Structure Distortions in Heteroatom-Substituted Cyclohexanones, Adamantanones, and Adamantanes: Origin of Diastereofacial Selectivity

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Received August 1, 1998 (Revised Manuscript Received February 11, 1999)

Contents

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I. Introduction

A. Concerning the Origin of Stereoselectivity in Nucleophilic Addition Reactions to Substituted Cyclohexanones

In nucleophilic additions to conformationally locked cyclohexanones, either equatorial attack (to give the axial alcohol) or axial attack (to give the equatorial alcohol) can occur; see Figure 1. Axial attack of nucleophiles on cyclohexanone is favored when steric hindrance is negligible.[1] Experimentally it has been

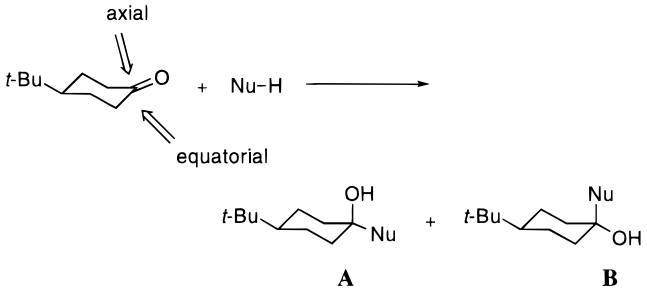

Figure 1. Nucleophilic addition to 4-*tert*-butylcyclohexanone. Either equatorial attack (to give the axial alcohol A) or axial attack (to give the equatorial alcohol B) can occur.

shown that small nucleophiles (such as $LiAlH_4$ and $NaBH_4$) preferentially add to unhindered cyclohexanones from the axial side to give equatorial alcohol.[2] In contrast, sterically demanding nucleophiles add from the equatorial side to give axial alcohol. Equatorial attack also predominates in ketones where axial approach is blocked by 3- and 5-axial substituents, such as in the case of 3,3,5-trimethyl-cyclohexanone.

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Published on Web 04/03/1999

Regarding the origin of the observed selectivity, there is general agreement that preferential equatorial attack by bulky reagents or with hindered ketones is due to steric interference on the axial side.[3] However, various hypotheses have been proposed to account for the fact that small nucleophiles add to unhindered ketones from the axial side. For example, "product development control" was suggested to explain the fact that axial attack produces the (more stable) equatorial alcohol in each case.[3] On the basis of frontier molecular orbital theory, several groups suggested the distortion of the carbonyl π and π^* orbitals to account for preferential axial attack.[4−9] That is, unequal distribution of electron or orbital density on the two faces of the carbonyl group leads to stereoselective attack. Force field models were developed that support the notion that stereoselectivity arises from a combination of torsional and steric effects.[10,11] The steric approach−product stability control hypothesis was further developed to equate the difference in activation energies ($\Delta\Delta G^{\ddagger}$) between formation of axial and equatorial alcohols with a linear combination of product stability (Δn) and steric strain ($\Delta\sigma$) terms: $\Delta\Delta G^{\ddagger} = a\Delta n + b\Delta\sigma$ (a and b are constants).[12]

B. The Felkin–Anh Model

However, the most widely accepted model is the so-called "Felkin−Anh" model, which is based on a combination of studies published by both Felkin[13] and Anh (Figure 2).[6] Felkin suggested that the preference

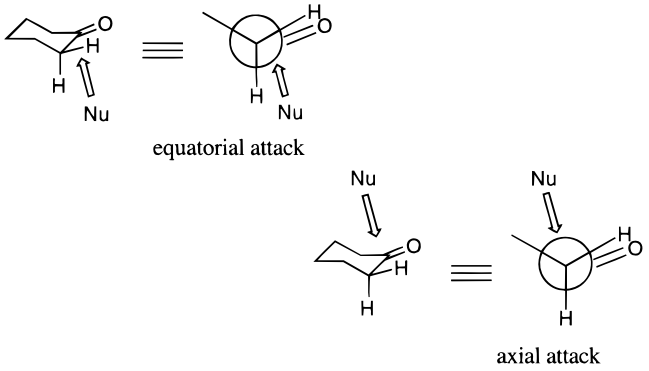


Figure 2. The Felkin−Anh model: the preference for axial attack on unhindered cyclohexanones is due to greater torsional strain in the transition state for equatorial attack.[13]

for axial attack on unhindered cyclohexanones is due to greater torsional strain in the transition state for equatorial attack.[13] Attack on the carbonyl group along any chosen trajectory is more "eclipsed" from the equatorial direction. Anh and Eisenstein carried out calculations that generally support the Felkin model, but these authors also emphasized the importance of another factor, namely attack antiperiplanar to a vicinal bond.[6] The basis for this geometric requirement is electronic in origin. The transition state is stabilized in this arrangement by delocalization of electron density from the nucleophile to the antibonding orbital of the antivicinal bond. This view implies that the transition state is electron-rich.

C. The Cieplak Hypothesis

The Felkin−Anh model has received widespread acceptance among organic chemists and is often cited to rationalize stereochemical results.[14] At least two advanced textbooks have adopted the Felkin−Anh model.[15,16] However, in 1981, Cieplak challenged the Felkin−Anh model and proposed a conceptually different hypothesis.[17,18] The Cieplak model can be summarized in one statement: nucleophilic additions to a carbonyl group occur preferentially in the direction antiperiplanar to the best electron-donor vicinal bond, and a C−H bond is a better donor than a C−C bond (Figure 3).[17] Thus, "the stereochemistry of

