroadamantanone were optimized with the 3-21G basis set. The distortion about the C_{sp^2}–C_α bonds and the pyrimidalization at the C_{sp^2} center are both enhanced by the fluoro substitution. The transition structures of the reactions of sodium hydride with propanal, 3-fluoropropanal, and 3-silylpropanal were located with the 3-21G and 6-31G* basis sets. Fluoro substitution was calculated to cause a notable stabilization of the *outside* transition structure. Electrostatic effects are shown to be an additional factor, along with torsional and steric effects, that influence nucleophilic addition stereoselectivities.

Introduction

Since first proposed by Felkin in 1968,[1] and subsequently supported by Anh and Eisenstein's ab initio calculations,[2] the torsional strain transition state model has been widely accepted and has played a significant role in understanding the stereoselectivities of variety of addition reactions.[3,4] Often called the Felkin–Anh model, it is based upon Felkin's recognition that allylic bonds tend to be staggered with respect to the partial bond to the attacking reagent as shown in **1**. Recently we have reported a



Felkin-Anh Torsional Strain Model

transition structure model which reproduces the experimental stereoselectivities of nucleophilic additions to cyclohexanones, cyclohexenones,[5] benzocycloheptenones,[6] acyclic α-chiral carbonyl compounds, cyclopentanones, and many bicyclic ketones.[7] Our model fully supports the Felkin–Anh model, since it shows that torsional and steric effects can account for the experimental results. Ab initio calculations which we performed indicate that electron-donating groups (D) disfavor electronically the anti-periplanar conformation, and electron-withdrawing groups (A) favors anti-periplanar conformation with respect to the incoming nucleophile, as shown in **2**. Steric effects favor an arrangement of allylic alkyl substituents as shown in **3**.[8] Cyclohexanone transition structures involve the distorted chair conformation shown in **4**. There is less torsional strain in the transition structure for axial attack than in the transition structure for equatorial attack, as proposed by Felkin.[1]

Several other models to explain the stereoselectivities of nucleophilic additions to cyclohexanones[9-12] are related to the Felkin–Anh model, but emphasize different features. For example, Klein,[10] Hudec,[11] and Ashby,[12] have emphasized the importance of unsymmetrical extensions of π and π^* orbitals about carbonyl plane which accompany geometrical distortion. These unsymmetrical orbital extensions have been suggested to influence the orbital overlap upon attack of nucleophiles on the two faces of the carbonyl groups.

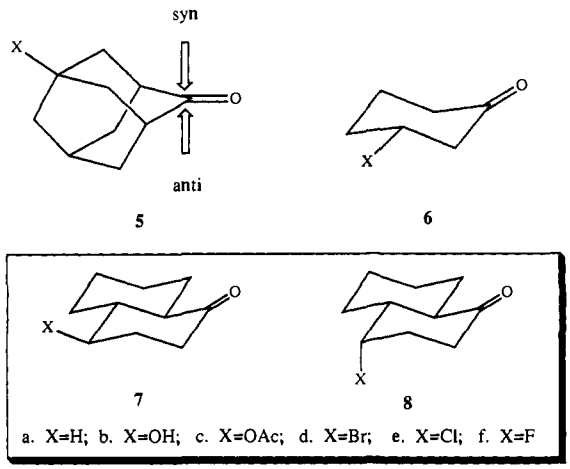
The Cieplak model focuses on the importance of stabilization of the transition state by anti-periplanar allylic bonds.[13,14] The model is based on two assumptions. The first is that stabilization

(1) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Cherest, M.; Felkin, H. *Ibid.* **1968**, 2205.
(2) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. Anh, N. T. *Fortschr. Chem. Forschung.* **1980**, *88*, 145.
(3) For a general account of theory of stereoselectivities, see: Houk, K. N.; Paddon-Row, M. N.; Rondan, G. N.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science (Washington, D.C.)* **1986**, *231*, 1108.
(4) Houk, K. N. In *Stereochemistry and Reactivity of Systems Containing π Electrons*; Watson, Ed.; Verlag Chemie: Deerfield Beach, FL, 1983; pp 1-40.
(5) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560. Trost, B. M.; Florez, J.; Jebaratnam, D. J. *Ibid.* **1987**, *109*, 613. Trost, B. M.; Florez, J.; Haller, K. J. *J. Org. Chem.* **1988**, *53*, 2396. Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* In press.
(6) Mukherjee, D.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1987.
(7) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. Houk, K. N.; Wu, Y.-D. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH Verlagsgesellschaft mbH: Weinheim, 1987; pp 247-260.
(8) The transition structure with larger alkyl group *inside*, smaller alkyl group *outside*, and hydrogen anti, which gives same product as **3**, is not favored because of severe steric strain.
(9) Dauben, W. G.; Fonken, G. J. *J. Am. Chem. Soc.* **1956**, *76*, 2579.
(10) Klein, J. *Tetrahedron Lett.* **1973**, *29*, 4307; **1974**, *30*, 3349. Eisenstein, O.; Klein, J.; Lefour, J.-M. *Tetrahedron* **1979**, *35*, 225.
(11) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459.
(12) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1977**, *42*, 264.
(13) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4550.
(14) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

0002-7863/91/1513-5018$02.50/0

of the transition state can occur by electron donation from an anti-periplanar σ orbital to a σ_4^* orbital, a low-lying vacant orbital of the forming bond. The second assumption is that electron-donating abilities of some common bonds are in the order: C–S > C–H > C–C > C–N > C–O. In the transition state of axial addition to cyclohexanone, there are two anti-periplanar C–H bonds, while in the transition state of equatorial addition, there are two anti-periplanar C–C bonds. Since C–H is postulated to be a better donor than C–C, the axial addition is favored despite unfavorable steric interactions. Cieplak rationalized a large variety of substituent effects on nucleophilic addition stereoselectivities with this model.[13] Nevertheless, there have been criticisms of the assumptions and predictions of this theory.[7,15,16]

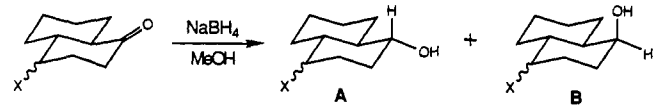
There have been recent reports of the effect of remote substituents on the stereoselectivities of nucleophilic additions to cyclohexanone and related compounds. le Noble et al. reported the stereoselectivities of addition reactions to 5-substituted adamantanone derivatives, **5**.[17-20] They observed that electron-



withdrawing 5-substituents generally cause a slight preference for syn addition, while electron-donating 5-substituents generally cause a small preference for anti addition. The effects are quite small, ranging from only 55 to 70% of the major product formed, considerably smaller than the axial preference for hydride reduction of cyclohexanones. Several assignments of stereochemistry in these studies have had to be revised.[21] Stereoselectivities were observed for many reactions: nucleophilic additions,[17] electrophilic additions,[18] thermal cycloadditions, photocycloadditions,[19] and the oxy-Cope rearrangement.[20] Johnson et al. studied the substituent effect on the stereoselectivities of nucleophilic additions and electrophilic additions to cyclohexanone derivatives, **6**, and found that there is an increase in axial addition if the 3-substituent, X, is electron-withdrawing, and a decrease in axial addition if X is electron-donating.[14,22] Once again, the stereoselectivities are small. These results were rationalized in terms of the Cieplak model.

In this paper we present experimental investigations of C_4-substituent effects on the stereoselectivities of hydride reduction of *trans*-decalones (**7** and **8**), and theoretical studies of a variety of related nucleophilic additions: the reactions of lithium hydride with cyclohexanone and 4-substituted cyclohexanones, and the reactions of sodium hydride with propanal and 3-fluoro- and 3-silylpropanals. The ground-state geometries of cyclohexanone, 3-fluoro- and 4-fluorocyclohexanones, and 5-fluoroadamantanone were also studied. We have found that electrostatic interactions can have an influence on stereoselectivities. There are also geometrical alterations of cyclohexanones induced by substituents. These studies lead to explanations for many apparent exceptions to the Felkin–Anh rule which have appeared in the recent literature.

Table I. Stereoselectivities of Reductions of 4-Substituted *trans*-Decalones with Excess $NaBH_4$ in Methanol at 25 °C



compd	X	% A[a]	% B[a]
7a	H	60	40
7b	eq OH	61	39
7c	eq OAc	71	29
7d	eq Br	66	34
7e	eq Cl	71	29
8b	ax OH	85	15
8c	ax OAc	83	17
8e	ax Cl	88	12
8f	ax F	87[b]	13[b]

[a] Relative yields determined by ^1H NMR integration and by capillary GC analysis of the corresponding acetates (DB-17 column). Values given represent an average of the two determinations, which agreed within 2% in each case except compound **8c** (6%). [b] Ratio determined by ^1H NMR only.

Results and Discussion

A. Experimental Results. Reduction of *trans*-decalone and the axial and equatorial 4-substituted derivatives gave mixtures of adducts, as shown in Table I. Product identities were determined by NMR spectroscopy, and ratios were determined independently by NMR and by capillary GC analysis of the derived acetates, as described in the Experimental Section. The parent system (**7a**) shows a small preference for axial attack. Equatorial electronegative groups (**7b–7e**) give small increases in the percentage of axial attack. These examples are analogous to those of le Noble et al. on substituted adamantanones.[17] The axial-substituted derivatives (**8b–8f**) show larger increase of axial attack. These trends agree with Monson's earlier observations of sodium borohydride reduction of *trans*-2-decalone, *trans*-10-carboxy-2-decalone, and *trans*-10-carbomethoxy-2-decalone, which give 76, 92, and 100% of axial addition, respectively.[23]

Equatorial electronegative substituents should interact more strongly with the $C_{2,3}$ and $C_{9,10}$ bonds of decalone than axial substituents. This is because the equatorial σ^*_{CX} orbital is aligned to overlap with $\sigma_{2,3}$ and $\sigma_{9,10}$, whereas the axial σ^*_{CX} bond is not. Consequently, the $C_{2,3}$ and $C_{9,10}$ bonds of the equatorial-substituted isomers should be poorer donors than those of the axial isomers. If nucleophilic addition occurs anti to the better donor σ bond,[13] then the equatorial isomers should have considerably more axial attack than the parent, while the axial isomers should have only slight increases in axial attack. Exactly the opposite is observed.

