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Distortion in the Structures of 5-Azaadamantanone and Its *N*-Oxide: Implication on Diastereofacial Selectivity

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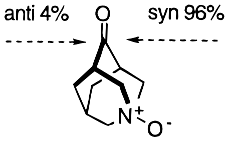
Ab initio molecular orbital studies of adamantanone (**1**), 5-azaadamantanone (**2**), and 5-azaadamantanone *N*-oxide (**3**) show that **2** and **3** have distorted structures. The torsional angle $\tau_{\mathrm{OCC}\alpha\mathrm{C}\beta}$ in the C_{2v} symmetric adamantanone **1** is 120.6°. $\tau_{\mathrm{OCC}\alpha\mathrm{C}\beta}$ is 124.0° in the piperidinedione ring of **3** and 117.8° in the cyclohexanone ring of **3**, indicating a significant distortion. The corresponding values for **2** are 122.5° and 120.3° indicating a slightly distorted structure. These structural results are consistent with the previously observed π-facial selectivity in $NaBH_4$ reduction of **2** and **3**, but contradict with the suggestion that they are symmetrical.

Introduction

Substituted adamantanone (**1**) derivatives are fascinating compounds which have been used to study electronic effects in diastereofacial selectivity[1−3] and hyperconjugation in carbocations[4] and in Lewis acid−ketone complexes.[5] Based on the cage structure, substituted adamantanones have been considered free of steric and torsional bias.[1−3] The π-facial selectivity observed in many experiments involving substituted adamantanones is in the range of ~60/40 (syn:anti),[1,3] which has been rationalized in terms of either the hyperconjugative model[1,2,6] or electrostatic effect.[3,7−9] In 1992, le Noble disclosed the results from the reduction of 5-azaadamantanone (**2**) derivatives and the π-facial selectivity reached 96 to 4 (syn:anti) in the case of 5-azaadamantanone *N*-oxide (**3**). The result of the observed high diastereofacial selectivity has been described as an excellent example of Cieplak model in operation.[2] To support the argument that **2** and **3** are free from distortion, three references of crystal structures of related compounds have been provided.[2,10−12]



In this manuscript, we report the structures of **1**−**3** calculated by *ab initio* molecular orbital methods.[13] It is shown that the structures of 5-azaadamantanone (**2**) and its *N*-oxide (**3**) are not symmetrical, and the previous interpretation of the crystal structures of related compounds was inaccurate.[2] The distortion of **3** is in the direction consistent with (a) 4-hetero atom substituted cyclohexanones[14] and (b) the superior π-facial selectivity of nucleophilic additions on **3**.[2] It is demonstrated that the structure of **3** is biased both sterically and torsionally, and the steric effect associated with the nucleophile trajectory may be the main factor governing the outcome of diastereofacial selectivity in 5-azaadamantanone oxide, **3**.[15]

Computational Methods. *Ab initio* calculations were performed with the GAUSSIAN 92 program[16] implemented on the Cray Y-MP/8 supercomputer. All initial structures were generated by interactive computer graphics[17] and then were fully optimized with the polarization basis set 6-31G* for adamantanone (**1**), 5-azaadamantanone (**2**), and 5-azaadmantanone *N*-oxide (**3**). The latter structure was further optimized using the polarization basis set 6-31G** (with a p-type function on hydrogen atom) and with the 6-31+G* (with diffuse functions) basis sets to better model the *N*-oxide function. Harmonic frequencies were calculated for each structure. The optimized structures all have all positive frequencies, which is an indication of true minima. Attempted calculations at the MP2/6-31* level was not successful due to computer memory and disk space limitations.

Results and Discussion

To better understand the structures of azaadamantanones, it is helpful to review the conformations of the

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⊗ Abstract published in *Advance ACS Abstracts,* December 15, 1995.

[1] (a) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874. (b) Chung, W. S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882−3 (c) Bodepudi, V.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001. (d) Li, H.; Mehta, G.; Padma, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2007.