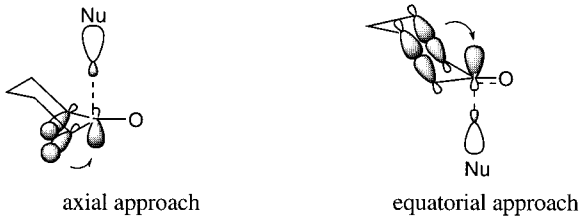


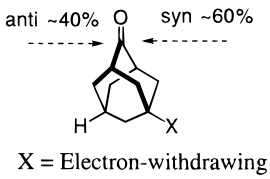
Figure 3. The Cieplak hypothesis: electron donation from the cyclohexanone σ_{CC} and σ_{CH} bonds into the $\sigma^*_{\neq}$ orbital favors axial approach because carbon−hydrogen bonds are better electron donors.

nucleophilic addition to 4-*tert*-butylcyclohexanone is proposed to result from a superposition of two effects: steric hindrance, which favors the equatorial approach, and electron donation from the cyclohexanone σ_{CC} and σ_{CH} bonds into the $\sigma^*_{\neq}$ (the antibonding orbital of the forming bond Nu−C) orbital, which favors the axial approach because the carbon−hydrogen bonds are better electron donors."[17]

The Cieplak theory has stimulated many groups to design model systems to examine its merit.[18] Among its supporters, le Noble and co-workers have reported studies using substituted adamantanones as sterically unbiased models. The next two sections introduce briefly these studies and their interpretations.

D. 5-Substituted Adamantanones as Sterically Unbiased Model Cyclohexanones

To study the validity of the Cieplak proposal, le Noble's group chose to separate the complicating factors, such as steric effect and torsional strain, from the hyperconjugative effects. The rigid structure of adamantanone can be viewed as two cyclohexanones sharing one carbonyl group. On the basis of the cage structure, substituted adamantanones are considered free of steric and torsional bias to either side of the carbonyl group.[19−28] le Noble and co-workers in 1986 published results of hydride reduction of 5-substituted-2-adamantanones and of solvolysis of 2-adamantyl substrates.[22]



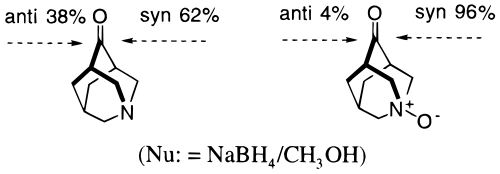
X = Electron-withdrawing group

The stereoselectivity observed for these rigid molecules was rationalized using the Cieplak model.[22] The widely accepted Felkin−Anh model would predict stereochemistry opposite to that observed. However, alternative explanations invoking electrostatic effects have been subsequently reported.[29−34]

The Cieplak model was extended by le Noble to explain many other observations, such as the nucleophilicity of the reagent group, solvent effects, and the direction of approach in electrophilic addition of carbocations, carbenes, and alkylating agents to olefins and enolates.[19−28] Is it possible that a universally applicable theory has been found, or are there other possible explanations for the reactions of adamantanone derivatives?

E. 5-Heteroatom-Substituted Adamantanones Give Dramatically Increased Diastereofacial Selectivity

The π-facial selectivity observed in many experiments involving substituted adamantanones is in the range of ~60/40 (syn:anti),[19−26] which has been rationalized in terms of either the hyperconjugative model or an electrostatic effect.[29−34] In 1992, the results from the reduction of 5-azaadamantanone derivatives were reported, and the π-facial selectivity reached 96/4 (syn:anti) in the case of 5-azaadamantanone *N*-oxide.[27] The result of the observed high



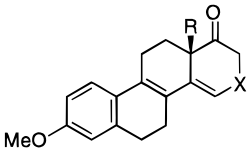
diastereofacial selectivity was described as an excellent example of the Cieplak model in operation. The Cieplak effect, like the Anh model, is stereoelectronic in origin. Normally, steric and electrostatic effects are dominant factors in diastereoselectivity. Is it likely that a stereoelectronic factor alone gives such high diastereofacial selectivity?

Is it possible that a nitrogen atom substitution distorts the C_{2v} symmetry of the adamantanone? We reported in 1994 the structures of 5-azaadamantanone and its *N*-oxide calculated by ab initio molecular orbital (MO) methods,[36] and we showed that these structures are not symmetrical according to ab initio MO theory. In this review, we first (section II) give a summary of previously observed distortions in heteroatom-substituted cyclohexanones which lead to variations in axial/equatorial attack. Computational studies from our own group are summarized in section III, including a brief account of the structures of 4-heteroatom-substituted cyclohexanones and 5-azaadamantanones. These are followed by new results describing a boron atom substitution in the adamantane system, which also causes distortion in the adamantane structure. The substitution of a positively charged nitrogen atom and a negatively charged boron atom distorts the adamantane structure in the opposite direction. In short, structure distortions are an important factor that can cause stereoselectivity variations in nucleophilic additions to heteroatom-substituted cyclohexanones and adamantanones.

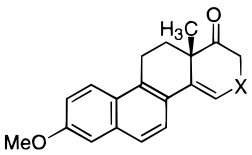
II. Experimental Studies of Nucleophilic Additions to Heteroatom-Substituted Cyclohexanones

A. Stereochemistry in the Reduction of Oxa- and Thia-Substituted Steroid Ketones

More than 20 years ago, Terasawa and Okada observed a substantial change in the stereochemistry of lithium aluminum hydride ($LiAlH_4$) reduction of steroid ketones (**1**−**8**) upon the introduction of a heteroatom in the ring.[37] The thia-ketones gave the

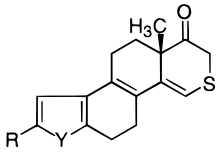


1 R = Me
2 R = Et

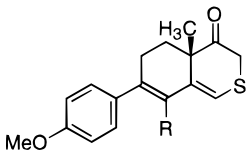


3

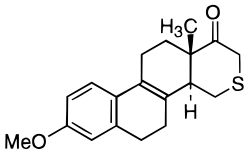
a: X = S
b: X = O



4 R = H, Y = S
5 R = Me, Y = O



6 R = H
7 R = Et



8

α-alcohol (hydroxyl group is trans to the methyl group) preferentially while the oxa-ketones afforded the β-alcohol (hydroxyl group is cis to the methyl group) exclusively. The results from the thia-ketones were inconsistent with the general observation that steroid ketones usually gave β-alcohols upon hydride reduction. To explore this observation, the authors conducted a thorough investigation by using a variety of hydride reagents and reaction conditions (Table 1).[37] The stereoselectivity of the reduction was found to be unaffected by solvents and temperatures. All thia-ketones except **2** retained a distinct preference for the production of the α-alcohols while the oxa-ketones gave β-alcohols. The preference for thia-ketones to give the α-alcohols was not limited to the unsaturated ketones. The saturated ketone **8** also gave predominantly α-alcohols.