In order to understand these results, further theoretical studies were undertaken, as described in the next section.

B. Computational Results. Transition structures for the axial and equatorial additions of lithium hydride to cyclohexanone have been located with full optimization with the 3-21G basis set.[24]

(15) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509. Meyers, A. I.; Sturgess, M. A. *Tetrahedron Lett.* **1988**, *29*, 5339.
(16) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456.
(17) le Noble, W. J.; Chiou, D.-M.; Okaya, Y. *Tetrahedron Lett.* **1978**, 1961; *J. Am. Chem. Soc.* **1979**, *101*, 3244. Cheung, C. K.; Tseng, L. T.; Lin, M. H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598; **1987**, *109*, 7239. Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836.
(18) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874.
(19) Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882.
(20) Lin, M.-H.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 998.
(21) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 7239 (correction).
(22) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5975.
(23) Monson, R. S.; Przybycien, D.; Baraze, A. *J. Org. Chem.* **1970**, *35*, 1700.
(24) All calculations were performed with Pople's GAUSSIAN series programs. GAUSSIAN 82: Binkley, J. S.; Frisch, M. J.; DeFrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, H. B.; Fluder, E. M.; Pople, J. A. Carnegie-Mellon University: Pittsburgh, PA, 1982. GAUSSIAN 86: Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachar, K.; Melius, R.; Martin, L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Fleuder, E. M.; Pople, J. A. Carnegie-Mellon Quantum Chemistry Publishing Unit: Pittsburgh, PA, 1986.

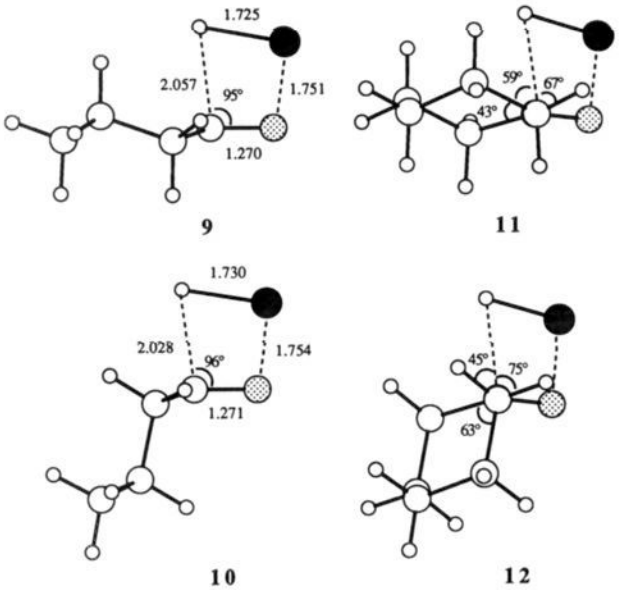


Figure 1. Side views and Newman projections along the C_2–C_1 bond of axial and equatorial transition structures of reaction of lithium hydride with cyclohexanone located with the 3-21G basis set.

These are shown in Figure 1. The axial transition structure (**9**) is more stable than the equatorial transition structure (**10**) by 1.0 kcal/mol at the 3-21G basis set level. This difference increases to 1.8 kcal/mol when the calculations are performed with the 6-31G* basis set on the 3-21G geometries. The calculated axial preference is in qualitative agreement with experimental observation of axial/equatorial ratio of about 90/10 for lithium aluminum hydride reduction of *tert*-butylcyclohexanone.[25]

The two transition structures are quite similar, but **10** is slightly "later" with respect to H---C bond formation, which is 0.03 Å shorter in **9**. As clearly indicated by the Newman projection looking down the C_2C_1 bond, there is nearly perfect staggering about the forming H---C bond in the axial transition structure, **11** (**9**). The dihedral angles of H---CCC are 59°, and the C_2H and C_6H bonds are perfectly anti-periplanar to the forming bond. There is, however, a partial eclipsing in the equatorial transition structure, as shown in the Newman projection, **12**. The H---CCH_{out} dihedral angles are 45°, and the H---CCC dihedral angles are 164°. Furthermore, the ring dihedral angles $C_6C_1C_2C_3$ are 63°, distorted from the 54° in cyclohexanone and 43° in **9**. These same features were observed earlier in the force field model that we developed for this reaction.[6,7] These geometrical differences are in full accord with the early deduction by Felkin.[1] Nucleophilic attack from the axial direction occurs with nearly perfect staggering and no strain in the six-membered ring. Equatorial attack occurs with some eclipsing, and strain induced in the six-membered ring to achieve even this degree of staggering. We have shown many examples of ring size and alkyl substituent effects which can be explained fully by this Felkin model.[5-7]

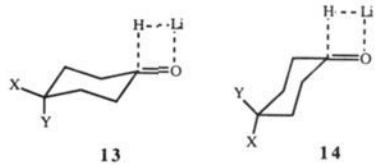
Substituent effects on the stereoselectivities of nucleophilic additions to cyclohexanones were studied by replacing the equatorial and axial C_4 hydrogens with electron-withdrawing groups, X or Y, where X and Y are F, Cl, OH, or NH_2, in standard geometries, as shown in drawings **13** and **14**. The energies were calculated for the unoptimized geometries with the 3-21G basis set. The calculated total energies and relative energies of these species are collected in Table II. When the substituent is equatorial (X = substituent, Y = H), very small variations in stereoselectivity are predicted for different substituents. The preference for the axial transition structure is increased with F and Cl substituents by about 0.3 kcal/mol, and for OH and NH_2 by 0.6 and 0.2 kcal/mol, respectively. When X is OH or NH_2, there are two possible conformations for the substituent. The conformations with one lone pair *inside* the ring (gauche to both C_3–C_4 and C_4–C_5 bonds) are less stable than the conformations with both lone pairs *outside* the ring. The calculated axial preference is 1.6 and 1.2 kcal/mol for X = OH and NH_2, respectively, when the lone pairs are outside. However, the axial preference is predicted to be only 1.0 and 0.6 for X = OH and NH_2, respectively, with an inside lone pair. The axial transition structure is destabilized by the electrostatic interaction between the nucleophile ($H^{\delta-}$) and the inside lone-pair electrons, but is stabilized by the electronegative substituent in other conformations.

When the substituent is axial (X = H), the calculations gave a significant additional stabilization for the axial transition structure in every case. These results are qualitatively in agreement with the experimental observations. The most stable conformations for OH and NH_2 have one lone pair inside the ring. The calculated axial preference is significant with these conformations. However, the predicted axial preference is about the same as in the unsubstituted case when the OH or NH_2 is in the less stable conformation, with a lone pair outside the ring.

For equatorial fluoro substitution, the equatorial and axial transition structures were also fully optimized with the 3-21G basis set. Both transition structures become "earlier" with respect to the cyclohexanone transition structures. The activation energies for the two transition structures with respect to the reactants are lower than those of the cyclohexanone reaction by about 6 kcal/mol. Although this effect is most likely exaggerated, it reflects the electron-withdrawing character of the substituent.[26-29] While there is almost no change in the torsional angles about the C–H forming bond in the axial transition structure, the allylic bonds in the equatorial transition structure become more nearly eclipsed by 2°. The axial transition structure is 1.2 kcal/mol more stable than the equatorial one, the same difference as that calculated without optimization.

The influence of substituents on the ground-state geometry of cyclohexanone was also examined. The optimized structures of cyclohexanone (**15**), 4-*eq*-fluorocyclohexanone (**16**), 4-*ax*-

Table II. Calculated Total Energies (–au) and Relative Energies of Axial and Equatorial Transition Structures of Substituted Cyclohexanones, **13** and **14**



X[a]	Y	E(13)	E(14)	ΔE,[b] kcal/mol
H	H	314.155 21	314.153 70	1.0
F	H	412.477 51	412.475 46	1.3
Cl	H	770.877 68	770.875 67	1.3
OH (outside)	H	388.590 54	388.588 04	1.6
OH (inside)	H	388.588 40	388.587 01	0.9
NH_2 (outside)	H	368.867 51	368.865 63	1.2
NH_2 (inside)	H	368.865 61	368.864 65	0.6
H	F	412.481 36	412.477 35	2.5
H	Cl	770.880 10	770.875 43	2.9
H	OH (outside)	388.587 46	388.585 83	1.0
H	OH (inside)	388.593 37	388.589 70	2.3
H	NH_2 (outside)	368.863 55	368.861 88	1.0
H	NH_2 (inside)	368.871 04	368.867 47	2.2

[a] inside, lone pair of the substituent is inside the ring; outside, lone pair of the substituent is outside the ring. [b] **13** is always more stable than **14**.

(25) Boone, J. R.; Ashby, E. C. In *Topics in Stereoselectivity*; Eliel, E. L., Allinger, N. L., Eds.; Interscience: New York, 1979; Vol. 11, p 53.

(26) Smith, G. G.; Bayer, R. P. *Tetrahedron* **1962**, *18*, 323. Perry, J. A.; Warren, K. D. *J. Chem. Soc.* **1965**, 4049. Bowden, K.; Hardy, M. *Tetrahedron* **1966**, *22*, 116. Ayres, D. C.; Sawdaye, R.; Kirk, D. N. *J. Chem. Soc. B* **1970**, 1133. Wiegers, K. E.; Smith, S. G. *Ibid.* **1977**, *99*, 1480.

