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Theoretical Studies of Stereoselectivities of Nucleophilic 1,2-Additions to Cyclohexenones. Transition Structures and Force-Field Models for Metal Hydride and Keteniminate Additions to Ketones

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The transition structures of the reaction of 2-cyclohexenone with lithium hydride have been located with the 3-21G basis set. The transition structure for axial addition is more stable than the transition structure for equatorial addition by 2.1 kcal/mol. The enone moiety is more nearly coplanar in the transition structure of axial addition than in that of equatorial addition, as indicated by the O═C—C═C dihedral angles of 162° and 146°, respectively. The axial transition structure is nearly perfectly staggered, while there is severe eclipsing in the equatorial transition structure. The high axial selectivity for the nucleophilic additions to cyclohexenones is caused mainly by torsional strain and poor orbital overlap in the equatorial transition structure. The transition structure for the reaction of lithium acetonitrile with acetone was located with ab initio molecular orbital calculations. It is a six-membered planar structure. The transition structure for the reaction of potassium acetonitrile has a nonplanar geometry. This difference between the transition structures is believed to cause the difference in stereoselectivity observed experimentally for the reaction of cyclohexanones and cyclohexenones with lithium and potassium propionitrile. A simple modification of the MM2 force field, based on the torsional strain model, qualitatively reproduces observed stereoselectivities.

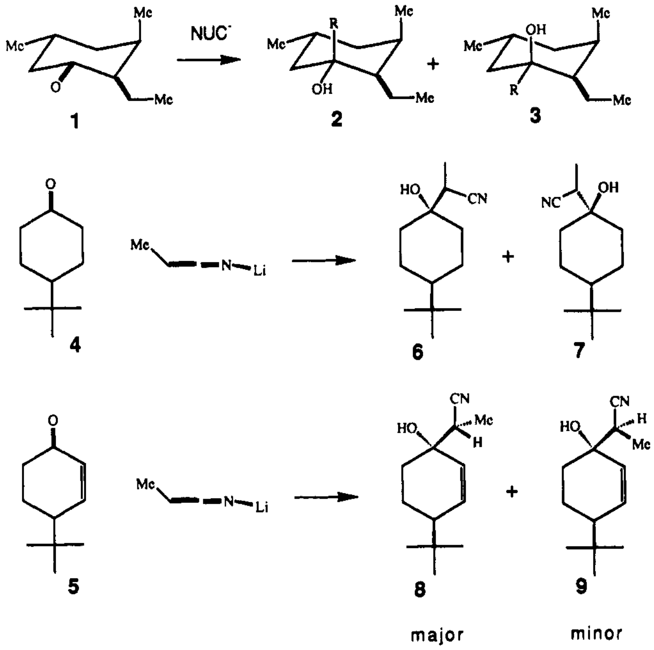
Introduction

In recent papers, we have studied stereoselectivities of nucleophilic additions to cyclohexanones[1] and have developed an MM2 force field based on ab initio calculations that reproduces the stereoselectivities of nucleophilic additions to α-chiral acyclic carbonyl compounds, cyclohexanones, cyclopentanones, benzocycloheptenones, many bicyclic ketones, and cyclohexenones.[2-4] In this paper, we present detailed studies of stereoselectivities of nucleophilic additions of hydride to cyclohexenones and extend these results to the additions of keteniminates. We have developed qualitative models of the transition structures and have tested our qualitative conclusions by modifying MM2 calculations to determine whether the qualitative model is capable of quantitation.

Background

Nucleophilic additions to cyclohexenones occur with significantly higher axial selectivity than the additions to the corresponding cyclohexanones.[5] Methylenecyclohexanones also exhibit this phenomenon. For example, Koreeda et al. recently observed that nucleophilic additions of sterically demanding carbanions to hindered 2-alkylidenecyclohexanones 1 occur with high axial stereoselectivity to give 2.[6,7] Nucleophilic additions to the corresponding cyclohexanone would lead to high equatorial stereoselectivity due to steric hindrance to axial attack caused by the axial methyl substituent (Scheme I).

Scheme I



The reaction of cyclohexanone 4 with lithium acetonitrile occurs with a 5.5:1 ratio of axial (6) to equatorial (7) addition, while the reaction of cyclohexenone 5 leads to a 23:1 axial–equatorial stereoselectivity.[8] Essentially, no 1,2-diastereoselectivity was observed for the reaction of 4 with lithium propionitrile, while the reaction of 5 gave high axial selectivity to form 8 and 9, as well as high diastereoselectivity to favor the formation of 8.[9] The metal counterion also affects the diastereoselectivities of additions of metalated nitriles. The effect is most noted in the additions of metalated propionitrile. In the case of 4-*tert*-butylcyclohexanone (4), a slight decrease in axial selectivity was observed with the potassium salt in THF

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(1) (a) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. (b) Houk, K. N.; Wu, Y.-D. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, B., Eds.; VCH Verlagsgesellschaft mbH: Weinheim, 1987; pp 247–260. (c) Wu, Y.-D.; Tucker, J.; Houk, K. N. *J. Am. Chem. Soc.*, in press.

(2) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560.

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(4) For related models for the nucleophilic additions, see: (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1986**, 2199. (b) Cherest, M.; Felkin, H. *Ibid.* **1968**, 2205. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (d) Anh, N. T. *Fortschr. Chem. Forschung.* **1980**, *88*, 145. (e) Dauben, W. G.; Fonken, G. S.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579. (f) Klein, J. *Tetrahedron Lett.* **1973**, *15*, 4307. (g) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (h) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *Ibid.* **1989**, *111*, 8447. (i) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459.

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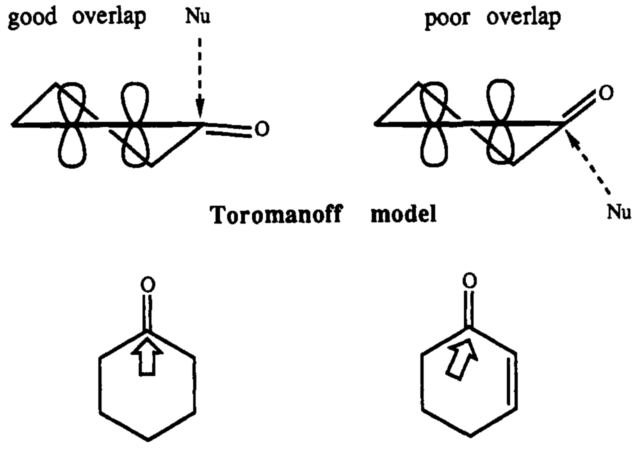
Chart I



(6:7 = 2.5:1), but no selectivity was observed in toluene (6:7 = 1.2:1). With the corresponding enone 5, both the axial selectivity (8:9 = 5.5:1) and the diastereoselectivity at the carbon α to the nitrile (1.6:1) were substantially diminished using the potassium derivative relative to the lithium salts. Unlike the lithium salts, for which the additions are irreversible up to room temperature, the additions of the potassium salts are irreversible for relatively short times at −78 °C but reversible at room temperature. The previous results derive from quenching the reaction at −78 °C after only 15 min to assure reactions are under kinetically controlled conditions.