To explain their observations, the authors considered a number of factors that might cause the difference between the thia- and the oxa-ketones. First, a possible metal chelate complex between the sulfur atom and the hydroxyl group of the product was thought to direct the reduction.

They next considered the possibility that an electronic effect from the sulfur atom might change the stereochemistry. The carbonyl infrared frequencies

Table 1. Stereochemical Outcome of Hydride Reduction of Steroid Ketones 1−8[37]

ketone	hydride	conditions[a]	α-OH/ β-OH	yield (%)
1a	$LiAlH_4$	THF (rt)	4.4:1	92.6
	$NaBH_4$	MeOH (0−5 °C)	2.5:1	96.3
	$LiAlH(t\text{-}BuO)_3$	THF (rt)	2.7:1	97.6
	$LiAlH(MeO)_3$	THF (0−5 °C)	2.0:1	86.0
	$NaAlH_2(OCH_2CH_2OCH_3)_2$	PhH (rt)	1:2.9	87.9
2a	$LiAlH_4$	THF (rt)	1:6.1	92.1
	$NaBH_4$	EtOH−THF (rt)	2.5:1	96.3
	$NaAlH_2(OCH_2CH_2OCH_3)_2$	PhH (rt)	1:19.5	89.8
1b	$LiAlH_4$	THF (rt)	β-OH only	70.5
2b	$LiAlH_4$	THF (rt)	β-OH only	89.7
3a	$LiAlH_4$	THF (rt)	1.4:1	88.0
3b	$LiAlH_4$	EtOH−THF (rt)	β-OH only	70.5
4	$NaBH_4$	EtOH−THF (rt)	2.3:1	85.9
5	$NaBH_4$	EtOH−THF (rt)	2.2:1	70.5
6	$LiAlH_4$	THF (rt)	1.4:1	88.0
	$NaBH_4$	MeOH (rt)	1.9:1	98.3
7	$LiAlH_4$	THF (rt)	1.9:1	49.0
8	$LiAlH_4$	THF (rt)	3.2:1	87.4
	$NaAlH_2(OCH_2CH_2OCH_3)_2$	PhH−THF (rt)	1.3:1	96.7

[a] Note: rt = room temperature.

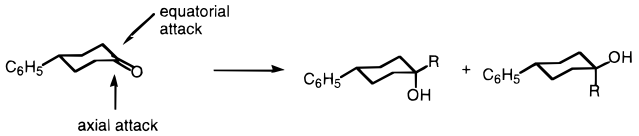
of the thia-ketones and the oxa-ketones were measured in solvents of various polarity. No clear evidence was uncovered for an electronic effect from the sulfur atom. Furthermore, no evidence of a metal chelate complex was found. It appears that steric effect is more important. Therefore, the chelation hypothesis and electronic effects were not supported by experimental facts.

Finally, by examining the Dreiding model of the molecules involved, the authors uncovered deformation in the structure of the heteroatom-substituted ketones. The introduction of a sulfur atom distorts the ring structure to a greater extent relative to an oxygen atom. The deformation alters the ring geometry to bend the carbonyl oxygen down (the ring becomes more puckered). The spatial environment around the carbonyl group was described by estimated dihedral angles. The steric requirement in the oxa-ketones favors hydride attack from the α-side (axial attack), leading to equatorial alcohols. On the other hand, a sulfur atom substitution makes the ring more puckered, and the thia-ketones favor hydride attack from the β-side (equatorial attack), leading to axial alcohols. Thus, the six-membered ring is flattened by an oxygen atom substitution and the presence of a double bond while the ring is made more puckered by a sulfur atom substitution. The authors explained the observations in terms of C−O and C−S bond lengths and C−O−C and C−S−C bond angles.

B. Stereoselectivity of Nucleophilic Additions to 4-Phenyl-cyclohexanone (9), 2-Phenyl-1,3-dioxan-5-one (11), and 2-Phenyl-1,3-dithian-5-one (13)

Jochims and associates conducted a study of nucleophilic additions to 2-phenyl-1,3-dioxan-5-one (**11**, Table 3), 2-phenyl-1,3-dithian-5-one (**13**, Table 4), and 4-phenyl-cyclohexanone (**9**, Table 2).[38] This is an excellent study in terms of comparisons of a substitution by oxygen and sulfur atoms in the structure of

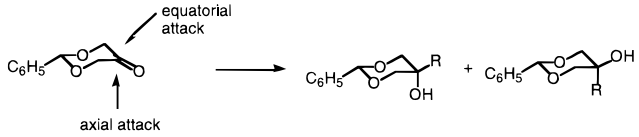
Table 2. Products from Nucleophilic Additions to 4-Phenylcyclohexanone (9)[38]



9 **10a** **10e**

nucleophile	% **10a**	% **10e**
$LiAlH_4$	4	96
CH_3MgI	48	52
C_2H_5MgI	52	48
$(CH_3)_2CHMgI$	60	40