(27) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894. Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411.

(28) Morris, D. G.; Shepherd, A. G. *Nouv. J. Chem.* **1988**, *12*, 277.

(29) Kwart, H.; Takeshita, T. *J. Am. Chem. Soc.* **1962**, *84*, 2833.

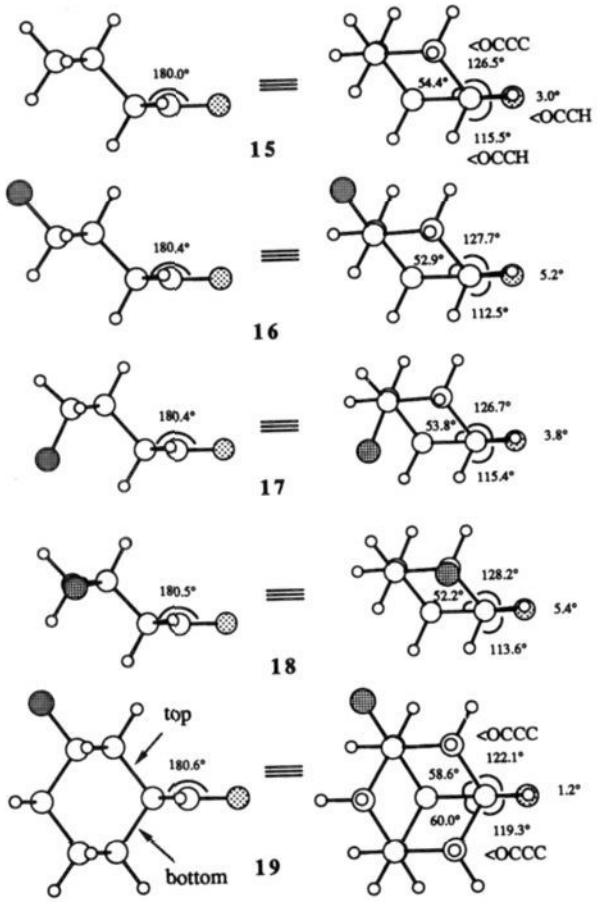


Figure 2. Side views and Newman projections along the C_1–C_2 bonds of 3-21G optimized cyclohexanone (**15**), 4-*eq*-fluorocyclohexanone (**16**), 4-*ax*-fluorocyclohexanone (**17**), 3-*eq*-fluorocyclohexanone (**18**), and 5-fluoroadamantanone (**19**).

fluorocyclohexanone (**17**), 3-*eq*-fluorocyclohexanone (**18**), and 5-fluoroadamantanone (**19**), are shown in Figure 2. The sense of pyramidalization at the carbonyl carbon is indicated by the out-of-plane angle of the C=O bond with respect to the C–C_{sp^2}–C plane. The geometrical distortions are indicated by dihedral angles about the C_{sp^2}–C_α bonds. The carbonyl carbon of a cyclohexanone is slightly pyramidalized to relieve the eclipsing strain due to the flanking CH bonds, which are rotated out of the plane of the carbonyl group owing to flattening of the six-membered ring.[1,7] The fluoro substitution increases such ring distortion and pyramidalization in every case.

The transition structures of the reactions of sodium hydride with propanal, 3-fluoropropanal, and 3-silylpropanal have been located with full geometrical optimizations with the 3-21G and 6-31+G* basis sets.[30] The 3-fluoro and 3-silyl substituents are in anti conformations with respect to the C_1C_2 bond so that they model the equatorial substituents at C_3 of cyclohexanone. The structures are shown in Figure 3. The energies of these transition structures were also evaluated with the MP2/6-31+G* single point calculations. Selected geometrical parameters of the transition structures are given in Table III. The calculated total energies are collected in Table IV. Table V summarizes the relative energies of the three staggered transition structures for each reaction.

Two geometrical features are noteworthy. (1) While all three transition structures for the reactions of propanal and 3-silylpropanal have very similar H---C and C=O bond lengths, the forming H---C bond in the anti transition structure of the reaction

(30) Throughout the paper, the basis set called 6-31+G* is the 6-31G* with the inclusion of an additional diffuse s and p orbitals on the hydride.

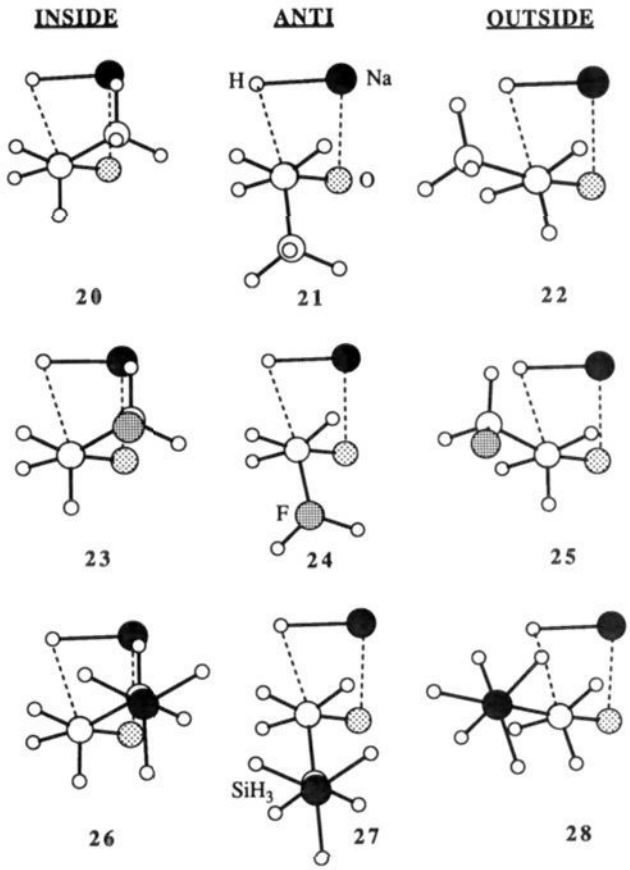


Figure 3. Newman projection views of transition structures of reactions of sodium hydride with propanal, 3-fluoropropanal, and 3-silylpropanal located with the 6-31+G* basis set.

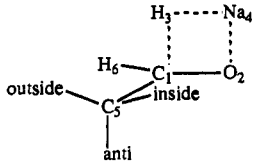
of 3-fluoropropanal (**24**) is longer than the H---C bond in the inside (**23**) and outside (**25**) transition structures by about 0.01 Å. Meanwhile, the C=O bond in the anti transition structure is shorter by about 0.005 Å. This means that the anti transition structure is somewhat earlier. (2) There are large variations in the H---C–C–C dihedral angles in the three outside transition structures. It is 56° in **22**, and decreases by 10° with fluoro substitution in **25**, and increases by 5° with silyl substitution in **28**.

Finally, CH_3CH_2CHO, FCH_2CH_2CHO, and $SiH_3CH_2CH_2CHO$ were optimized with the 6-31G* basis set with the constraint of one of the allylic bonds to be 90° with respect to the carbonyl bond. Figure 4 shows the degrees of pyramidalization at the carbonyl carbons in each of the conformations. The pyramidalization angles are defined as the deviation from 180° of the angle between O=C—C plane and O=C—H plane. The direction of the pyramidalization is opposite to the perpendicular bond in each structure. The relative energies (MP2/6-31G*) of the structures are shown with respect to the most stable conformations, namely, those conformations with eclipsed C_2C_3 and C=O bonds.

C. Discussion. 1. Conformational Preferences of Allylic Groups in Transition Structures of Hydride Addition. Among the three transition structures of the reaction of propanal with sodium hydride, **20** is most stable at every level of calculation. At the highest level of calculation, **20** is more stable than **21** and **22** by 1.4 and 1.7 kcal/mol, respectively. Substitution of SiH_3 at C_3 has a small effect on the relative stabilities of the three transition structures. Fluorine substitution, on the other hand, has a significant effect on the relative stabilities of the three structures. The structures **26** and **28** are more stable than **27** by 2.3 and 1.6 kcal/mol, respectively, at the MP2/6-31+G* level. The outside transition structure (**28**) benefits most from the fluorine substitution.

To help understand these features, we first describe the con-

Table III. Selected Geometrical Parameters of Transition Structures of the Reactions of Sodium Hydride with Propanal Derivatives, RCH_2CH_2CHO, R = H, F, and SiH_3



D1: $<H_3$-C_1-C_5-inside
D2: $<H_3$-C_1-C_5-anti
D3: $<H_3$-C_1-C_5-outside

R		1-2	1-3	2-4	3-4	2-1-3	3-1-5	3-1-6	D_1	D_2	D_3
					3-21G						
H	inside	1.256	2.015	2.109	2.053	102.6	96.5	86.8	-81.1	159.2	43.1
H	anti	1.256	2.029	2.108	2.054	102.7	96.6	87.1	-72.6	167.8	47.0
H	outside	1.256	2.027	2.102	2.053	102.0	97.5	86.9	-66.1	178.9	59.0
F	inside	1.253	2.069	2.128	2.050	101.3	96.5	86.1	-80.4	160.6	42.7
F	anti	1.246	2.164	2.141	2.042	101.1	96.6	84.9	-65.2	176.0	55.2
F	outside	1.251	2.059	2.114	2.055	101.8	97.1	86.2	-81.1	162.4	44.2
SiH_3	inside	1.253	2.039	2.115	2.051	102.5	95.9	86.9	-79.5	160.5	48.2
SiH_3	anti	1.254	2.046	2.113	2.053	102.4	96.4	87.2	-73.7	166.7	45.9
SiH_3	outside	1.254	2.035	2.107	2.053	102.0	97.0	86.9	-63.8	-178.8	61.0
					6-31+G*						
H	inside	1.235	1.922	2.164	2.047	105.8	96.8	87.2	-77.3	162.7	48.2
H	anti	1.235	1.928	2.164	2.046	105.9	96.7	87.3	-70.0	169.8	48.3
H	outside	1.235	1.943	2.163	2.042	105.2	97.4	87.2	-70.3	176.5	56.2
F	inside	1.233	1.960	2.183	2.047	105.0	96.5	87.7	-76.3	164.5	48.2
F	anti	1.229	2.015	2.195	2.039	105.4	96.1	85.6	-65.6	174.9	54.1
F	outside	1.233	1.943	2.168	2.051	105.5	97.0	86.9	-80.7	164.4	45.7
SiH_3	inside	1.235	1.941	2.164	2.048	105.5	96.4	87.1	-77.1	162.7	48.4
SiH_3	anti	1.235	1.943	2.164	2.048	105.7	96.3	87.3	-70.6	169.1	47.5
SiH_3	outside	1.234	1.938	2.164	2.047	105.4	97.0	87.2	-64.8	-177.9	61.4