[2] Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916.

[3] Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.*, **1994**, *59*, 1867−1876.

[4] Laube, T.; Hollenstein, S. *Helv. Chim. Acta* **1994**, 77, 1773−80.

[5] Laube, T.; Stilz, H. U. *J. Am. Chem. Soc.* **1987**, *109*, 5876.

[6] (a) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. (b) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

[7] (a) Wu, Y. D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (b) Paddon-Row, M. N.; Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638−10639.

[8] Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327−330. *Aust. J. Chem.* **1991**, *44*, 765−770.

[9] Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678−11688.

[10] Fernandez, M. J.; Galvez, E.; Lorente, A.; Soler, J. A.; Florencio, F.; Sanz, J. *J. Heterocycl. Chem.* **1989**, *26*, 349.

[11] McCabe, P. H.; Milne, N. J.; Sim, G. A. *Acta Crystallogr.* **1989**, *C45*, 114.

[12] Goncharov, A. V.; Panov, V. N.; Maleev, A. V.; Potekin, K. A.; Kurkutova, E. N.; Struchkov, Y. T.; Palyvulin, V. A.; Zefirov, N. S. *Dokl. Akad. Nauk. SSSR* **1991**, *318*, 907−910.

[13] Hehre, W. J.; Radom, L.; Schleyer, P. v. P.; Pople, J. A. *Ab initio Molecular Orbital Theory*, Wiley, New York, 1986.

[14] Gung, B. W.; Wolf, M. A.; Mareska, D. A.; Karipides, A. *J. Org. Chem.*, **1994**, *59*, 4899.

[15] Recently, a study of the transition state (3-21G*) for AlH_3 addition to **3** has appeared. However, distortion of the ground state configuration was not discussed. See: Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418−427.

[16] Gaussian 92, Revision B, M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1992.

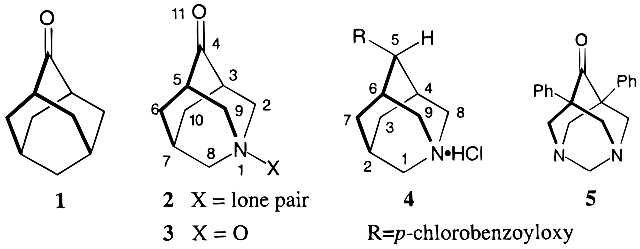
[17] Still, W. C. MacroModel 2.5, Columbia University.

0022-3263/96/1961-0232$12.00/0

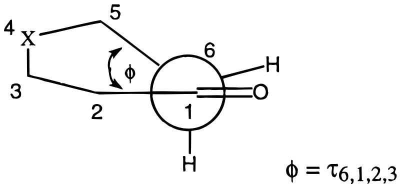
Table 1. Total Energies for Adamantanone (1), 5-Azaadmantanone (2), and 5-Azaadmantanone *N*-Oxide (3)

	1	2	3		
basis set	6-31G*	6-31G*	6-31G*	6-31G+*	6-31G**
total energy (au)	−461.724424	−477.698179	−552.477139	−552.493729	−552.496746

Chart 1



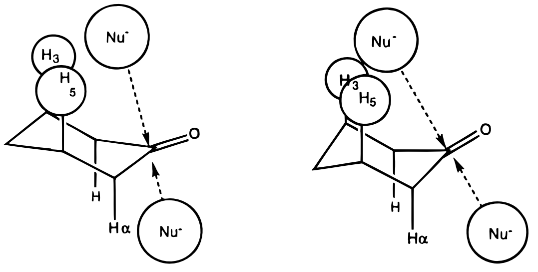
4-hetero atom substituted cyclohexanones.[14] There is a relationship between the carbon−hetero atom bond length and the endocyclic torsional angle ϕ, which was defined as shown below. It involves the four consecutive carbon atoms around the carbonyl carbon. The angle ϕ decreases as the C−X bond length becomes shorter. Thus, the following order of ϕ is found: 4-tetrahydropyranone (X = O, $\phi = 44.5°$) < 4-piperidinone (X = N, $\phi = 47.1°$) < cyclohexanone (X = C, $\phi = 49.1°$) < 4H-thiopyran-4-one (X = S, $\phi = 53.6°$). The magnitude of ϕ is inversely proportional to the C−X bond distance. In other words, the shorter the C−X bond is, the flatter the ring is.