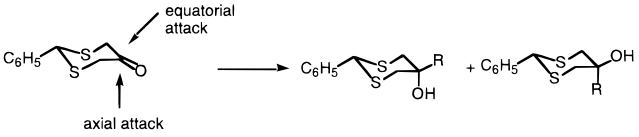
Table 3. Products from Nucleophilic Additions to 2-Phenyl-1,3-dioxan-5-one (11)[38]



11 **12a** **12e**

nucleophile	% **12a**	% **12e**
$LiAlH_4$	6	94
CH_3MgI	0.3	99.7
C_2H_5MgI	2	98
C_2H_5MgBr	3	97
$(CH_3)_2CHMgI$	4	96
$(CH_3)_2CHMgBr$	10	90

Table 4. Products from Nucleophilic Additions to 2-Phenyl-1,3-dithian-5-one (13)[38]



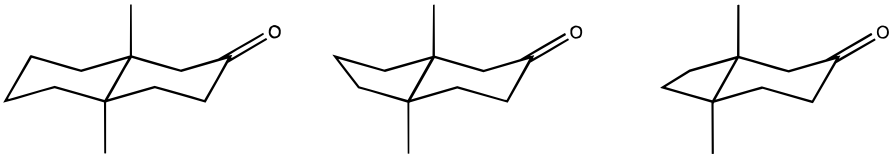
13 **14a** **14e**

nucleophile	% **14a**	% **14e**
$LiAlH_4$	85	15
CH_3MgI	93	7
C_2H_5MgI	89	11
$(CH_3)_2CHMgI$	91	9

cyclohexanones and the consequences of the resulting structure distortion on the stereochemistry of nucleophilic additions. They reported that nucleophiles such as $LiAlH_4$ and Grignard reagents add to 2-phenyl-1,3-dioxan-5-one (**11**) through axial attack regardless of their steric size, leading to equatorial alcohols. In sharp contrast, the same nucleophiles add to 2-phenyl-1,3-dithian-5-one (**13**) exclusively through equatorial attack independent of steric size, leading to axial alcohols. The stereoselectivity that was observed for nucleophilic additions to 4-phenylcyclohexanone (**9**) was intermediate between these two extremes for the Grignard reagents. Small nucleophiles such as $LiAlH_4$ add to 4-phenylcyclohexanone (**9**) through axial attack to give equatorial alcohols, while larger nucleophiles gave axial alcohols through equatorial attack.

While the stereochemistry of nucleophilic additions to 4-phenylcyclohexanone was normal in comparison to other substituted cyclohexanones, the results from

Chart 1



Percentage of axial attack:			
$LiAlH_4$	85%	90%	94%
$NaBH_4$	88%	90%	94%
MeMgI	32%	43%	55%

the dioxanone and the dithianone were surprising. Products of opposite stereochemistry were obtained for the oxygen- and the sulfur-substituted cyclohexanones, respectively. These results were explained in terms of Felkin's torsional strain model for **11** and **13** and in terms of torsional strain plus steric interactions for cyclohexanone **9**.

The authors examined the axial and equatorial attacks on each compound using Newman projections (Figures 4 and 5). The axial attack on 1,3-dioxan-5-

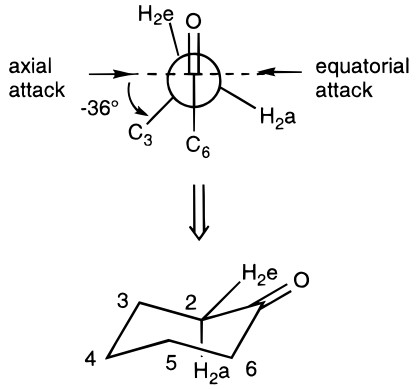


Figure 4. Newman projection of cyclohexanone looking along the C_1-C_2 bond.

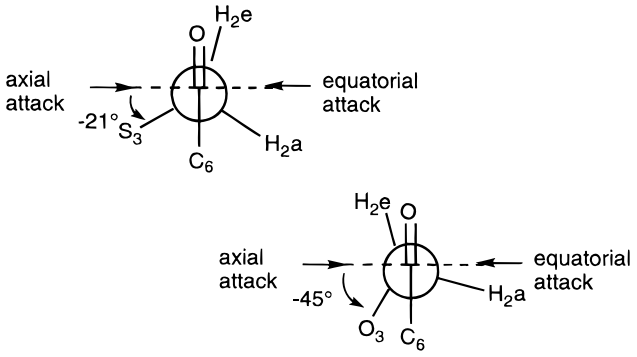


Figure 5. Newman projections of 1,3-dithian-5-one (**13**) and 1,3-dioxan-5-one (**11**) looking along the C_5-C_4 bond.

one (**11**) enjoys a staggered conformation while the equatorial attack suffers a torsional strain between the incipient bond and the C_2-H_{axial} bond. On the contrary, the axial attack on 1,3-dithian-5-one does not enjoy a complete staggered conformation and the corresponding equatorial attack suffers a minimal amount of torsional strain. The dihedral angles depicted in the Newman projections were based on examination of an X-ray structure of the 1,3-dithian-5-one.[38] The dihedral angle of $C_6-C(O)-C_2-X_3$ (X = C, O, or S) increases from X = O (1,3-dioxan-5-one), through X = C (cyclohexanone), to X = S (1,3-dithian-5-one). This dihedral angle is an indication of the flatness of the rings. The smaller the angle is, the flatter the ring is. Therefore, the conclusion from this study of stereoselectivity for the three compounds is that more axial attack occurs on the flatter rings. A related theoretical study by Wu and Houk is in support of this analysis.[39]

C. Stereochemistry in Nucleophilic Additions to Other Distorted Cyclohexanones

Many other cyclohexanones with structure distortion but without a heteroatom substitution were also studied with respect to the stereochemical course of nucleophilic additions. One of the studies that follows the ring flattening rule was reported by Casadevall and Pouet,[40] who carried out nucleophilic additions on fused cyclohexanones with the results that are summarized in Chart 1. Each of the three compounds is a cyclohexanone fused with a ring at the C_3-C_4 positions. The fused rings are six-, five-, and four-membered cycles. The increasing flatness of the adjacent ring forces the attached cyclohexanone ring to become increasingly flat as well. As a result, increasingly more axial attack by nucleophiles should occur, and this was indeed observed. More puckered rings are preferentially attacked from the equatorial side.