Table IV. Calculated Energies (au) of the Transition Structures of the Reactions of Sodium Hydride with Propanal Derivatives, RCH_2CH_2CHO, R = H, F, and SiH_3

		3-21G TS			6-31+G* TS	
R		3-21G	6-31+G*	MP2/6-31+G*	6-31+G*	MP2/6-31+G*
H	inside	352.278 97	354.335 52	354.918 96	354.337 31	354.920 29
H	anti	352.276 01	354.334 26	354.916 58	354.335 73	354.918 03
H	outside	352.276 21	354.334 17	354.916 62	354.335 70	354.917 57
F	inside	450.594 50	453.182 86	453.882 36	453.185 52	453.883 31
F	anti	450.589 18	453.180 27	453.878 50	453.182 55	453.879 60
F	outside	450.592 69	453.182 32	453.881 41	453.184 77	453.882 12
SiH_3	inside	640.827 62	644.410 08	645.072 39	644.412 29	645.073 94
SiH_3	anti	640.824 94	644.409 18	645.070 04	644.411 00	645.071 72
SiH_3	outside	640.824 99	644.409 02	645.070 37	644.411 03	645.071 82

Table V. Calculated Relative Energies (kcal/mol) of the Transition Structures of the Reactions of Sodium Hydride with Propanal Derivatives, RCH_2CH_2CHO, R = H, F, and SiH_3

	R = H			R = F			R = SiH_3		
	inside	anti	outside	inside	anti	outside	inside	anti	outside
3-21G	0.0	1.8	1.7	0.0	3.3	1.2	0.0	1.7	1.7
6-31+G*//3-21G	0.0	0.8	0.8	0.0	1.6	0.3	0.0	0.6	0.7
MP2/6-31+G*//3-21G	0.0	1.5	1.5	0.0	2.5	0.6	0.0	1.5	1.3
6-31+G*	0.0	1.0	1.0	0.0	1.9	0.5	0.0	0.8	0.8
MP2/6-31+G*//6-31+G*	0.0	1.4	1.7	0.0	2.3	0.7	0.0	1.4	1.3

formational preferences of these carbonyl compounds in the ground state. Propanal prefers the conformation in which the allylic methyl group is eclipsed with the carbonyl bond.[31] Wiberg has explained this with a dipole–dipole interaction argument.[32] That is, the carbonyl bond induces a dipole about the C_2C_3 bond, so that there is a stabilizing interaction between the two dipoles. It is conceptually equivalent to the electrostatic attraction of the partially positively charged methyl group and the partially negative carbonyl oxygen. As shown in Figure 4, the three conformations with a perpendicular allylic bond all resemble the conformations of the aldehydes in the three transition structures. Conformation **31**, which has the methyl near the carbonyl oxygen, is most stable. Fluoro substitution should increase the positive charge at C_3. Therefore, the electrostatic effect becomes more significant. Indeed, conformation **30** is calculated to be more stable than **33** and **36** by 1.5 and 1.9 kcal/mol, respectively. On the other hand, SiH_3 substitution reduces the electrostatic effect by electron donation to C_3, and the energetic differences among **32**, **35**, and **38** are slightly smaller.

It is interesting to note that conformations **34** and **35** are expected to be more stable than conformations **37** and **38**, respectively, since they are sterically less crowded and also benefit from electrostatic interactions. Nevertheless, **34** and **35** are calculated to be slightly less stable than **37** and **38**. This can be explained by a destabilizing interaction between the π-orbital of the carbonyl and the perpendicular σ_{C-C}, which is a better donor than σ_{C-H}. In other word, a perpendicular donor group is most destabilizing in the ground state. This argument is in accord with the generally accepted explanation of conformational preferences

(31) Pickett, H. B.; Scroggin, D. G. *J. Chem. Phys.* **1974**, *61*, 3954. Butcher, S. S.; Wilson, E. B., Jr. *Ibid.* **1964**, *40*, 1671. Durig, J. R.; Compton, D. A.; McArver, A. Q. *Ibid.* **1980**, *73*, 719. Rondan, N. G.; Paddan-Row, M. N.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436. Allinger, N. L.; Hickey, M. J. *J. Mol. Struct.* **1973**, *17*, 233.

(32) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035.

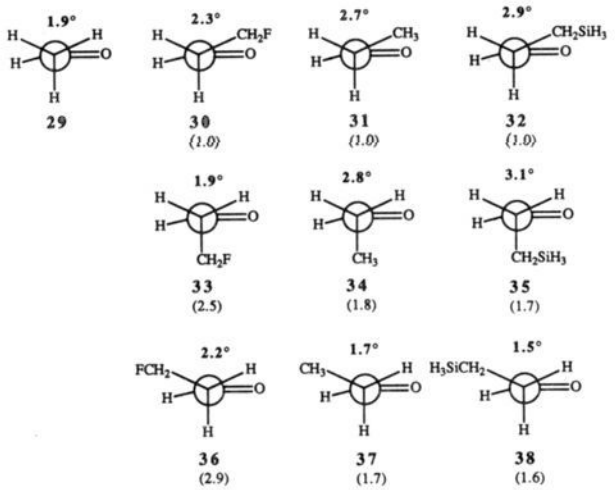


Figure 4. Pyramidalization and relative energies of the conformations of acetone, propanal, 3-fluoropropanal, and 3-silylpropanal with the constraint of one of the allylic bonds perpendicular to the carbonyl bond. The relative energies (in parentheses) are relevant to the best eclipsed conformation with MP2/6-31G*//6-31G* calculations.

of propene, acetaldehyde, and related molecules: the eclipsed conformation is more favorable than the staggered conformation because of larger repulsive interaction between the π-orbital of the double bond and π_{CH_3} in the staggered conformation.[33]

In general, these conformational features should be reflected in the transition structures. Thus, the inside transition structure is most stable for each of the three reactions. However, the relative stabilities of the transition structures are also influenced by the steric and electronic effects introduced by the presence of the nucleophile. Sterically, it is apparent that the outside transition structure is most crowded and the anti transition structure is least crowded. Electronically, there is electron transfer from the nucleophile to the π^*-orbital of the carbonyl. The Mulliken population analysis indicates that the hydride has a charge of −0.6, while the sodium has a charge of +0.7 in these transition structures. Overall, about 0.1 unit of negative charge is transferred from sodium hydride to the aldehyde. Electron donors destabilize, while electron acceptors stabilize, the transition structures when the substituents are anti-periplanar.

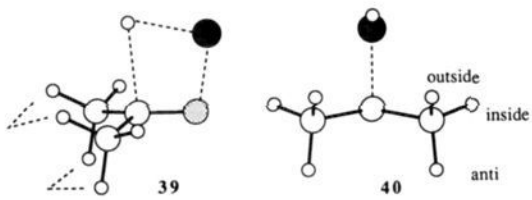
Superimposed on this electronic effect is the electrostatic interaction between the nucleophile and the allylic groups. This becomes significant when the allylic position is substituted by a polar group. In the case of 3-fluoropropanal, there is significant positive charge at C_3. It is expected that the outside and inside transition structures benefit from this electrostatic interaction, which brings the partially positive allylic carbon near the negative attracting nucleophile. This interaction is particularly important in the outside transition structure. The H---CCC dihedral angle in the outside transition structure decreases from 56° in the propionaldehyde reaction to 46° in the 3-fluoropropanal reaction. This dihedral angle increases to 61° in the outside transition structure of the 3-silylpropanal reaction, to avoid repulsive electrostatic interactions.[34]

The overall stabilities of the three transition structures involve all of these effects. For propanal, the anti transition structure benefits from steric effects, but is destabilized by both the anti-periplanar and electrostatic effects. These roughly cancel each other, resulting in similar stabilities of the anti and outside transition structures. With fluoro substitution, the anti transition structure slightly benefits from the antiperiplanar effect, but the inside and outside transition structures benefit more from the electrostatic effect. If the allylic methyl group is replaced by a fluoro or a hydroxyl group, both the anti-periplanar effect and electrostatic effect favors the *anti* transition structure, leading to overall preference for the anti transition structure.[16,35,36]

Paddon-Row and Wong have located transition structures for nucleophilic additions of a variety of nucleophiles to aldehydes with chiral allylic centers. These results provide a quantitative assessment of these effects for a variety of reactions at a high computational level.[16,36]

2. The Effect of Geometrical Distortions on the Stereoselectivity of Nucleophilic Additions to Cyclohexanone. The origin of the lower energy of axial attack of nucleophiles on unhindered cyclohexanones has been suggested by Felkin, Anh, Kobayashi, and ourselves.[1,2,7,37] As shown in Figure 3, the equatorial C_2H and C_6H bonds of cyclohexanone are not in the plane of the carbonyl bond. The calculated O=CCH dihedral is 3°. This is somewhat smaller than the experimentally observed value, which is about 6°.[38] The O=$C_1C_2C_3$ dihedral angle is 127°, which is about 11° larger than the other O=C_1C_2H dihedral angle. Overall, the ring is flattened. This geometrical distortion is mainly caused by ring strain.