Several explanations have been proposed for the high axial stereoselectivity of nucleophilic additions to cyclohexenones. Removal of one axial hydrogen at the 3-position of cyclohexanone to form cyclohexenone reduces the steric hindrance to axial attack that exists for large nucleophiles in attack on cyclohexanone. Toromanoff emphasized the importance of orbital overlap between the forming bond and the $C_\alpha{=}C_\beta$ bond and suggested that the axial addition is stereoelectronically allowed because this orbital overlap is maintained in the course of the axial addition, while the equatorial addition is stereoelectronically disfavored because the orbital overlap is disrupted during the equatorial addition of the nucleophile (Chart I).[5] This interpretation was invoked recently by Stork[10] and Koreeda.[6] Baldwin proposed that due to double bond character of the $C_1{-}C_2$ bond, the attack trajectory of the nucleophile is different from that on a saturated ketone. Baldwin hypothesized that the vector of the nucleophilic addition is tilted toward the side of saturated carbon chain, so that the nucleophile experiences larger steric interactions with the axial substituent at C_6 upon equatorial attack.[11]

Results and Discussion

A. Hydride Model. The transition structures for the reaction of 2-cyclohexenone with lithium hydride were located with Pople's GAUSSIAN 86 program.[12] The geometries were fully optimized with the 3-21G basis set, and energies were also obtained with the 6-31+G basis set, which involves the addition of a set of diffuse s and p orbitals to the heavy atoms and the hydride. The geometries of the transition structures are shown in Figure 1.

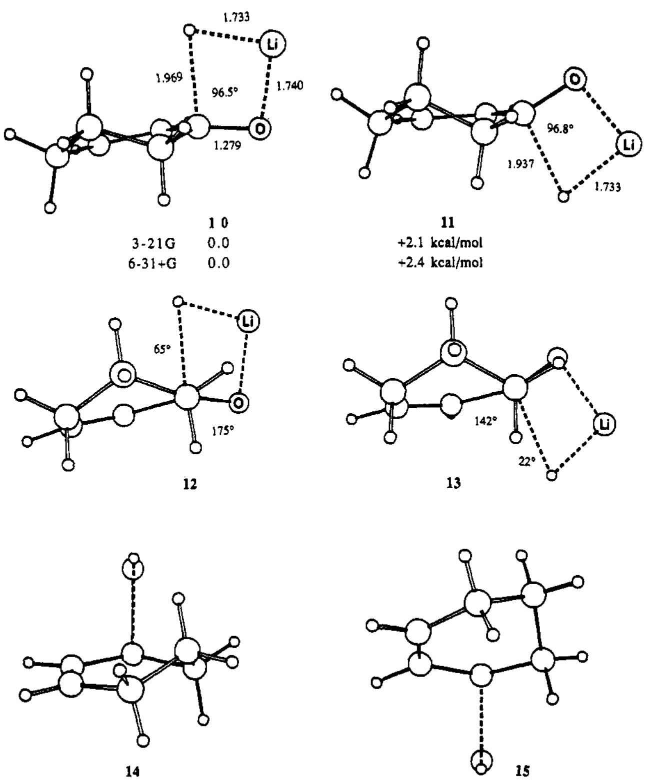


Figure 1. Transition structures of the reactions of lithium hydride with 2-cyclohexenone located with the 3-21G basis set. Structures 10, 12, and 14 are views of axial attack, and 11, 13, and 15 are views of equatorial attack.

The axial transition structure is calculated to be 2.1 and 2.4 kcal/mol more stable than the equatorial transition structure with the 3-21G and 6-31+G basis sets, respectively. This axial preference is larger than that of the cyclohexanone–LiH reaction, which is calculated to be 1.0 and 1.7 kcal/mol with the 3-21G and 6-31+G basis sets, respectively. The higher axial selectivity for the reaction of cyclohexenone with respect to the reaction of cyclohexanone is in agreement with the experiment observations.

The axial transition structure 10 has perfect staggering about the forming bond as indicated by the Newman projection 12. The equatorial structure 13 has severe eclipsing. One of the $C_7{-}H$ bonds is eclipsed with the carbonyl bond, while the other has a torsional angle of 22° with respect to the forming C---H bond. The forming C---H bond length is 1.97 Å in 10. This is longer than that in 11 by 0.03 Å, reflecting an early transition structure and lower activation energy for the axial addition than for the equatorial. The C---H bond in the two structures is shorter

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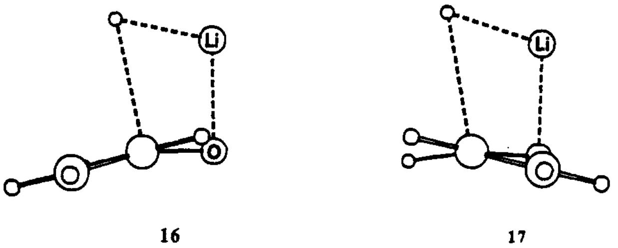
[13] According to previous published calculations on the reaction of lithium hydride with formaldehyde, the transition-structure geometry changes little with better basis sets, see ref. 27a. Our recent calculations on the reactions of sodium hydride with RCH_2CH_2CHO, where R=H, F, and SiH_3 indicate that 6-31+G* transition structures are very similar to the 3-21G transition structures: ref 1c.

Table I. Calculated Relative Energies (kcal/mol) and O═C—C═C and H---C—C═C Dihedral Angles of the Axial and Equatorial Transition Structures of Hydride Addition with Different Torsional Parameters for the O═C—C═C and H---C—C═C Dihedral Angles

entry	O═C—C═C parameters			H---C—C═C parameters			<O═C—C═C		<H---C—C═C		*E*(eq)–*E*(ax) (kcal/mol)
							ax	eq	ax	eq	
1	0.0	1.0	0.0	0.0	6.0	0.0	167.5	161.7	92.6	102.1	2.11
2	0.0	1.0	0.0	0.0	5.0	0.0	167.4	160.4	92.7	103.2	2.07
3	0.0	1.0	0.0	0.0	4.0	0.0	167.3	158.2	92.8	105.2	2.01
4	0.0	1.0	0.0	0.0	3.0	0.0	167.2	154.9	93.0	107.8	1.98
5	0.0	1.0	0.0	0.0	2.0	0.0	167.0	151.4	93.1	110.8	1.80
6	0.0	1.0	0.0	0.0	1.0	0.0	166.9	147.4	93.3	114.1	1.65
7	0.0	1.0	0.0	0.0	0.0	0.0	166.8	143.2	93.5	117.8	1.46
8	0.0	0.0	0.0	0.0	0.0	0.0	165.3	135.8	94.3	122.4	1.08



16
anti

17
syn

Figure 2. Newman projections of anti and syn transition structures of the reaction of acrolein with lithium hydride located with the 3-21G basis set.

than that in the transition structures of reaction of LiH with cyclohexanone by ~0.1 Å. The O═C---H angle is 97° in both of the structures. The enone moiety is slightly nonplanar. The O═C—C═C dihedral angles are 162° and 146° in **10** and **11**, respectively. The forming C---H bond is nearly perpendicular to the C═C bond in **10** as indicated by a H---C—C═C dihedral angle of 95°. The H---C—C═C dihedral angle in **11** is 113°. Overall, there is relatively good orbital overlap in both of the structures, but the overlap in the axial structure is better, in agreement with Toromanoff's suggestion.