III. Computational Study of Distortions in Heteroatom-Substituted Cyclohexanone, Adamantanone, and Adamantane

A. Structure Distortion in 4-X Cyclohexanones

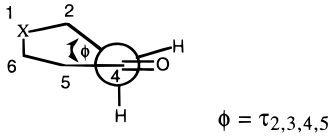
An adamantane structure is simply two cyclohexane rings joined together by a methylene group at the fourth carbon. It is therefore helpful to examine the substitution of a carbon atom by a heteroatom in a cyclohexanone ring before we investigate the adamantane system. The following is a summary of what we reported in 1994 about the influence of a heteroatom substitution on the conformation of the 4-X-cyclohexanones.[36b] The calculated total and relative energies (in parentheses) for the chair and the twist conformers and the ring inversion barrier of cyclohexanone, tetrahydropyran (THP), and 2-hydroxy-4-tetrahydropyranone (THPN) are listed in Table 5 along with the experimental values where they are available.

For convenience of the discussion, the endocyclic torsional angle ϕ, which has direct consequence on π-facial selectivity, is defined as shown below. It

Table 5. Gaussian 92 Computed Energies, au (kcal/mol)[36b]

conformation	3-21G//3-21G	6-31G*//3-21G	6-31G*//6-31G*	expt (kcal/mol)[41,42]
		Cyclohexanone		
chair	−306.1916217 (0.00)	−307.9045971 (0.00)	−307.9059163 (0.00)	0.0
twist	−306.1852887 (3.97)	−307.8985319 (3.81)	−307.8997880 (3.85)	
barrier	−306.1826603 (5.62)	−307.8985633 (3.79)	−307.8995844 (**3.97**)	4.0 ± 0.1
		Tetrahydropyran (**THP**)		
chair	−268.5256008 (0.00)	−270.0154349 (0.00)	−270.0179072 (0.00)	0.0
twist	−268.5175789 (5.03)	−270.0056675 (6.13)	−270.0084758 (5.92)	
barrier	−268.5079881 (11.05)	−269.9991809 (10.20)	−270.0016963 (**10.17**)	10.1 ± 1.2
		2-Hydroxy-4-THPN (**4**)		
chair				
(axial-OH)	−416.2509141 (0.00)		−418.5789945 (0.00)	
(eq-OH)	−416.2454384 (3.44)		−418.5767289 (1.42)	
twist	−416.2453278 (3.51)		−418.5746557 (2.72)	
barrier				
(eq-OH)	−416.2375006 (8.42)		−418.5713429 (4.80)	
(axial-OH)	−416.2443783 (4.10)		−418.5743297 (**2.93**)	

involves the four consecutive carbon atoms around the carbonyl carbon.



To explore the relationship between the endocyclic torsional angle ϕ and the bond lengths C−X in a 4-X-cyclohexanone, we have carried out ab initio calculations on the nitrogen and sulfur analogues of 4-THPN (Table 6). The bond lengths are in the order of C−O < C−N < C−C < C−S, and the flattening of the ring is in the same order: 4-THPN (ϕ = 44.5°) < 4-piperidinone (ϕ = 47.1°) < cyclohexanone (ϕ = 49.1°) < 4*H*-thiopyran-4-one (ϕ = 53.6°). Thus the 4-THPN with the shortest bond (C−O = 1.40 Å) has the flattest ring, and the 4*H*-thiopyran-4-one with the longest bond (C−S = 1.81 Å) has the most puckered ring.

Table 6. Structural (6-31G*) Relationship between the Bond Length C−X (Å) and the Endocyclic Torsional Angle (ϕ) in the 4-X-Cyclohexanone System

1-X-Cyclohexan-4-one

entry	X	name	C−X (Å)	ϕ (deg)	$\angle_{612}$
1	O	4-THPN	1.40	44.5	113.2
2	N−H (axial)	4-piperidinone	1.45	47.1	112.7
3	N−H (eq)	4-piperidinone	1.45	45.2	112.3
4	CH_2	cyclohexanone	1.53	49.1	111.1
5	S	4*H*-thiopyran-4-one	1.81	53.6	97.7

By comparing the structures in Table 6, a trend in the torsional angle ϕ becomes obvious. First, all structures in Table 6 have smaller values of ϕ than do a normal cyclohexane ring. The endocyclic torsional angle in the ring of cyclohexane is about 55° (gas-phase electron diffraction and low-temperature X-ray structure).[44] Ab initio calculations at various levels of theory (STO-3G, DZ, and DZP) agree with this value.[45] The calculated and experimental values for the torsional angle ϕ of cyclohexanone are 49° (entry 4, Table 6) and 52.7° (microwave),[46] respectively. Thus, the incorporation of a sp^2 carbon atom in the cyclohexane cycle will cause a flattening of the ring, and the incorporation of an oxygen atom causes a flattening of the part of the ring involving the 2−3−4−5 torsional angle, ϕ.