Upon the attack of nucleophile, further ring distortion occurs. The axial attack is more favorable because the staggered conformation is achieved without introducing much ring strain. This is the essence of the Felkin–Anh torsional strain model for stereoselectivity of nucleophilic additions to cyclohexanone.[1,2] Our calculations on the transition structures of LiH–cyclohexanone reaction are in full agreement with this torsional strain model. As shown in Figure 1, the axial transition structure is perfectly staggered, while partial eclipsing exists in the equatorial transition structure. To have a better understanding of this, transition structures of axial and equatorial attacks can be constructed from the transition structure of the acetone reaction. Structure **40** is a view of the transition state of the reaction of lithium hydride with acetone (**39**) looking toward the CO bond. The two methyl



39 40

groups are perfectly staggered with respect to the forming H---C bond. The two outside C–H bonds are almost parallel, and when they are replaced by a trimethylene chain to form the axial transition structure, little ring strain is introduced. Therefore, the axial transition structure maintains perfect staggering. On the other hand, the two anti CH bonds point away from each other. When they are replaced by a trimethylene chain to form a perfectly staggered equatorial transition structure, ring strain is introduced. Rotations about the C_1C_2 and C_1C_6 bonds are necessary to reduce this ring strain, which inevitably causes torsional strain about the forming bond.

3. Substituent Effect on the Geometries and Stereoselectivities of Reactions of Cyclohexanones. Distortion of the cyclohexanone ring may cause variations in stereoselectivity, because this will alter the ease of achieving the ideal staggered transition structures.

(33) Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6591.

(34) In the cases of electrophilic addition reactions, opposite electrostatic effect is expected if the electrophile is partially positively charged. For example, in the case of alkylation of ester enolate, McGarvey et al. found that allylic CH_2OR group prefers anti and allylic methyl group prefers outside: McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435. The same phenomenon was observed for hydroborations of homoallylic ethers: Kishi, Y. *Aldrichim. Acta* **1980**, *13*, 23. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. However, in the cases of osmium tetroxide dihydroxylation and nitrile oxide cycloaddition reactions, partially negatively charged oxygen atom attacks the alkene terminal adjacent to allylic groups. In such cases, the electrostatic effect is same as in nucleophilic additions: Houk, K. N.; Moses, S.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. Vedejs, E.; Dent, W. H., III *J. Am. Chem. Soc.* **1989**, *111*, 6861.

(35) Wu, Y.-D. Ph.D. Thesis, University of Pittsburgh, 1986.

(36) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327.

(37) Kobayashi, Y. M.; Lambrecht, J.; Jochims, J. C.; Burkert, U. *Chem. Ber.* **1978**, *111*, 3442.

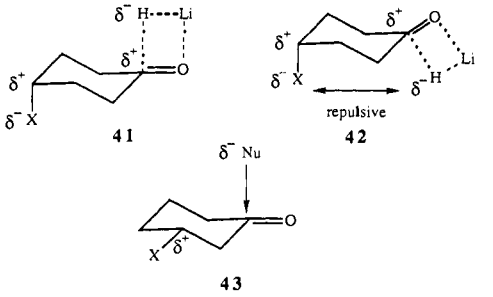
Anh noted more than 10 years ago that ring flattening increases axial selectivity, and ring puckering reduces the axial selectivity.[2] This concept has been applied to rationalize the variations of stereoselectivities of nucleophilic additions to C_3 and C_5 heteroatom derivatives of cyclohexanone.[7,37,38] Hydride reductions of 1,3-dioxolan-5-ones occur with higher axial selectivity than the additions to cyclohexanones, since the short ring CO bonds make the six-membered ring significantly flatter than cyclohexanone. On the other hand, reduction of 1,3-dithiolan-5-one occurs with high equatorial selectivity. X-ray analysis revealed that the ring in the latter compound is distorted in the opposite direction to cyclohexanone. This is caused by long ring C–S bonds which make the ring more puckered. The variation of the stereoselectivity is reproduced nicely by a MM2 transition structure force field which was developed based on the torsional strain model.[7] Benzocycloheptenones, which are analogous to cyclohexanone but have more puckered conformations, were predicted by the MM2 force field to favor the equatorial addition; this was confirmed experimentally.[6]

As shown in Figure 2, small geometrical distortions of the cyclohexanone ring are induced by fluoro substitution at the C_3 or C_4 positions. The O=C–C_2–H out-of-plane dihedral angle increases from 3° in cyclohexanone to 5° in 4-*eq*-fluorocyclohexanone (**16**) and 3-*eq*-fluorocyclohexanone (**18**). The ring is flattened by these fluoro substitutions. However, 4-*ax*-fluoro substitution has almost no effect on the geometry. The C–C_{sp^2}–C–C angles are more indicative of this ring flattening. The angle drops from 54.4° in cyclohexanone, **15**, to 52.9° and 52.2° in **16** and **18** with 4-*eq*- and 3-*eq*-fluoro substituents, respectively.

We have also optimized the structure of 5-fluoroadamantanone (**19**). This compound is related to the equatorial fluoro derivative (**16**) of cyclohexanone. There is also geometrical distortion in this adamantanone derivative. The top six-membered ring (with the fluoro substituent) is flatter than the bottom six-membered ring, as indicated by larger O=C–C–C dihedral angle (2.8°) and smaller C–C_{sp^2}–C–C dihedral angle (1.4°) of the top ring than those of the bottom ring. Accompanying this ring distortion, a small pyramidalization at the carbonyl carbon is also introduced by the fluoro substitution.

The C–C bonds geminal to the C–F bond in **16–19** are shorter than a normal CC bond by 0.015 Å; this bond contraction is commonly attributed to hyperconjugation.[39] It is well known that the Me/X geminal interaction in CH_3CH_2X, where X is F, OH, Cl, and NH_2, is stabilizing, and the C–C bond length in these species is shorter than the normal C–C bond length.[39a] This CC bond length shortening in the six-membered ring results in ring flattening. On the other hand, if the substituent is electron-donating, for example, $SiMe_3$, the geminal C–C bonds become longer. This enhances ring puckering. Therefore, electron-withdrawing substituents can increase axial addition, and electron-donating groups can reduce axial addition, merely by geometrical distortion, which shows up in the transition structures as altered torsional effects.

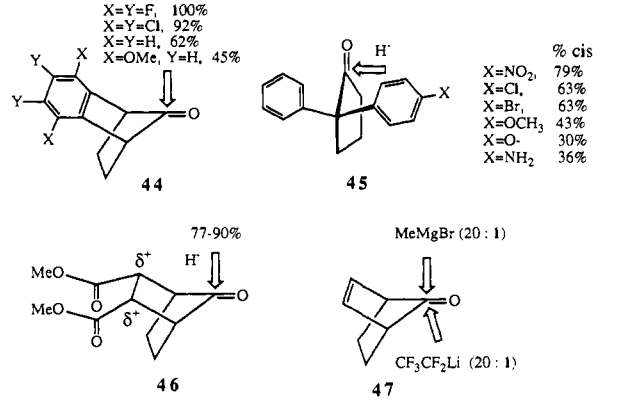
4. Remote Electrostatic Effects on Stereoselectivity. Why do axial electron-withdrawing substituents at C_4 of decalone cause noticeably larger increases in axial $NaBH_4$ addition than equatorial (Table I)? As noted, this result is not easily explained by the Cieplak model,[13] since an axial substituent has less effect on the electron-donating ability of the C_2C_3 and C_9C_{10} bonds than an equatorial substituent. We believe that electrostatic or dipole effects are responsible for this phenomenon. As shown in **41** and **42**, equatorial attack by the nucleophile is destabilized by a electrostatic repulsive interaction with the axial substituent, while axial attack is favored by the interaction. The strong orientational preferences of OH and NH_2 groups in the transition structures support this assessment.



The electrostatic effect on the ground state conformational preferences of 4-substituted-cyclohexanones have been well documented.[40,41] The 4-fluoro, chloro, and methoxy substituents on cyclohexanone are predominantly axial in nonpolar solvents, but the axial preference drops when the solvent becomes more polar. The conformational behavior can be calculated by classical Coulombic interactions.[42]

In the case of 3-substituted cyclohexanones (**6**) the calculational results for **20–28** can be directly applied to explain the variation in stereoselectivity. An electron-withdrawing substituent induces positive charge at C_3, which stabilizes a negatively charged nucleophile upon axial attack, as shown in **43**. Thus, the invocation of an anti-periplanar hyperconjugation effect is not necessary.[13,14]

The electrostatic effect is important in other systems as well. Okada et al. observed that reduction of **44** by $LiAlH_4$ in THF gave 62% syn addition products when X and Y are H. The syn addition increases to 92% and 100% when X and Y are Cl and F, respectively.[43] The anti addition becomes slightly favored when X is OMe. The fluoro and chloro substituents make the benzene ring relatively electron-poor, and the hydride in the syn addition transition structure is stabilized. The methoxyl group, on the other hand, increases electron density on the benzene ring, and introduces electrostatic repulsion for the hydride in the syn addition transition structure. The same argument can be applied to explain the variation of stereoselectivity of reduction of 2,2-diarylcyclopentanones (**45**) reported by Halterman et al.[44] The situation



in **46** is similar to that of 3-substituted cyclohexanones, and syn attack is stabilized by electrostatic interactions.[45] Another ex-

(38) Terasawa, T.; Okada, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1252.
(39) (a) For a general review, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Theory*; Wiley: New York, 1986; p 356 ff. (b) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467. (c) Schleyer, P. v. R.; Kos, A. J. *Tetrahedron* **1983**, *39*, 1141. (d) Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6393. Reed, A. R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 7362. (e) Wu, Y.-D.; Kirmse, W.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4557.