The tilting of the addition vector suggested by Baldwin is not supported by the calculations. This is clearly shown in **14** and **15**, which are side views of **10** and **11**, respectively, looking along the carbonyl bond. The four-center transition structure is planar in both of the structures. There is little tilting of the nucleophile with respect to the carbonyl normal plane. The hydride is very slightly moved toward the side of the C═C bond, opposite to Baldwin's prediction.

Figure 2 shows the Newman projections along the C_2—C_3 bond of anti and syn transition structures of acrolein–LiH reaction calculated with the 3-21G basis set. In the structure with an s-trans acrolein moiety **16**, the H---C—C═C dihedral angle is 93° and the O═C—C═C dihedral angle is 164°. There is near coplanarity of the enone, and the forming bond and C═C bond are nearly perpendicular. In the syn transition structure **17**, the O═C—C═C and H---C—C═C dihedral angles are 11° and 114°, respectively. While there is tendency for coplanarity of the enone moiety, the forming C---H and C═C bonds are far from perpendicular.

How much energy is required to distort the enone away from coplanarity? Structure **16** was reoptimized with the constraint of the forming H---C bond length and with different values of the H---C—C═C dihedral angle. Each structure was optimized with the 3-21G basis set, and the energies were evaluated with MP2/6-31G* calculations. The energy increases are 0.1, 0.5, and 1.2 kcal/mol when the H—C—C═C dihedral angle increases from the equilibrium value of 93° to 103°, 113°, and 123°, respectively. This corresponds to a barrier of 4–5 kcal/mol with respect to the rotation of the enone moiety if a normal cos Φ relationship is followed.

By use of this information, an MM2 force field has been developed for nucleophilic additions to cyclohexenones. It is an extension of the one developed earlier for cyclohexanones.[1] The only change is the incorporation of the coplanarity of the enone system. In the MM2 force field,[14] the torsional energy is determined by the parameters *A B C* as defined in eq 1. Table I summarizes the calculated

$$E = A/2(1 + \cos \alpha) + B/2(1 - \cos 2\alpha) + C/2(1 + \cos 3\alpha) \qquad (1)$$

energy difference between the axial and equatorial transition structures for the reaction of cyclohexenone for different values of the torsional parameters. The torsional parameter for the H---C—C_{sp^2}-H dihedral angle was varied from 0.0 6.0 0.0 to 0.0 0.0 0.0 to test the influence of orbital overlap on the stereoselectivity. Such a procedure gives a scan of barrier to the rotation about the C_1-C_2 bond from ~7 to 1 kcal/mol. When the rotational barrier is above 4 kcal/mol, the calculated stereoselectivity is almost constant. In such cases, coplanarity of the enone moiety is attained in both of the axial and equatorial transition structures and the torsional strain in the equatorial transition structure reaches a maximum. When the rotational barrier is reduced, the calculated axial preference is lowered. While the geometry of the axial transition structure changes very little, the equatorial transition structure sacrifices some coplanarity to release torsional strain. When the enone moiety is rotationally unrestricted (entry 8), there is a 1.1 kcal/mol preference for the axial transition structure. These calculations indicate that the orbital overlap effects noted by Toromanoff and Stork do have an influence on the stereoselectivities of nucleophilic additions to cyclohexenone. However, the maintenance of the coplanarity primarily magnifies the differences in torsional strain between the axial and equatorial transition structures. This is why we have proposed that the stereoselectivity of nucleophilic additions to cyclohexenones is mainly caused by differences in torsional strain in the two transition structures.[2]

In the remaining calculations, we used the parameters given in entry 4; that is, a 4 kcal/mol barrier was assumed for the enone moiety. This assumption is consistent with the following facts: (1) The rotational barrier for acrolein is reported to be 4–9 kcal/mol.[15,16] (2) A 4 kcal/mol

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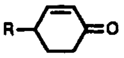
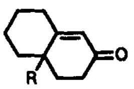
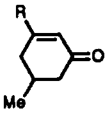
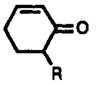
(14) Burkert, U.; Allinger, N. L. Molecular Mechanics; American Chemical Society: Washington, DC, 1982.

(15) Cherniak, E. A.; Costain, C. C. *J. Chem. Phys.* **1966**, *45*, 104. DeGroot, M. S.; Lamb, J. *Proc. R. Soc. London, A* **1957**, *242*, 36.

(16) (a) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14. (b) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129. (c) Marriott, S.; Topsom, R. D. THEOCHEM **1984**, *106*, 277. (d) George, P.; Boch, C. W.; Trachtman, M. *Ibid.* **1980**, *69*, 183. (e) Devaquet, A. J. P.; Townshend, R. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 4068.

Table II. MM2 Calculated Conformational Preferences, ΔE (Ground), MM2 Transition-Structure Force-Field Predictions of Stereoselectivities, ΔE (TS), and Observed Stereoselectivities of Hydride Additions to Conformationally Flexible Cyclohexenones

			ΔE (ground) (kcal/mol)	ΔE (TS) (kcal/mol)	exptl ax:eq
	22	R = Me	0.6	0.7	trans major
	23	R = *i*-Pr	0.1	0.6	75:25
	24	R = *t*-Bu	1.5	2.0	
	25	R = H	0.7	0.8	80:20
	26	R = Me	2.6	1.5	90:10
	27	R = H	1.1	1.9	93:7
	28	R = Me	1.1	1.9	90.5:9.5
	29	R = Me	1.4	1.4	
	30	R = *i*-Pr	1.1	0.6	64:35

barrier is reasonable on the basis of calculations on the acrolein–LiH system. (3) The MM2 calculated geometries of the axial and equatorial transition structures with these parameters (**18** and **19**, Figure 3) are very close to the ab initio transition structures (**12** and **13**). (4) The MM2 calculated energy difference between the axial and equatorial transition structures is close to that of the ab initio value and in good agreement with the experimentally observed stereoselectivities.

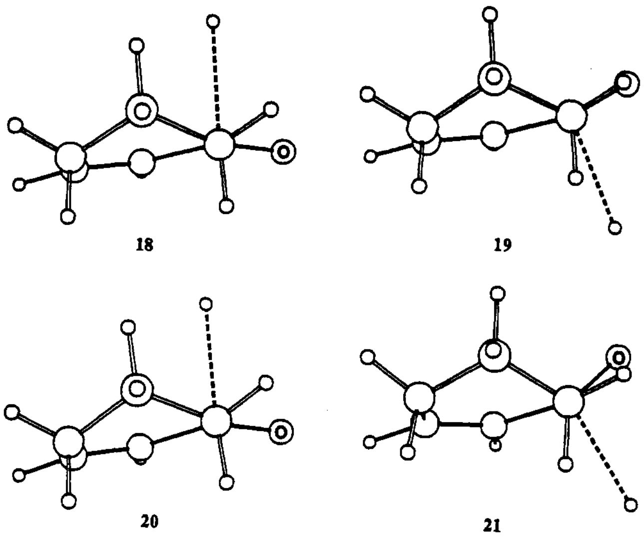


Figure 3. MM2 transition structures calculated with the parameters given in the entry 4 of Table I (**18** and **19**) and with free rotation about the C_1—C_2 bond (**20** and **21**).