The incorporation of a sp^2 carbon atom into a six-membered cycle flattens the ring since the sp^2 carbon is trigonal planar. However, the reasons why an oxygen atom causes the flattening of the ring are less obvious. It has been suggested that the difference between the C−O and the C−C bond lengths (1.40 Å for C−O vs 1.53 Å for C−C) was responsible for this distortion.[37] Early conformational studies of 4-heteroatom-substituted cyclohexanones by NMR, IR, and ultraviolet spectroscopies by Lambert, and by Hirsch, indicate chair conformation is preferred.[48]

B. Distortion of 5-Azaadamantanone and Its *N*-Oxide

In 1996, we extended our study to adamantanone derivatives using the ab initio MO methods.[36a,43] Adamantanone (**15**) has a C_{2v} symmetry with the C_2 axis oriented along the carbonyl C=O bond (see Figure 6).[49] However, this symmetry is lost in the nitrogen-substituted analogues **16** and **17**. The hybridization of the nitrogen does not seem to play a big role in the structure of the adamantanone derivatives. From the results of the previous section, one would expect that **16** is distorted, while **17** may not be because of the sp^3 hybridization of the nitrogen atom. However, the piperidinone ring in **17** is considerably flatter than the opposing cyclohexanone ring according to the ab initio calculations.[36a] This can be seen from the endocyclic dihedral angles ϕ, Figure 6. The endocyclic dihedral angle ϕ is 59.3° in adamantanone. Using it as a standard, the ϕ in the piperidione ring of **3** (56.9°) is smaller; therefore, the piperidione ring of **17** is flatter than the cyclohexanone in **15**. On the other hand, the ϕ in the cyclohexanone ring of **17** (61.3°) is larger than that in adamantanone; therefore, it is more puckered. The carbonyl group is pyramidalized and is bent away from the nitrogen-containing ring. During a search for experimental parameters for comparison to our calculation, the crystal structure for 4-α-*p*-chlorobenzoyloxy-1-azaadamantane hydrochloride was found to be distorted.[50] The distortion observed in the crystal of this compound is in the same direction as in the calculated structure of **17**, i.e., the piperidine ring is flatter than the cyclohexane ring.

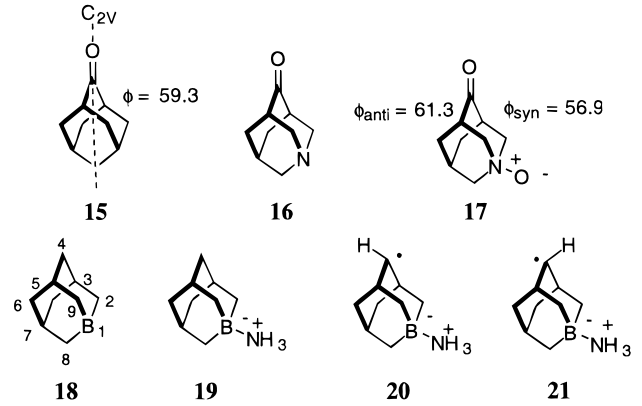


Figure 6. Adamantanone (**15**), 5-azaadamantanone (**16**), its oxide (**17**), 5-boraadamantane (**18**), its ammonia complex (**19**), and their free radicals (**20** and **21**).[36a]

C. Distortion of 5-Boraadamantane (18) and Its B–Ammonia Complex (19)

Both 5-boraadamantane (**18**) and its ammonia complex (**19**) have a C_{3v} symmetry with the C_3 axis going through the boron atom and the center of the opposing cyclohexane ring (see Figure 7). However,

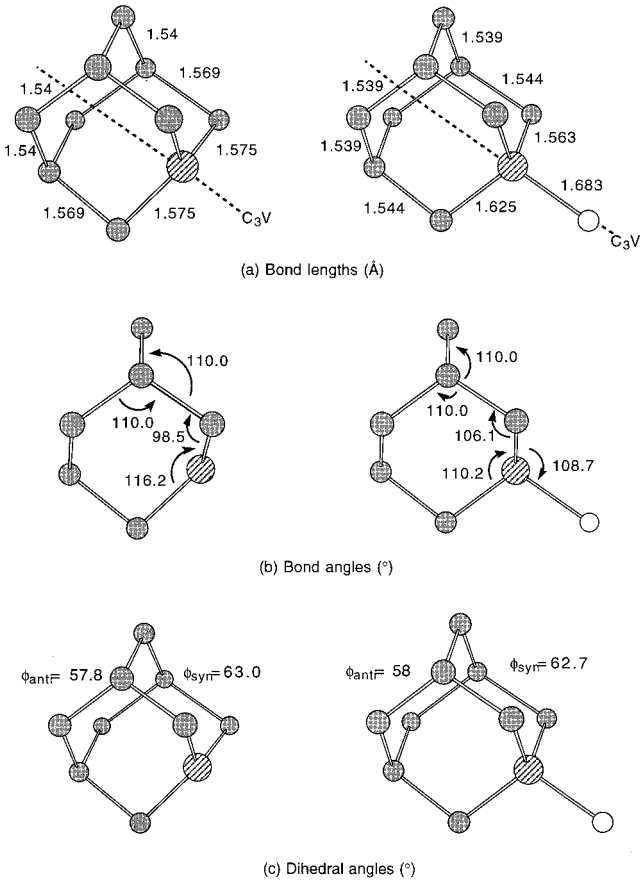
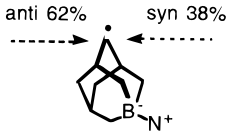


Figure 7. Optimized (6-311G*) structures of 5-boraadamantane (**18**) and its ammonia complex (**19**).

the relevant symmetry concerning diastereofacial selectivity is located elsewhere. A symmetrical boraadamantane cage should have a plane of symmetry going through two bridgehead methine carbons (C_3 and C_5) and two methylene carbons (C_4 and C_8). This plane of symmetry, if it exists, can provide identical steric environments for either side of the plane. Using the definition described above for the endocyclic dihedral angle ϕ, the 4-boracyclohexane ring in both **18** (ϕ_{syn} = 63°) and **19** (ϕ_{syn} = 62.7°) are more puckered than the opposing cyclohexane ring (ϕ_{anti} = 57.8°, 58°), respectively (Figure 7). Note that puckered rings hinder the attack of a reagent. Thus, the distortion of 5-boraadamantane (**18** and **19**) is again consistent with the observed diastereoselectivity (Table 7).