(40) Lichanot, A.; Grenier-Loustalot, M. F.; Loudet, M. *Theor. Chim. Acta* **1978**, *23*, 73. Lichanot, A.; Grenier-Loustalot, M. F.; Iratcabal, P.; Loudet, M.; Metras, F. *Theor. Chim. Acta* **1978**, *25*, 307.
(41) Baldry, K. W.; Gordon, M. H.; Hafter, R.; Robinson, M. J. T. *Tetrahedron* **1976**, *32*, 2589.
(42) Dosen-Micovic, L.; Jeremic, D.; Allinger, N. L. *J. Am. Chem. Soc.* **1983**, *105*, 1723.
(43) Okada, K.; Tomita, S.; Oda, M. *Tetrahedron Lett.* **1986**, *27*, 2645. and references therein.
(44) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690.
(45) Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140; *J. Chem. Soc., Chem. Commun.* **1991**, 18.

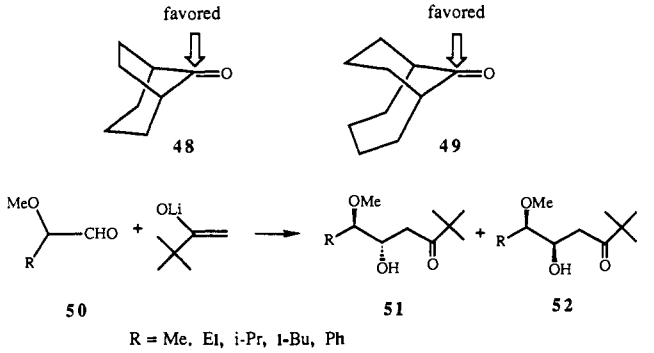
ample is the reaction of **47**. While the addition of methyl Grignard reagent occurs predominantly from the side of the C=C bond,[46] Gassman et al. observed that the addition of perfluoroethyllithium occurs preferentially from the opposite face of C=C bond.[47] The preferred anti addition in the latter case can be rationalized by strong electrostatic repulsion between the fluorines of the perfluoroethyl group and the π electrons of the double bond in the syn addition transition structure.[48]

5. C–C versus C–H Donating Ability. There is much evidence that C–C is better donor than C–H.[49] One example is the structure of the 1-propyl cation. Extensive calculations have concluded that the methyl-bridged structure is more stable than the hydrogen-bridged structure by 1.4 kcal/mol.[50] Schleyer and Liu have recently performed high level calculations on a variety of carbocations and concluded that nonclassical bridged cation structure is a general feature.[51] They found that in every case it is β–C–C which is involved in hyperconjugation bridging instead of β-C–H.[52,53]

We suggest that the pyramidalization at carbonyl carbon reflects the electron-donating ability of allylic substituents.[54] As shown in Figure 4, the pyramidalization in the methyl perpendicular structure is 2.8°. It drops to 1.9° in the CH_2F perpendicular structure, and increases to 3.1° when the perpendicular group is CH_2SiH_3.[55] We also see that the pyramidalization caused by perpendicular CH_2F (**33**) is similar to perpendicular H (**29**). Since electron-donating ability is clearly in the order $CH_2F < CH_3 < CH_2SiH_3$, this indicates that C–CH_3 is a better donor than C–H. This is also supported by relative energies of these conformations as discussed before.

It has been well established that electron-withdrawing substituents increase the rate of nucleophilic additions, and electron-donating substituents retard the rate of nucleophilic additions.[26,27] If C–H were a better donor than C–C, one would observe rate acceleration by methyl substituents at the C_2 and C_6 positions of cyclohexanone. Kinetic studies indicated that hydride reduction of 2,2-dimethylcyclohexanone by sodium borohydride is slower by a factor of ~4.4 than that of 2-methylcyclohexanone (corresponding to a 0.9-kcal/mol difference in activation energy).[27] Since the transition structure of axial attack is predominant for reaction of 2-methylcyclohexanone with the methyl group at the inside position (or equatorial), the factor of 4.4 decrease in reaction rate for 2,2-dimethylcyclohexanone is mainly due to the electronic destabilization caused by the additional anti methyl group (axial). Therefore, the methyl group is electron-donating and destabilizes the transition state.

6. Further Support of the Torsional Strain Model. The torsional strain model competently predicts the stereoselectivities of nucleophilic additions to bicyclic ketones. In these cases, Cieplak theory becomes awkward, because there are two C–C bonds on each side of the carbonyl, and steric effects must be invoked in order to rationalize the stereoselectivity.[14] The torsional model predicts stereoselectivities based on the flatness of the ring on the two sides. For example, nucleophilic additions to the 5/6 fused ketone (**48**) and 6/7 fused ketone (**49**) occur with preference for additions from the side of smaller ring, because it is flatter; consequently, torsional strain about the C_{CO}–C_α bond is smaller in the transition state.[56,57]



Although the Cieplak model frequently gives the correct prediction for the stereoselectivity of nucleophilic additions to cyclohexanone derivatives, it does not explain the stereoselectivity of nucleophilic additions to chiral acyclic carbonyl compounds. When the allylic chiral center bears an electron-withdrawing group such as OR and NR_2, the stereoselectivity is best explained by Felkin–Anh model, **2**, in which the electron-withdrawing group is antiperiplanar.[58-60] Such a model has been generally supported by theoretical calculations.[2,16,35,36] In particular, Heathcock et al. observed that the formation of erythro product (**51**) increases as the size of the alkyl group increases. They noted that Cieplak model would predict the opposite trend of stereoselectivity.[59]

Conclusion

We have designed additional experiments to show that remote polar substituents can have an effect on the stereoselectivity of nucleophilic additions to cyclohexanones. The observation that the 4-axial substituents have a considerably larger effect than the 4-equatorial substituents is explained by a remote electrostatic effect. The calculations strongly suggest that the preferential axial attack of hydride to cyclohexanone is due to torsional strain in the transition state of equatorial attack. With the combination of the torsional strain and electrostatic effects, all the experimental observations suggested to be explainable only by the Cieplak model can be rationalized.

In the absence of polar groups, nucleophilic (and indeed, radical and electrophilic) additions occur in such a fashion as to minimize

(46) Warentin, J. *Can. J. Chem.* **1970**, *48*, 1391.
(47) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481.
(48) For another explanation, see: Lin, M.-H.; Silver, J. E.; le Noble, W. J. *J. Org. Chem.* **1988**, *53*, 5155.
(49) Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 1189.
(50) Schleyer, P. v. R.; Raghavachari, K.; Whiteside, R. A.; Pople, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5649. Koch, W.; Liu, B.; Schleyer, P. v. R. *Ibid.* **1989**, *111*, 3479.
(51) Schleyer, P. v. R.; Laidig, K.; Wiberg, K. B.; Saunders, M.; Schindler, M. *J. Am. Chem. Soc.* **1988**, *110*, 300. Koch, W.; Liu, B.; DeFrees, D. J. *Ibid.* **1989**, *111*, 1527. Also see: Buffam, D. J.; Sorensen, T. S.; Whitworth, S. M. *Can. J. Chem.* **1990**, *68*, 1889.
(52) Several authors have recently expressed the possibility that C–H is better donor than C–C. However, some experimental observations can be also interpreted as C–C bridging (see ref 53): Kirchen, R. P.; Ranganayakulu, K.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7811. Finne, E. S.; Gunn, J. R.; Sorensen, T. S. *Ibid.* **1987**, 7816. Laube, T.; Ha, T.-K. *Ibid.* **1988**, *110*, 5511. Laube, T.; Stilz, H. U. *Ibid.* **1987**, *109*, 5876. Dutler, R.; Rauk, A.; Sorensen, T. S.; Whitworth, S. M. *Ibid.* **1989**, *111*, 9024.
(53) Schleyer, P. v. R.; Lenoir, D.; Mison, P.; Liang, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 683. Lenoir, D.; Hall, R. E.; Schleyer, P. v. R. *Ibid.* **1974**, *96*, 2138. Storesund, H. J.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1452. Nordlander, J. E.; Haky, J. E. *J. Am. Chem. Soc.* **1981**, *103*, 1518.
(54) This is just another description of the torsional explanation proposed previously: Jeffrey, G. A.; Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Mitra, J. *J. Am. Chem. Soc.* **1985**, *107*, 321. Houk, K. N.; Rondan, G. N.; Brown, F. K.; Jorgensen, W. L.; Madura, J. D.; Spellmeyer, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 5980. Houk, K. N.; Rondan, G. N.; Brown, F. K. *Isr. J. Chem.* **1983**, *23*, 3. Houk, K. N. In Stereochemistry and Reactivity of Systems Containing π Electrons; Watson, Ed.; Verlag Chemie: Deerfield Beach, FL, 1983; pp 1–40. For a recent review see: Borden, W. T. *Chem. Rev.* **1989**, *89*, 1095.
(55) The pyramidalizations caused by the perpendicular C–H and C–CH_3 in **29** and **33** were also calculated with the MP2/6-31G* basis set; they are 2.5° and 3.8°, respectively.
(56) Perlberger, J.-C.; Muller, P. *J. Am. Chem. Soc.* **1977**, *99*, 6316.
(57) Hahn, W. E.; Jatczak, M. *Pol. J. Chem.* **1979**, *53*, 1221.
(58) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629; **1985**, *107*, 8294.
(59) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.
(60) Reetz, M. T.; Rõhrig, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1706. Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem.* **1987**, *99*, 1186.. Reetz, M. T.; Drewes, M. W.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 3295.
(61) Preparation of 4-hydroxydecalones: Hückel, W.; Kraus, W. *Chem. Ber.* **1962**, *95*, 233.
(62) Preparation of fluoro compounds using diethylaminosulfur trifluoride: Miiddleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

eclipsing strain. Steric effects can also be influential.[3] This is the same as the principles governing conformations of nonpolar hydrocarbons. Polar substituents may influence the stereoselectivity of nucleophilic additions by orbital interactions as well as through-space electrostatic effects just as they can influence ground-state conformations.[3]

Experimental Section

***trans*-1-Decalone (7a)** was used as obtained from the Aldrich Chemical Co. The purity of this material was determined to be 99% by capillary GC analysis (SE-30 column). A control experiment demonstrated tha' the cis and trans isomers are well resolved under these analysis conditions.