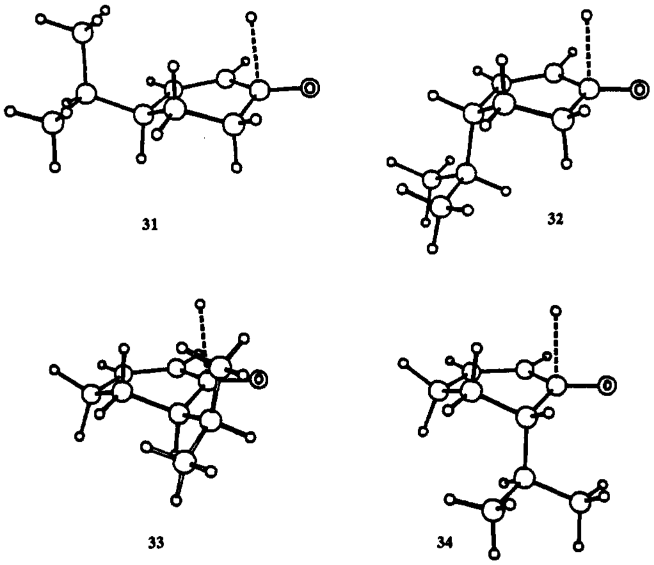
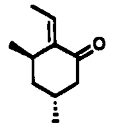
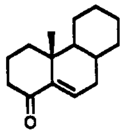
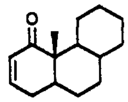
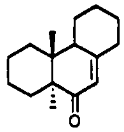
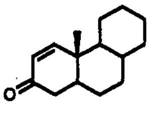
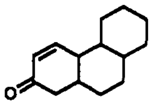
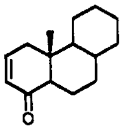


Figure 4. MM2 transition structures of hydride additions to 4-isopropyl-2-cyclohexenone (**31** and **32**) and to 6-isopropyl-2-cyclohexenone (**33** and **34**).

Conformationally Flexible Compounds. Tables II and III give a summary of the MM2 calculations and a comparison with experimental results. For conformationally flexible cyclohexenones, attack is primarily axial and the stereoselectivity is determined mainly by the competition among the axial addition transition structures. This is different from additions to cyclohexanones, where a substituent in the axial conformation is usually significantly less stable than one in the equatorial conformation. For example, 4-methyl-2-cyclohexenone (**22**) exists in two conformations of similar energy. When the six-membered ring is in a half-chair conformation, the methyl group can be either pseudoequatorial or pseudoaxial. MM2 calculations give a 0.6 kcal/mol preference for the pseudoequatorial conformation (Table II). Our MM2 transition structure force-field calculations indicate that axial attack is ~2 kcal/mol easier than equatorial attack on either conformation. The transition structure of the pseudoequatorial methyl conformation, which leads to the trans product, is 0.7 kcal/mol more stable than the transition structure of the pseudoaxial methyl conformation. Experimentally, the formation of the trans product was ob-

Table III. Experimental (and MM2-Predicted) Percentages of Axial Attack on Cyclohexenones and Cyclohexanone. Predicted Stereoselectivities Were Calculated on the Basis of the Assumption of 25 °C Reaction Temperature.

				
	35	**36**	**37**	**38**
cyclohexenone	>97 (98)	>95 (95)	>70 (93)	0 (24)
cyclohexanone		<15 (4)	35 (33)	1 (8)

			
	39	**40**	**41**
cyclohexenone	70–80 (90)	(96)	(27)
cyclohexanone	91 (93)	(87)	(4)

served to be dominant.[17] MM2 calculations predict a small pseudoequatorial preference for 4-isopropyl-2-cyclohexenone (**23**). Our force-field calculations gave a 0.6 kcal/mol preference for the formation of the trans product, in good agreement with the experimental observation.[18] The transition structures for the formation of the trans and cis products are shown by **31** and **32** (Figure 4). When the C_4-substituent is *t*-Bu, there is a 1.5 kcal/mol preference for the pseudoequatorial conformation. The pseudoaxial conformation is mainly destabilized by the methyl group inside the ring. The force-field calculations predicted that the pseudoaxial *t*-Bu group causes even larger steric problems in the transition structure.

Bicyclic compounds **25** and **26** are also somewhat flexible. When R = H, there is a 3–4:1 selectivity favoring the formation of trans product.[19] The stereoselectivity increases when R is methyl. MM2 calculations indicated that the pseudoequatorial conformation (axial R) is more stable than the pseudoaxial conformation (equatorial R) by 0.7 kcal/mol when R is H. The transition-structure model calculations gave a 0.8 kcal/mol preference for the formation of the trans product, resulting from axial attack. The conformational preference becomes much larger (2.6 kcal/mol) when R is a methyl group. Our force-field calculations indicated that the strain in the pseudoaxial conformation (Me equatorial) is released to some extent upon hydride addition from the axial direction. Nevertheless, the transition structure for the hydride addition to the pseudoaxial conformation is still 1.5 kcal/mol less stable.[17,20]

The axial and equatorial positions at C_5 differ more sterically than those at C_4. For 5-methyl-2-cyclohexenone (**27**), the equatorial methyl conformation is 1.1 kcal/mol more stable than the axial methyl conformation according to the MM2 calculations. The transition-structure force-field calculations indicate that the two stereoisomers come from axial and equatorial attack on the equatorial methyl conformation. This leads to high stereoselectivity, as observed.[21]

A methyl group at C_6 of cyclohexenone (**29**) has a large preference (1.4 kcal/mol) for the equatorial position. The transition-structure force-field calculations predict a 1.4 kcal/mol preference for the axial addition of hydride on the equatorial conformation as compared to axial attack on the axial conformation. The equatorial addition of the hydride is much disfavored. The MM2 calculations also predict a 1.1 kcal/mol preference for the equatorial conformation when R is an isopropyl substituent. However, it is predicted that the transition structure with the equatorial substituent **33** is only 0.5 kcal/mol more stable than the transition structure with the axial conformation **34** in good agreement with the experimental observation.[18] When the isopropyl group is equatorial, the two methyls are in the arrangement shown in **33**. There is steric interaction between the nucleophile and one of the methyl groups of the isopropyl. When the isopropyl group is axial, it is arranged in the conformation with the methyl groups outside the ring. Although the axial isopropyl causes steric problems in the ground state, no additional steric interaction is introduced in the transition structure upon the addition of nucleophile from the axial direction.