D. 5-Bora-2-Adamantyl Radicals Are Pyramidalized

Since the reaction conducted on the 5-boraadamantane system was free radical substitution of a chlorine atom by a hydrogen atom, we thought it would be prudent to explore the stability of the free radical intermediates. As shown in Figure 8, two free radical

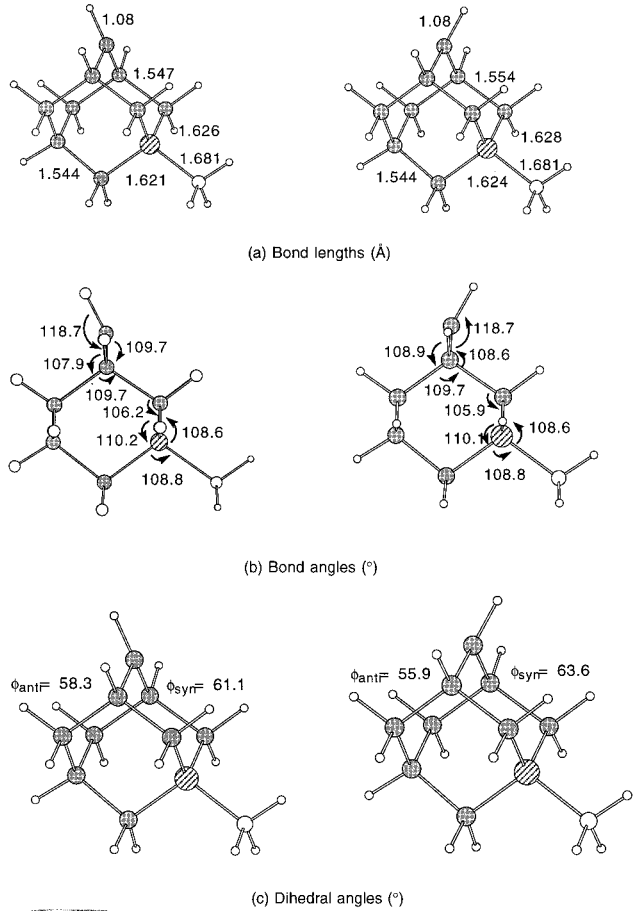


Figure 8. Optimized (6-311G*) structures of *cis*-5-bora-2-adamantyl radical (**20**) and *trans*-5-bora-2-adamantyl radical (**21**).

species are located on the ab initio MO potential surfaces. The carbon bearing the unpaired electron (C_4) is clearly pyramidalized. The C_4–H bond is either leaning toward the direction of the boron-substituted cyclohexane ring **(21)** or in the opposite

Table 7. Ab Initio Total Energies in Atomic Units for 5-Boraadamantane 18, Ammonia Complex of 18 (19), *cis*-5-Bora-2-adamantyl Radical 20, and *trans*-5-Bora-2-adamantyl Radical 21

		basis set			
entry	compd	6-31G*	6-31G*(dp)	6-31G* (diffuse)	6-311G*
1	**18**	−374.24456	−374.26801	−374.27062	−374.30624
2	**19**	−430.46007	−430.49347	−430.49762	−430.53829
3	**20**	−429.83021	−429.86238	−429.86764	−429.90874
4	**21**	−429.83057	−429.86273	−429.86804	−429.90910

direction **(20)**. Attempted modeling of the transition state between these two radicals was unsuccessful. Starting structures with a C−H bond midway between that in **20** and **21** always fall into either the cis radical **(20)** or the trans radical **(21)** during computation. If the C_4−H bond is constrained to be in the plane, the boron−NH_3 distance increases to 3.5 Å, and the energy of the complex rises to 18 kcal/mol relative to **21**. The trans radical **(21)** is more stable than the cis radical **(20)** by 0.23 kcal/mol at the 6-311G* level of theory (see Table 8). It should

Table 8. Relative Energies (kcal/mol) for *cis*- and *trans*-5-Bora-2-adamantyl Radicals 20 and 21

		basis set			
entry	compd	6-31G*	6-31G* (dp)	6-31G* (diffuse)	6-311G*
1	*cis*-**20**	0.23	0.22	0.25	0.23
2	*trans*-**21**	0	0	0	0

be noted that le Noble had anticipated possible pyramidalization of the radical species in his 1996 article.[28] However, the possibility of pyramidalization was dismissed by noting that 2-adamantyl radical is known to be planar.[51] The fact is that the referenced 2-adamantyl radical is a symmetrical adamantane derivative, rather than a 5-heteroatom-substituted adamantane system. Therefore, once a heteroatom is present at C_5 of the adamantane system, it can no longer be claimed to be a sterically unbiased system.

IV. The Origin of Diastereofacial Selectivity

The reduction of **16** and **17** with $NaBH_4$ in methanol results in 95% syn attack on **17** and 62% syn attack on **16**. The observed diastereofacial selectivity can be accounted for by distortion in the azaadamantanone structure. The steric effect related to the Bürgi−Dunitz trajectory is relevant; see Figure 9.[52a]

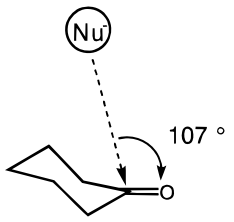


Figure 9. Illustration of the Bürgi−Dunitz trajectory. The angle $\angle_{NuCO}$ is 107 ± 5°.