(1*S*,5*S*,6*S*)*-5-Hydroxybicyclo[4.4.0]decan-2-one (7b) and (1*S*,5*R*,6*S*)*-5-hydroxybicyclo[4.4.0]decan-2-one (8b) were prepared by reducing decalin-1,4-dione with 0.25 molar equiv of sodium borohydride according to the procedure of Hückel.[61] After separating the two isomers by chromatography on alumina (5:1 petroleum ether/ethyl acetate), the equatorial isomer was freed of traces of the axial isomer by crystallization from cyclohexane. The axial isomer was freed of trace amounts of the equatorial isomer by a second chromatography (silica, 9:1 CH_2Cl_2/EtOAc). The purity of each isomer was established by TLC and ^1H NMR analysis (>98%).

(1*S*,5*S*,6*S*)*-5-Acetoxybicyclo[4.4.0]decan-2-one (7c). To a solution of 0.30 g (1.79 mmol) of equatorial ketol **7b** in 15 mL of CCl_4 were added 0.22 mL (2.68 mmol) of pyridine and 0.19 mL (2.68 mmol) of acetyl chloride. After 2 h the solution was washed twice with 50 mL of 0.5 N hydrochloric acid, then dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was dissolved in 2 mL of pentane. Cooling this solution to −20 C gave 0.33 g (88%) of the title compound as white crystals, mp 46–47 °C. The purity of this material was established by ^1H NMR, TLC, and capillary GC (SE-30 column) analysis: ^1H NMR ($CDCl_3$, 360 MHz) d 4.93 (d of t, J = 4.4, 10.8 Hz, 1 H), 2.50 (d of d of t, J = 1.1, 6.1, 14.3, 1 H), 2.45–2.35 (m, 1 H), 2.35–2.25 (m, 1 H), 2.14–2.05 (m, 1 H), 1.99 (s, 3 H), 2.02–1.93 (m, 2 H), 1.84–1.67 (m. 3 H), 1.65–1.52 (d of q, J = 2.0, 12.2, 1 H), 1.30–1.01 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) d 210.67, 171.56, 75.14, 51.85, 47.88, 39.28, 31.70, 30.83, 25.84, 25.80, 25.74, 21.98. High-resolution MS: Calcd for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1257 (M^+, 3%), 168 ($M^+ - C_2H_2O$, 22%), 150 ($M^+ - CH_3CO_2H$, 100%).

(1*S*,5*S*,6*S*)*-5-Chlorobicyclo[4.4.0]decan-2-one (7e). To a solution of 1.32 g (3.58 mmol) of trioctylphosphine in 50 mL of CCl_4 was added 0.300 g (1.79 mmol) of axial ketol **8b**. After refluxing 1 week the mixture was cooled and the solvent was evaporated in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O, and the organic phase was dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with 1:1 CH_2Cl_2/C_6H_{12} to give 90 mg of a colorless oil. This material was dissolved in 1.5 mL of pentanes and the solution was cooled to −15 °C. The resulting crystals were collected and recrystallized three more times in the same manner to give 37 mg (11%) of a white solid, mp 52–53 °C. This material was free (<1%) of isomeric impurities as indicated by ^1H NMR spectroscopy and capillary GC analysis (SE-30 column): R_f 0.48 (silica, CH_2Cl_2); ^1H NMR ($CDCl_3$, 360 MHz) d 3.95 (d of t, J = 3.9, 11.5, 1 H), 2.57–2.42 (m, 3 H), 2.40–2.32 (m, 1 H), 2.14–1.94 (m, 3 H), 1.86–1.74 (m, 2 H), 1.58 (d of q, J = 3.2, 10.9, 1 H), 1.29–1.01 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) d 209.20, 62.59, 52.94, 50.60, 40.39, 36.49, 31.85, 25.22, 25.14, 25.02. High-resolution MS: calcd for $C_{10}H_{15}ClO$: 186.0811. Found: 186.0808 (M^+, 22%), 188 ($M^+ + 2$, 5%), 151 ($M^+ - Cl$, 15%).

(1*S*,5*S*,6*S*)*-5-Bromobicyclo[4.4.0]decan-2-one (7d). To a mixture of 0.468 g (1.78 mmol) of triphenylphosphine and 0.592 g (1.78 mmol) of CBr_4 in 3 mL of toluene was added 0.150 g (0.89 mmol) of axial ketol **8b**. The solution turned bright yellow and a precipitate formed. The mixture was heated to 95 °C for a period of 5 min then cooled to 0 °C to give a clear solution and a sticky solid precipitate. The liquid was decanted and the solid was washed with 3 mL of 9:1 pentanes/CH_2Cl_2 twice. The combined supernatant and washes were directly (without prior evaporation of the solvent) chromatographed on 20 mL of silica gel eluting with 1:1 CH_2Cl_2/hexanes to give 67 mg of a colorless oil. This material was dissolved in 0.5 mL of pentanes. Cooling the solution to −20 °C gave 49 mg (24%) of a white solid, mp 69–70 °C: ^1H NMR, TLC, and capillary GC (SE-30 column) analysis of this material showed it to be free of isomeric impurities (<1%): R_f 0.64 (silica, 7:3 CH_2Cl_2/hexanes); ^1H NMR ($CDCl_3$, 360 MHz) d, 4.08 (d of t, J = 4.3, 10.9, 1 H), 2.70–2.63 (m, 1 H), 2.49–2.33 (m, 3 H), 2.25 (d of q, J = 6.5, 13.0, 1 H), 2.09–1.93 (m, 2 H), 1.85–1.75 (m, 2 H), 1.65 (d of q, J = 3.1, 11.3, 1 H), 1.31–1.02 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz) d 209.04, 55.53, 53.98, 51.04, 41.64, 37.54, 33.53, 25.44, 25.24, 25.15. High-resolution MS: Calcd for $C_{10}H_{15}BrO$: 230.0306. Found: 230.0310 (M^+, 20%), 232 ($M^+ + 2$, 19%), 151 ($M^+ - Br$, 28%).

(1*S*,5*R*,6*S*)*-5-Acetoxybicyclo[4.4.0]decan-2-one (8c). To a solution of 0.105 g (0.625 mmol) of axial ketol **(8b)** in 15 mL of CCl_4 were added 0.058 mL (0.812 mmol) of acetyl chloride and 0.076 mL (0.939 mmol) of pyridine. The mixture was refluxed 10 h, then cooled, and diluted with 15 mL of CH_2Cl_2 and 5 mL of 2 N hydrochloric acid. The phases were separated and the organic extract was washed with 5 mL of 2 N hydrochloric acid, then washed with brine. The solution was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was dissolved in 2 mL of pentanes. Cooling this solution to −15 °C gave 70 mg of (53%) white crystals, mp 57.5–58.5 °C. The ^1H NMR and TLC analysis of this material showed it to be free of isomeric impurities: R_f 0.55 (silica, 3:17 EtOAc/CH_2Cl_2); ^1H NMR ($CDCl_3$, 360 MHz) d 5.06 (q, J = 2.3, 1 H), 2.61 (d of t, J = 7.2, 14.0, 1 H), 2.47–2.38 (m, 1 H), 2.33–2.22 (m, 2 H), 2.16 (s, 3 H), 2.06–1.96 (m, 1 H), 1.88 (d of d of t, J = 2.5, 5.0, 14.4, 1 H), 1.83–1.59 (m, 4 H), 1.41–1.22 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) d 211.37, 170.54, 71.18, 48.52, 46.66, 36.43, 30.65, 29.52, 25.42, 25.02, 24.96, 21.12. High-resolution MS: Calcd for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1273 (M^+, 1.4%), 150 ($M^+ - CH_3CO_2H$, 100%).

(1*S*,5*R*,6*S*)*-Fluorobicyclo[4.4.0]decan-2-one (8f). To a −78 °C solution of 0.236 mL (1.79 mmol) of diethylaminosulfur trifluoride[62] in 10 mL of CCl_3F was added 0.300 g (1.79 mmol) of equatorial ketol **(7b)**. The mixture was maintained at −78 °C for 5 min, then warmed to 0 °C. The mixture was diluted with 5 mL of H_2O, then with 10 mL of CH_2Cl_2. The phases were separated and the organic phase was dried ($MgSO_4$). The solvent was evaported in vacuo and the residue was chromatographed on silica gel eluting with 1:1 C_6H_{12}/CH_2Cl_2. The resulting oil was crystallized by dissolving it in 2 mL of hexanes and cooling the solution to −20 °C. The recovered product is a white solid (40 mg, 13% overall yield), mp 41–43 °C. ^1H NMR and capillary GC (SE-30 column) analysis of this material showed it to be free of isomeric impurities. R_f 0.48 (silica, CH_2Cl_2); ^1H NMR ($CDCl_3$, 200 MHz) d 4.68 (d, J_{H-F} = 48, 1 H), 2.71 (d of t, J = 6.2, 14.4, 1 H), 2.55–2.23 (m, 3 H), 2.09–1.90 (m, 2 H), 1.90–1.49 (m, 5 H), 1.37–1.12 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) d 211.25, 90.84 (d, J_{C-F} = 171), 48.02, 47.29, 36.04, 31,25, 29.29, 25.73, 25.65, 24.99. High-resolution MS: Calcd for $C_{10}H_{15}FO$: 170.1107. Found: 170.1106 (M^+, 100%), 132 ($M^+ - HF - H_2O$, 54%).