$\phi = \tau_{6,1,2,3}$

The flattening or puckering of the ring measured by ϕ is of significant interest due to the fact that it directly influences the diastereofacial selection in nucleophilic addition to the carbonyl group.[18,19] A small ϕ indicates a flat ring, which suffers from high axial nucleophilic attack. The preferential axial attack on flat rings has been attributed to the antiperiplanarity of the nucleophile to the Cα−H bond and the minimization of torsional strain in the transition state.[18,19] We have suggested that the steric effect resulting from the trajectory change of the attacking nucleophile should be the most important factor.[14] The flat ring causes the trajectory of the axial attack to move away from the 3,5-diaxial substituents, Figure 1a. Consequently, less steric interaction is experienced by the nucleophile. The result of ring-puckering has the opposite effect. There is more steric interaction between the nucleophile and the 3,5-disubstituents on axial attack while less torsional strain on equatorial attack, Figure 1b. Therefore, equatorial attack is favored for puckered rings.

The distortion of the azaadamantanones **2** and **3** is in the direction consistent with the observations on 4-X-cyclohexanones.[14] The structures of **2** and **3** are made of two six-membered rings sharing a three-carbon (CαCOCα′) unit including the carbonyl group and connected by a methylene group at the other end of the rings. On the basis of the previous results, the six-membered ring containing a nitrogen atom should be flatter than the cyclohexanone ring since the C−N bond is shorter than the C−C bond. This is indeed the case. The piperidinedione ring has a smaller ϕ than the cyclohexanone ring in both **2** and **3**.



(a) flat ring favors axial attack

(b) puckered ring favors equatorial attack

Figure 1. Illustration of steric and torsional effects during a nucleophilic attack on a flat and a puckered cyclohexanone system.

Table 2. Optimized Structural Parameters for Adamantanone (1), 5-Azaadmantanone (2), and 5-Azaadmantanone *N*-Oxide (3)

	1	2	3		
	6-31G*	6-31G*	6-31G*	6-31G+*	6-31G**
		Bond Lengths (Å)			
R_{N1-C2}		1.457	1.484	1.486	1.484
R_{N1-C8}		1.460	1.485	1.487	1.485
R_{N1-C9}		1.457	1.484	1.486	1.484
R_{N1-O12}			1.358	1.361	1.358
R_{C2-C3}	1.542	1.546	1.535	1.535	1.535
R_{C3-C10}	1.542	1.543	1.542	1.542	1.542
R_{C3-C4}	1.518	1.517	1.519	1.518	1.519
R_{C4-C5}	1.518	1.517	1.519	1.518	1.519
R_{C4-O11}	1.193	1.193	1.190	1.192	1.191
R_{C6-C7}	1.537	1.538	1.537	1.536	1.537
R_{C7-C8}	1.536	1.536	1.530	1.530	1.530
R_{C7-C10}	1.537	1.538	1.537	1.536	1.537
		Bond Angles (deg)			
$\angle_{N1C2C3}$		111.3	111.1	111.1	111.1
$\angle_{C2C3C4}$	108.2	107.5	108.4	108.4	108.4
$\angle_{C3C4C5}$	112.8	112.0	111.7	111.8	111.7
$\angle_{C4C5C6}$	108.3	108.4	108.0	108.0	108.0
$\angle_{C5C6C7}$	109.8	109.0	108.7	108.7	108.7
$\angle_{C2N1C8}$		110.3	109.7	109.6	109.7
$\angle_{C2N1C9}$		110.0	109.4	109.3	109.4
$\angle_{C8N1C9}$		110.3	109.7	109.6	109.7
$\angle_{C2C3C10}$	109.5	108.6	109.2	109.3	109.3
$\angle_{C3C4O11}$	123.6	124.0	124.2	124.1	124.1
$\angle_{C5C4O11}$	123.6	124.0	124.2	124.1	124.1
$\angle_{C2N1O12}$			109.3	109.4	109.3
		Dihedral Angles (deg)			
$\tau_{C2C3C4C5}$	−59.3	56.9	56.9	57.0	56.9
$\tau_{C6C5C4C3}$	−59.3	60.2	61.3	61.3	61.3
$\tau_{C2C3C4O}$	120.6	−122.5	−124.0	−124.0	−124.0
$\tau_{C6C5C4O}$	120.7	−120.3	−117.8	−117.8	−117.8
$\tau_{OC4C3C5}$	180.0	180.6	179.2	179.1	179.1
τ_{OC4C3H}	0.0	−1.2	−3.86	−4.04	−3.89