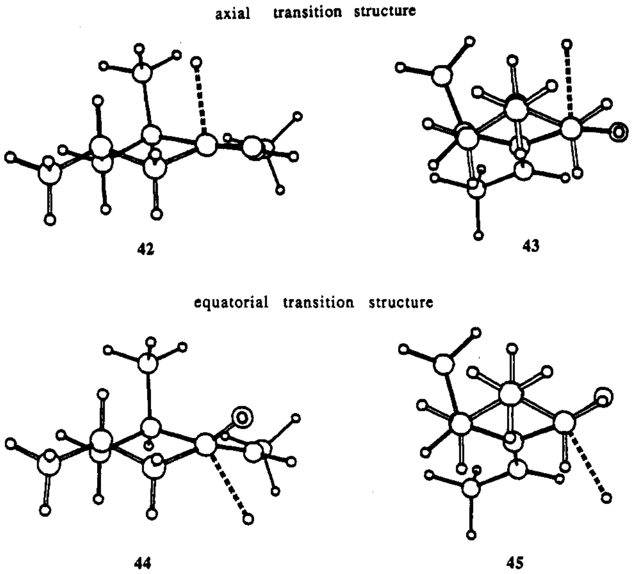


Figure 5. Newman projections of axial and equatorial transition structures of hydride addition to **35**.

Conformationally Rigid Molecules. Collected in Table III are the observed and calculated (in parentheses) stereoselectivities of hydride additions to conformationally rigid cyclohexenones and the corresponding cyclohexanones. In every case except **39** there is a larger preference for axial addition to cyclohexenone than to the corresponding cyclohexanone. In the cases of **36** and **37**, the stereoselectivities reverse from equatorial attack on the saturated compounds to axial in the cyclohexenone.

While 2-cyclohexenone exists in a half-chair conformation, 2-alkylidenecyclohexanone **35** exists in a chair conformation. The enone is nonplanar dihedral C═C—C═O, and the angle is 41° calculated by MM2 in the MACROMODEL program.[6,22] The transition structures of the axial and equatorial additions by hydride calculated by the transition-structure force field are shown in Figure 5. The axial transition structure has only a small O═C—C═C dihedral angle, and the forming C---H bond is nearly perpendicular to the C═C bond (**42**). This arrangement is very close to that in the transition structure of *cis*-acrolein–LiH (**17**). The smaller distortion of the enone moiety in the axial transition structure than in the ground state arises from the release of ring strain upon the pyramidalization of the carbonyl carbon. This pyramidalization increases the distortion of the enone moiety. There is poor orbital overlap between the forming C---H bond and the C═C bond, and the enone moiety is far from planar (**44**). These calculations confirm the analysis of Koreeda et al.[6] Torsional strain is also important. While there is perfect staggering in the axial transition structure as shown by Newman projection **43**, severe eclipsing exists in the equatorial transition structure **44**.

This discussion can also be applied to **36**.[23] The compound is in the conformation similar to that of **35** due to the ring fusion. Its high axial stereoselectivity is quite different from its cyclohexanone counterpart. The equatorial selection in the latter is due to the steric congestion in the transition structure of axial addition.

The only case where the axial stereoselectivity is lower for cyclohexenone with respect to cyclohexenone is **39**.[24]

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(21) Goering, H. L.; Banchard, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 5405. Asato, G. Univ. Microfilms, Inc., Ann Arbor, MI, 1961, order No. 61.5692.

(22) Singh, R. D.; Keiderling, T. A. *J. Am. Chem. Soc.* **1987**, *109*, 613.

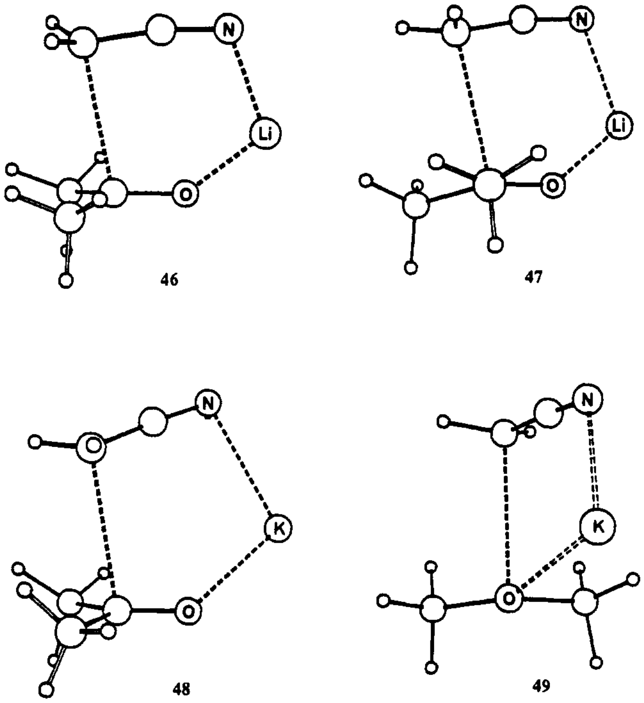
(23) Becker, E. J.; Wallis, E. S. *J. Org. Chem.* **1955**, *20*, 353.

Table IV. Selected Geometrical Parameters and Energies (-au) of ab Initio Transition Structures of the Reactions of Lithium Acetonitrile and Potassium Acetonitrile with Acetone

	46 STO-3G	46 3-21G	48 STO-3G
1-2	1.240	1.249	1.231
1-3	2.795	2.661	2.865
3-4	1.342	1.363	1.351
4-5	1.198	1.170	1.190
5-6	1.800	1.903	2.511
2-6	1.658	1.742	2.483
2-1-3	96.5	102.1	99.8
3-4-5	173.8	171.8	176.5
4-5-6	104.4	108.6	105.0
2-6-5	116.2	108.2	94.9
1-2-6	142.9	141.5	128.0
3-1-7	100.1	105.6	98.7
4-3-8	156.7	151.9	153.3
2-1-3-4	0.0	0.0	35.1
3-1-2-6	0.0	0.0	52.9
E_{total}	326.57699	328.94411	912.28650

This is caused by the methyl substituent. When the methyl group is replaced by a hydrogen, as in compound **40**, the calculations predict that the axial addition is more favored for the unsaturated species and is less favored for the saturated species.

B. Metal Keteniminates. The reactions described in the introduction represent striking examples of stereoselectivity differences between cyclohexanones and cyclohexenones for synthetically valuable carbon–carbon bond forming reactions. We undertook an investigation of these reactions to see if the principles and force field developed for hydride additions could be extended to reactions of larger nucleophiles. The transition structure for the reaction of lithium acetonitrile with acetone was first located with the STO-3G basis set and subsequently studied with the 3-21G basis set.[25] Since lithium cations are believed to be involved in the transition states of reactions of organolithiums with carbonyl compounds,[26,27] we assumed initially that the reaction occurs via a six-membered transition structure with C_s symmetry, as shown in Figure 6. Vibrational frequency calculations gave one imaginary frequency and confirm that the structure is an authentic transition structure. The geometrical parameters are collected in Table IV. It is an early transition structure, with a forming C---C bond length of 2.66 Å. Nevertheless, there is considerable pyramidalization at the two carbon centers. The attack angle on the ketone is 102°, and the ketenimine moiety is slightly bent, with an angle of 172°. As in the transition structure for reaction of LiH with acetone,[28] the two methyl groups are staggered with respect to the forming C---C bond, due to the pyramidalization at the carbonyl carbon. The geometry of the STO-3G transition structure is very similar to that of the 3-21G transition structure.