Through the study of X-ray structures of amino ketones, Bürgi and Dunitz proposed that the optimal trajectory for nucleophilic addition to carbonyl compounds should be around 107°. This was later confirmed by theoretical calculations.[52b] The optimal trajectory proposal was supported by the observation that in the nucleophilic additions of $LiAlH_4$ to α-phenyl ethyl alkyl (R) ketones the asymmetric induction increases with the steric bulk of the alkyl group, R.[53] Anh has concluded that the Felkin model for nucleophilic addition to α-chiral ketones works best when the Bürgi−Dunitz trajectory is considered.[5]

The theoretical study by Liotta, Burgess, and Eberhardt describes the origin of the optimal trajectory as a combination of attractive and repulsive interactions between the nucleophile and the carbonyl group.[54] Thus a nucleophile with high HOMO energy would have greater attacking angle than one with lower HOMO. The importance of the Bürgi−Dunitz trajectory theory was further highlighted by Heathcock through a study of Lewis acid mediated additions of enolsilanes to chiral aldehydes.[55] On the basis of the aforementioned literature precedents, the approach of a nucleophile to a carbonyl group should proceed with an angle greater than 90°. Taking into account this trajectory analysis, the attack on the two faces of the 5-azaadamantanone oxide (**17**) shows significant difference in steric interactions (Figure 10).

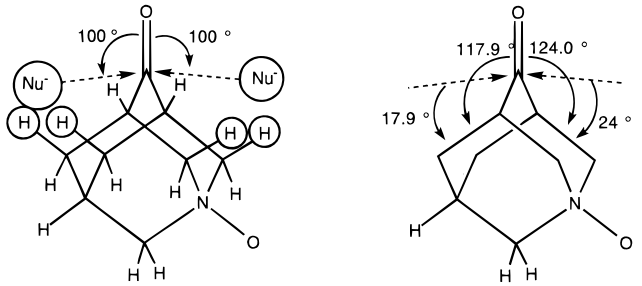


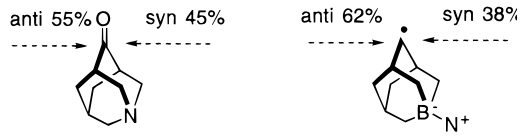
Figure 10. Differences in steric interactions for syn and anti attack on 5-azaadamantanone *N*-oxide (**17**).

An attack angle of 100° is depicted to illustrate the difference in steric interactions resulting from the distortion of the azaadamantanone skeleton. It can be seen that the cyclohexanone part (opposite to the ring containing nitrogen atom) of the ring of **17** is more puckered. Anti attack suffers more steric hindrance caused by the 3,5-diaxial hydrogen than syn attack. Thus the observed high ratio of syn attack could have been the result of the structure distortion. As mentioned in the Introduction, the π-facial selectivity observed in many experiments involving substituted adamantanones is in the range of ∼60/40 (syn:anti).[19−26] These results of modest diastereofacial selectivity have been rationalized in terms of either the hyperconjugative model or an electrostatic effect. However, a selectivity of 96:4 (syn:anti) was observed for 5-azaadamantanone *N*-oxide (**17**).[27] le Noble has shown that by changing the reaction media there was no significant change in stereoselectivity. This indicates that polar effects alone are probably not accountable for such a dramatic increase in π-facial selectivity. However, hyperconjugative effects alone could not lead to the observed high ratio of products. On the basis of the current results, we believe that structure distortion is mainly responsible for the

superior diastereofacial selectivity observed on 5-aza-adamantanone oxide (**17**).

V. Concluding Remarks

The ab initio calculations at the 6-31G* through 6-311G* levels result in two pyramidal structures (**20** and **21**) rather than one planar structure for the ammonia complex of 5-boraadamantyl radical. Therefore, is it appropriate to use this system in the study of stereoelectronic effects even when the calculation shows a pyramidalized trigonal carbon? As mentioned above, the referenced 2-adamantyl radical is symmetrical because it does not have a heteroatom substitution.[51] Once a heteroatom substitutes for a carbon atom, the resulting cage structure is no longer symmetrical at the carbonyl group. It is interesting to note that the calculated energy difference between the cis radical (**20**) and the trans radical (**21**) correlates with the observed selectivity in the radical substitution of 5-bora-2-adamantyl chloride.[28]



16 (Nu: = MeLi/THF) **20** and **21** Free radical substitution

Not only the direction of attack but also the ratio of syn/anti attack is consistent with the calculated results. Thus, for the 5-heteroatom-substituted adamantane system, the observed diastereofacial selectivity is accountable by structure distortion and the widely accepted Bürgi−Dunitz trajectory analysis. The only documented difference between the observed selectivity and the calculated distortion is the MeLi/THF addition to 5-azaadamantanone (**16**).[27] However, the observed selectivity is small (55:45), which could be due to possible hyperconjugation and/or electrostatic effects. This small difference between calculated distortion and observed selectivity does not negate the remarkable consistency in the results of the more distorted structures, such as 5-azaadamantanone *N*-oxide (**17**) and 5-boraadamantyl radical ammonia complex (**20** and **21**).

More than 20 years ago, Anh and co-workers pointed out the importance of structure distortion in relation to stereoselectivity.[56] It was stated that the cyclohexanone ring may be flattened so that the attacking nucleophile from the axial side may reach antiperiplanarity with the C_2-H and C_6-H bonds. On the other hand, puckering the ring will destroy this antiperiplanarity. The so-called flattening rule states the following: the more flattened the ring, the more axial attack. Theoretical studies by Houk and co-workers also support this "flattening rule".[39] The current review emphasizes steric effects associated with ring distortion rather than hyperconjugative effects. The important point is that a heteroatom substitution distorts a cyclohexanone ring, which in turn affects the stereochemical outcome of nucleophilic additions.

VI. Acknowledgment

The author is grateful to Rachael Crist for her help in the computations of 5-boraadamantane derivatives and to Melissa Roehm for her help in the preparation of this manuscript.

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CR980365Q