(1*S*,5*R*,6*S*)*-5-Chlorobicyclo[4.4.0]decan-2-one (8e). To a solution of 0.62 g (2.37 mmol) of triphenylphosphine in 100 mL of CCl_4 was added 0.422 g (2.15 mmol) of equatorial ketol **(7b)**. After refluxing 48 h, the mixture was cooled to 25 °C and 100 mL of H_2O was added. The phases were separated, and the organic phase was dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with 1:1 CH_2Cl_2/C_6H_{12} to give a colorless oil. The ^1H NMR of this oil revealed the presence of a 95:5 mixture of axial chloride **8e** and equatorial chloride **7e**. This material was dissolved in 2 mL of petroleum ether and the solution was cooled to −20 °C. After 24 h, 0.12 g (30%) of white crystals, mp 62–63 °C, were collected by filtration. Analysis of this material by ^1H NMR showed no detectable amount (<2%) of the corresponding equatorial isomer: R_f 0.28 (silica, 1:1 hexanes/CH_2Cl_2); ^1H NMR ($CDCl_3$, 360 MHz) d 4.30 (d, J = 2.3, 1 H), 2.85 (d of t, J = 6.2, 14.6, 1 H), 2.52–2.42 (m, 1 H), 2.41–2.27 (m, 2 H), 2.17 (t of t, J = 3.6, 14.5, 1 H), 2.05–1.97 (m, 1 H), 1.81–1.58 (m, 5 H), 1.27–1.14 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) d 210.62, 63.11, 48.29, 47.75, 36.15, 34.68, 31.07, 25.33, 24.92, 24.76. High-resolution MS: calcd for $C_{10}H_{15}ClO$: 186.0811. Found: 186.0811 (M^+, 60%), 188 ($M^+ + 2$, 16%), 151 ($M^+ - Cl$, 78%).

Reductions of Substituted Decalones. The procedure used for the reduction of the equatorial 4-acetoxydecalone (**7c**) is representative. Sodium borohydride (0.145 g, 3.81 mmol) was added to 5 mL of vigorously stirred CH_3OH. As soon as $NaBH_4$ completely dissolved (20–30 s) a solution of 0.100 g (0.476 mmol) of **7c** in 4 mL of CH_3OH was added in one portion. After 24 h, 2 mL of H_2O was added followed by 3.2 mL of 3 N hydrochloric acid. The mixture was stirred 2 min, then poured into a mixture of 50 mL of brine, 2.0 mL of 5.0 N NaOH, and 35 mL of ether. A small amount of precipitate formed which redissolved upon addition of 2 mL of H_2O. The phases were separated and the aqueous phase was washed four times with 10 mL of ether. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure to yield 0.096 g of a colorless oil. To a solution of this oil in 10 mL of CCl_4 were added 0.100 mL of acetic anhydride and 200 mg of 4-(dimethylamino)pyridine. After stirring 18 h, the solution was washed with 2 mL of 3 N hydrochloric acid. The aqueous phase was washed three times with 10 mL of CCl_4; then the combined organic extracts were washed with 5 mL of brine. The solution was dried ($MgSO_4$). The TLC of the reaction mixture at this point showed that no acetate hydrolysis had occurred during the isolation procedure. The

^{1}H NMR ($CDCl_3$, 360 MHz) of this mixture showed a doublet (J = 2.1) at d 4.86 and a complex multiplet at d 4.44-4.57 ppm. The integrated areas of these peaks were in the ratio 5.76:1, corresponding to a 70:30 ratio of axial to equatorial attack. Capillary GC analysis (DB-17 column) revealed the presence of two products in the ratio 69:31. In the cases of substrates other than **7c** and **8c**, the ratio of equatorial to axial products was determined by ^{1}H NMR analysis of the reduction product mixture prior to acetylation. The ratios determined in this way were in good agreement with those determined by capillary GC analysis after acetylation.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research, to Reza Goharderakhshan for technical assistance, and to Professor Michael N. Paddon-Row for helpful discussions and exchanges of unpublished results.

Molecular Dynamics of B-DNA Including Water and Counterions: A 140-ps Trajectory for d(CGCGAATTCGCG) Based on the GROMOS Force Field

S. Swaminathan,† G. Ravishanker, and D. L. Beveridge*

Contribution from the Chemistry Department, Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06457. *Received November 13, 1990*

Abstract: A theoretical study of the dynamical structure of the DNA dodecamer d(CGCGAATTCGCG) based on 140 ps of molecular dynamics simulation including water and counterions is reported. The simulation involved the dodecamer and 1927 water molecules and 22 Na^+ counterions treated under periodic boundary conditions in a hexagonal prism elementary cell. The force field for the simulation is GROMOS supplemented with a restraint potential for maintaining Watson-Crick base pairing. Extensive Monte Carlo equilibration of the solvent was necessary to prepare the system in a suitable state to perform a stable dynamical trajectory. The structure at the termination of the trajectory resides clearly in the B-DNA family, 2.3 Å root-mean-square deviation from the corresponding canonical form. The analysis of the simulation reveals good accord with a number of features seen in the X-ray crystal structure of the dodecamer, including local axis deformation near the GC/AT interfaces in the sequence and large propeller twist in the base pairs. The narrowing of the minor groove in the AT region of the crystal structure is not observed over the time course of the simulation, but it may be a crystal-packing effect. The DNA base pairs show a consistent inclination in the simulation, in accord with the interpretation of results obtained from flow dichroism studies of DNA in solution. A comparison of the calculated dynamical structure with a recently proposed NMR structure of the dodecamer in solution is provided. In an additional simulation carried out without the Watson-Crick restraint function, more pronounced axis deformations and base pair openings are observed. A corresponding in vacuo simulation shows that explicit inclusion of the water molecules is necessary to properly support the major and minor groove structure of the DNA helix.

I. Introduction

Molecular dynamics (MD) simulation is a powerful theoretical and computational approach to the study of the structure and molecular motions of macromolecules,[1] and several free dynamics simulations have now been reported for DNA[2-11] and RNA[12] systems. The MD method together with a prescription for the molecular force field, a means of treating hydration and ion atmosphere effects, and a particular simulation protocol combine to produce a "dynamical model" of a DNA oligonucleotide on a picosecond level time scale. An accurate dynamical model for DNA can provide a general theoretical basis for understanding sequence-dependent fine structure and flexibility in DNA, and for subsequent studies of important drug-DNA and protein-DNA interactions. The issue currently at hand is the stability and accuracy of the various possible dynamical models of DNA obtained from MD simulation.

The treatment of environmental effects in the simulation differentiates dynamical models into two broad classes: in vacuo and solvated models. In vacuo models leave out explicit consideration of water and in some cases counterions as well. Some of the effect of water can be reintroduced by means of a distance-dependent dielectric screening of coulombic terms in the force field. counterions are included either explicitly[4] or implicitly by use of either reduced coulombic charges on the anionic phosphates of the DNA backbone[2,3] or a salt-dependent potential of mean force between phosphates.[13] The net dimensionality of the problem is thus considerably reduced in an in vacuo simulation model, and the calculations become feasible in a computer workstation environment. However, in the absence of water the model structure typically undergoes a contraction. Distortions affecting particularly residues on the surface, only a small fraction of a globular protein but nearly *all* of a DNA molecule, are also a possible problem.

The solvated models include water and counterions explicitly in the simulation, and thus provide a more realistic physical

† Present address: Pharmaceutical Research and Development Division, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 96492.

(1) McCammon; A. J.; Harvey, S. C. *Dynamics of Proteins and Nucleic Acids*; Cambridge University Press: Cambridge, 1986.
(2) Levitt, M. *Cold Spring Harbor Symp. Quant. Biol.* **1983**, *47*, 251.
(3) Tidor, B.; Irikura, K. K.; Brooks, B. R.; Karplus, M. *J. Biomol. Struct. Dyn.* **1983**, *1*, 231.
(4) Singh, U. C.; Weiner, S. J.; Kollman, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 755.
(5) Siebel, G. L.; Singh, U. C.; Kollman, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6537.
(6) Van Gunsteren, W. F.; Berendsen, H. J.; Guersten, R. G.; Zwinderman, H. R. *Ann. N. Y. Acad. Sci.* **1986**, *482*, 287.
(7) Westhof, E.; Chevrier, B.; Gallion, S. L.; Weiner, P. K.; Levy, R. M. *J. Mol. Biol.*, **1986**, *190*, 699.
(8) Swamy, K.; Clementi, E. *Biopolymers* **1987**, *26*, 1901.
(9) Ravishanker, G.; Swaminathan, S.; Beveridge, D. L.; Lavery, R.; Sklenar, H. *J. Biomol. Struct. Dyn.* **1989**, *6*, 669.
(10) Srinivasan, J.; Withka, J. M.; Beveridge, D. L. *Biophys. J.* **1990**, *58*, 533.
(11) Zielinski, T. J.; Shibata, M. *Biopolymers* **1990**, *29*, 1027.
(12) Prabhakaran, M.; Harvey, S. C.; Mao, B.; McCammon, J. A. *J. Biomol. Struct. Dyn* **1983**, *1*, 357.
(13) Klement, R.; Soumpasis, D. M.; Kitzing, E. V.; Jovin, T. M. *Biopolymers* **1990**, *29*, 1089.

0002-7863/91/1513-5027$02.50/0