46 47 48 49

Figure 6. Front view and Newman projection about C-C$_\alpha$ bond of the 3-21G transition structure of the reaction of lithium acetonitrile with acetone (**46** and **47**) and front and side views of the STO-3G transition structure of the reaction of potassium acetonitrile with acetone (**48** and **49**).

To gain some information about the flexibility of the transition structure (planar versus nonplanar), the STO-3G transition structure was reoptimized with different torsional angles, O=C---C=C and a constant forming C---C bond length of 2.795 Å. The structure is destabilized by 0.2, 0.8, and 1.7 kcal/mol, respectively, when the keteniminate is distorted by 10°, 20°, and 30°. This increase in energy is mainly caused by unfavorable lithium coordination, because steric effects would favor the distortion. Thus, the ordered transition structure is favored, but it is reasonably flexible. We expect that this flexibility is even more significant in solution due to solvation of the cation and possible aggregation of the organolithium species. It is also expected that replacement of lithium by sodium or potassium should lead to more flexibility, due to the longer O---metal bonds.

Indeed, the transition structure of the reaction of potassium keteniminate with acetone located with the STO-3G basis set is nonplanar, as shown in Figure 6. There is a 35° dihedral angle between the C=O bond and the C=C bond, as can best be seen in **49**. K^+ coordinates at the side of the carbonyl carbon. The O—K and N—K bonds are very long. The six-membered ring is flexible enough to adapt a staggered conformation about the forming C---C bond. A structure was also calculated with the constraint of C_s symmetry. This structure is only 0.6 kcal/mol less stable than **48**.

We tested a simple modification of the hydride addition force-field to determine whether the same effects were operative in these more elaborate reactions. The 3-21G transition structure of lithiated acetonitrile attack on acetone was used for the equilibrium geometry of transition structure. The parameters developed are collected in Table V, and the atom labeling is designated in **50**. For the rest of the parameters, the default MM2 values were used. The stretching and bending force constants for the bonds and bond angles involving bond breaking and bond formation were set to be half the values for normal bonds

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(24) (a) Plattner, P. A.; Furst, A.; Els, H. *Helv. Chim. Acta* **1954**, *37*, 1399. (b) Bergman, W.; Kita, M.; Giancola, D. J. *J. Am. Chem. Soc.* **1954**, *76*, 4974. (c) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1956**, 3289. (d) Albrecht, R.; Tamm, C. *Helv. Chim. Acta* **1957**, *40*, 2216.

(25) We were unable to locate a transition structure for the reaction of lithium acetonitrile with formaldehyde due to the very high exothermicity of this reaction at the 3-21G basis set level.

(26) (a) Zimmerman, H. E.; Traxler, M. J. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Dubois, J. E.; Dubois, M. *Bull. Soc. Chim. Fr.* **1969**, 3120, 3553. (c) Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, *1225*. (d) Heathcock, C. H. In Comprehensive Carbanion Chemistry, Part B; Buncel, E. Durst, T., Eds.; Elsevier: Amsterdam, 1984; pp 177–237.

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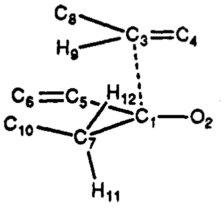
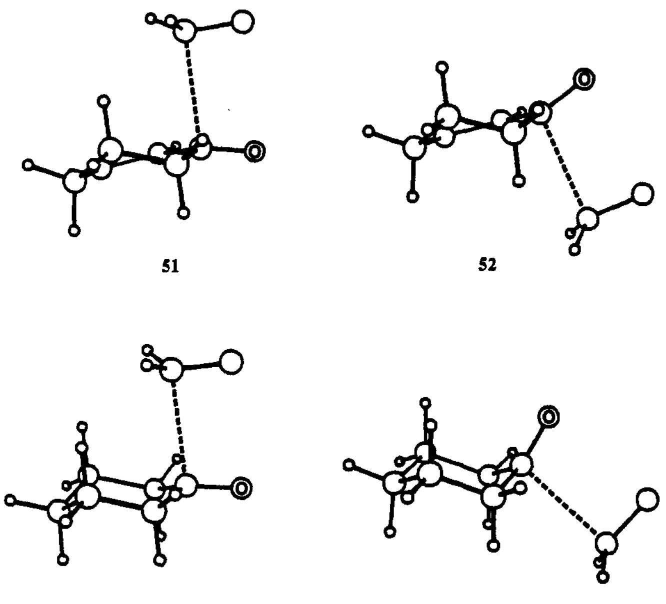
Table V. MM2 Parameters for the Metalated Keteniminate Addition Model



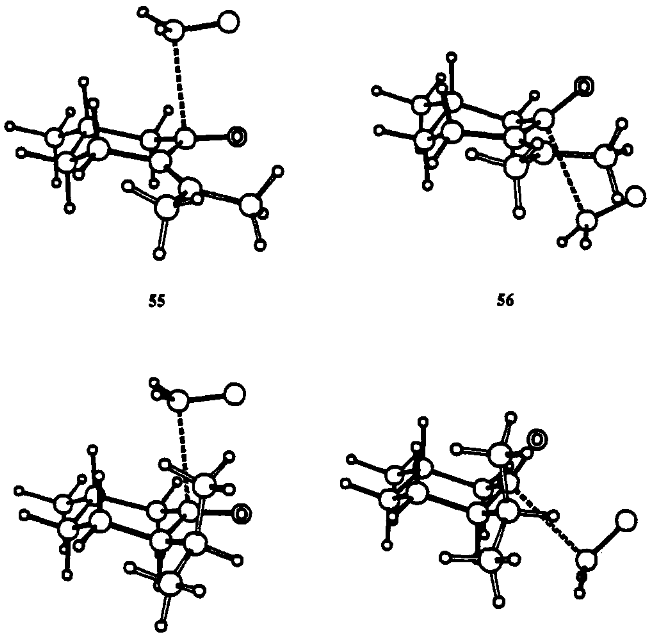
50

bond stretching parameters			angle bending parameters			torsional parameters			
1-2	5.36	1.25	2-1-3	0.25	102.1	2-1-3-4	0.0	6.0	0.0
1-3	2.00	2.66	1-3-4	0.40	87.8	2-1-3-8	0.0	0.0	0.0
1-5	4.40	1.49	1-3-8	0.30	105.5	2-1-3-9	0.0	0.0	0.0
1-7	4.40	1.51	1-3-9	0.30	105.5	2-1-3-6	0.0	1.0	0.0
3-4	6.00	1.36	8-3-9	0.36	116.7	2-1-7-10	−0.4	0.5	−0.2
3-8	3.50	1.51	4-3-8	0.36	117.7	2-1-7-11	0.0	0.0	0.18
3-9	3.50	1.09	4-3-9	0.36	117.7	3-1-5-6	0.0	−3.0	0.0
5-6	8.00	1.34	2-1-5	0.60	120.2	3-1-7-10	−0.2	−0.2	0.4
			2-1-7	0.60	120.2	3-1-7-11	0.0	0.0	0.3
			5-1-7	0.45	117.1	5-1-7-10	0.6	0.4	0.7



51 52 53 54

Figure 7. MM2 model transition structures for the reactions of metalated acetonitrile with 2-cyclohexenone and cyclohexanone.



55 56 57 58

Figure 8. MM2 model transition structures for the reactions of metalated acetonitrile with pulegone (**55** and **56**) and with menthone (**57** and **58**).

and angles. Bond lengths and bond angles are difficult to deform; the calculational results for the modeling of intermolecular reactions are insensitive to the stretching and bending parameters.[29] The parameters are similar to those for the hydride addition force field, which is shown in the Appendix. The parameters for the incorporation of the coplanarity of the enone system of cyclohexenone are the same as those in the hydride model. Although the metal cation coordination is vital to the flexibility to transition state, in our model the Li and N atoms are not included. This is a drastic simplification, but it works for the following reasons. First, the N and Li atoms are far away from the cyclohexanone or cyclohexenone ring atoms and cause little steric interaction. Second, the flexibility of the six-membered transition structure can be incorporated by adjusting the torsional parameters for the dihedral angles around the forming C---C bond. In our model, the V_2 torsional parameter for $O_2{=}C_1{-}{-}{-}C_3{=}C_4$ is set to 6.0 while the $O_2{=}C_1{-}C_3{-}C_8$ and $O_2{=}C_1{-}C_3{-}H_9$ torsional parameters were all set to 0. This results in distortion energies similar to those given by the STO-3G calculations. The first torsional parameter was also varied, as described in the following text, to probe the sensitivity of the model to a variation in torsional flexibilities.

The model was first applied to the reactions of metalated acetonitriles with 2-cyclohexenone and cyclohexanone. The transition structures of axial and equatorial additions are given in Figure 7. In each of the transition structures the O=C---C=C is nearly coplanar. There is a 1.7 kcal/mol preference for axial attack on cyclohexenone **51**. This axial preference is slightly smaller than that calculated for the hydride addition discussed earlier. The axial transition structure of cyclohexanone **53** is more stable than the equatorial transition structure **54** by 0.5 kcal/mol. This axial preference is 0.7 kcal/mol smaller than that calculated for the hydride addition. The reduced axial preference reflects the larger steric interaction in the axial transition structure caused by the acetonitrile CH_2 group.

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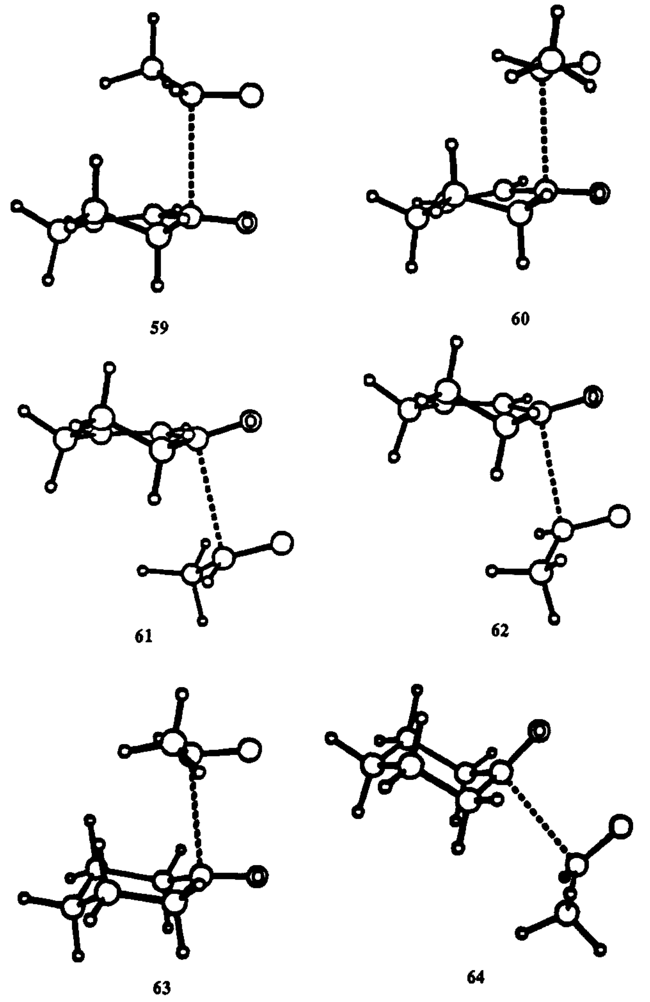
[29] Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

Table VI. Relative Energies of MM2 Transition Structures for the Reactions of Metalated Alkylacetonitriles with 2-Cyclohexenone and Cyclohexanone. Energies Are in kcal/mol and Values in Parentheses Are Dihedral Angles, Φ, between Ketenimine and Carbonyl Bonds.

torsional parameters			59	60	61	62	63	64
					$R = CH_3$			
0.0	6.0	0.0	0.0 (3°)	1.6 (23°)	1.9 (−1°)	2.8 (1°)	0.4 (5°)	0.0 (1°)
0.0	4.0	0.0	0.0 (4°)	0.8 (37°)	1.8 (11°)	2.8 (−10°)	0.4 (25°)	0.0 (1°)
0.0	2.0	0.0	0.0 (4°)	0.4 (47°)	1.5 (23°)	2.4 (−49°)	0.0 (40°)	0.1 (5°)
0.0	4.0	2.0	0.0 (28°)	−0.2 (46°)	1.3 (40°)	1.9 (−49)	0.0 (42.7)	0.5 (35°)
					$R = C(CH_3)_3$			
0.0	6.0	0.0	0.0 (18°)	2.7 (43°)	1.8 (−9°)	3.8 (11°)	1.4 (46°)	0.0 (−10°)
0.0	4.0	0.0	0.0 (22°)	1.8 (49°)	2.0 (−15°)	4.1 (45°)	0.4 (52°)	0.0 (43°)
0.0	2.0	0.0	0.0 (27°)	0.9 (54°)	1.9 (−22°)	3.0 (55°)	0.0 (56°)	0.4 (50°)



59

60

61

62

63

64

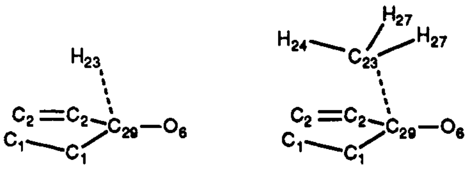
Figure 9. MM2 model transition structures for the reactions of metalated propionitrile with 2-cyclohexenone (59–62) and with cyclohexanone (63 and 64).

It is apparent that cyclohexanone is more sensitive to the size of nucleophile than cyclohexenone because there are two 1,3-diaxial interactions in the axial transition structure of the former and only one in the latter.

In order to check the sensitivity of the stereoselectivity toward the flexibility of transition structure model, the calculations were carried out with reduced coplanarity restrictions by setting V_2 of O=C---C=C to 4.0 or 2.0. The geometries of the transition structures are not changed, and the calculated stereoselectivities are not affected by these torsional parameter changes.

It has been observed that the reaction of lithiated acetonitrile with menthone gave a 20:1 ratio of products favoring equatorial addition, while the same reaction with pulegone leads to a 22:1 ratio of products, favoring axial addition.[7] For the reaction of pulegone, our calculations gave a 0.9 kcal/mol preference for the axial transition structure. The transition structures are shown in Figure 8. For the reaction of menthone, the calculations gave a 1.5 kcal/mol preference for the equatorial transition structure 58 over the axial transition structure 57. There is a 1,3-diaxial interaction between the nucleophile and one

Table VII. Parameters for the MM2 Transition-Structure Models of Hydride and Methyl Anion Additions to Cyclohexanones, Cyclohexenones, and Acyclic Carbonyl Compounds



hydride model methyl model

21	6	0	14			
6	29	23	24	1.000	0.000	0.000
6	29	23	27	0.000	0.000	0.000
5	29	23	27	0.000	0.000	0.000
5	29	23	24	0.000	0.000	0.000
1	29	23	27	0.000	0.000	0.000
1	29	23	24	0.000	0.000	0.000
6	29	2	2	0.000	1.000	0.000
6	29	2	1	0.000	0.000	0.000
6	29	2	5	0.000	0.000	0.000
23	29	2	2	0.000	3.000	0.000
23	29	2	1	0.000	0.000	0.000
23	29	2	5	0.000	0.000	0.000
6	29	1	1	−0.4	0.500	−0.2
6	29	1	5	0.000	0.000	0.18
23	29	1	1	−0.20	−0.20	0.40
23	29	1	5	0.000	0.000	0.30
23	29	1	2	−0.20	−0.20	0.40
6	29	1	2	−0.40	0.50	−0.2
1	29	1	1	0.600	0.40	0.7
1	29	1	2	0.600	0.40	0.7
5	29	1	1	0.600	0.400	0.7
6	29	5.36	1.269			
23	29	2.0	2.035			
1	29	4.4	1.510			
5	29	4.6	1.077			
2	2	8.0	1.340			
2	29	4.4	1.49			
23	29	6		0.250	96.277	
1	29	5		0.360	114.28	
1	29	1		0.450	115.59	
1	29	2		0.450	115.59	
6	29	1		0.600	120.503	
6	29	2		0.600	120.503	
6	29	5		0.500	120.26	
23	29	1		0.250	96.079	
23	29	2		0.250	96.079	
23	29	5		0.250	86.814	
29	23	24		0.25	68.371	
29	23	27		0.30	126.593	
24	23	27		0.36	105.760	
27	23	27		0.36	106.442	

of the methyl groups in **57**, and this interaction is absent in **58**.

For the reactions of metalated propionitriles with 2-cyclohexenone, there are four transition structures. Two of them, **59** and **60**, are derived from axial addition, and the two others, **61** and **62**, correspond to equatorial addition (Figure 9). These transition structures lead to four diastereomeric products if the cyclohexenone is substituted. Structures **63** and **64** are transition structures of axial and equatorial additions to cyclohexanone. The relative energies of these transition structures and the dihedral angles of C4=C3---C1=C2 (Φ) are given in Table VI. The dihedral angle is defined in such a way that if the rotation brings the methyl group inside the ring, it is negative, and if the rotation brings the methyl group outside the ring, it is positive.

For 2-cyclohexenone, the axial addition transition structures are predicted to be favored over the equatorial addition transition structures significantly. In both axial and equatorial additions, the methyl group prefers to be on the side of the α,β-unsaturated bond (**59** and **61**). Therefore, both high axial addition and diastereoselectivity observed experimentally are reproduced by the model calculations. The axial transition structures **59** and **60** have nearly perfect staggering of the forming C---C bond and the α-bonds, while the equatorial transition structures **61** and **62** are more nearly eclipsed and therefore are disfavored. The methyl group in **59** sits comfortably above the α,β-double bond as indicated by the 3° dihedral angle Φ. The methyl group in **60** is more crowded; in order to avoid the steric interaction with C_5 axial hydrogen, it rotates away from of the ring to a Φ of 26°.

As also shown in Table VI, when the torsional parameters for Φ are varied, axial selectivity is influenced only slightly. The 1,2-diastereoselectivity, on the other hand, drops steadily when the transition structure becomes more flexible. This is simply because the methyl group in **60** can rotate more easily to avoid steric interactions.

Conclusion

The higher axial selectivity of nucleophilic addition to cyclohexenone than to cyclohexanone is reproduced by ab initio calculations. Both orbital overlap and torsional strain are responsible for this higher axial selectivity. The tendencies of coplanarity of the enone moiety and of perpendicular relationship between the forming bond and the $C_\alpha{=}C_\beta$ bond in the transition structures cause larger torsional strain in the transition structure of equatorial addition. The MM2 transition structure force field developed on the basis of the torsional strain model reduces the experimental stereoselectivities very well.

The degree of coplanarity of the six-membered transition structures of the reactions of metalated alkyl nitriles is dependent upon the nature of the metal cation. The lithium counterion causes less flexibility, and the transition structures tend to be coplanar. The potassium counterion allows more flexibility, and the transition structures prefer to be twisted. The influence of this difference on stereoselectivity is reproduced by the force-field model.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research.

Appendix

A listing of the MM2 parameters is given in Table VII.

Comparison of the Magnetic Anisotropy of the Cyclopropane and Cyclobutane Ring Systems as Probed by the Proton NMR Spectroscopy of Spiro[cycloalkanefluorenes]

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Monsanto Chemical Company, 800 North Lindbergh Boulevard, St. Louis, Missouri 63167

Received October 23, 1990

A series of fluorenes in which the 9-position is either substituted with two hydrogens or is part of a three-, four-, or five-membered cycloalkane and the 2-position is substituted with H, NO_2, or NH_2 has been prepared and the proton and carbon-13 NMR spectra measured. The proton NMR chemical shifts and coupling constants were obtained from the LOACOON fitting procedure. The geometries and conformational equilibria were obtained by molecular mechanics methods and used to calculate an average van der Waals' strain energy for the H1′ and H8′ protons. The fluorene and spirocyclopentylfluorene were used as model compounds so that the "special" magnetic anisotropy effects of cyclopropane and cyclobutane rings could be estimated. The typical behavior of cyclopropane was confirmed: upfield shifts of protons located above and below the plane of the ring. A small downfield shift was found for the spirocyclobutanes; however, it is not large enough to force the conclusion that cyclobutane has a group magnetic anisotropy similar but opposite in direction to cyclopropane. Proton chemical shifts in this series of compounds cannot be used as an argument for the antiaromaticity of cyclobutane.

Introduction

Among the fascinating properties of the smallest cyclic hydrocarbon, cyclopropane,[2] is its often studied and poorly understood magnetic anisotropy. Cyclopropane has been observed to have a large magnetic anisotropy relative to other cyclic hydrocarbons.[3] Recently, the tensor contributions of the diamagnetic and paramagnetic susceptibility to the bulk anisotropy have been determined[4] and have

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(1) (a) Work performed in part at Amherst College. (b) Taken in part from P.R.K. Senior Thesis, Amherst College.

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