The total energies of adamantanone (**1**) and 5-azaadamantanone (**2**) at the 6-31G* level and 5-azaadamantanone *N*-oxide (**3**) at various levels of theory are listed in Table 1. The optimized parameters for **1**−**3** are compiled in Table 2. It can be seen from Table 2 that the agreement is excellent among the three basis sets for the structure of **3**. To highlight some structure

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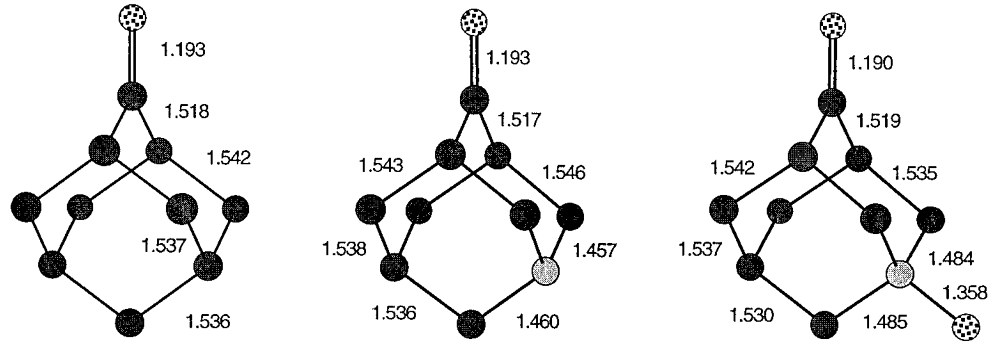
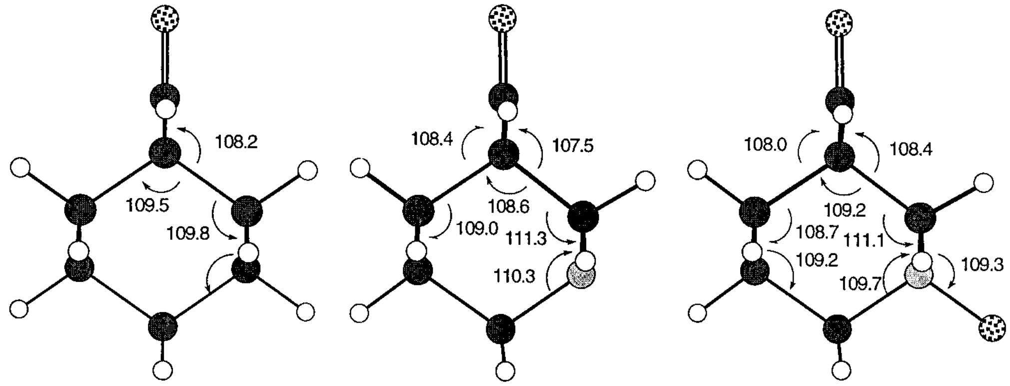
[18] Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

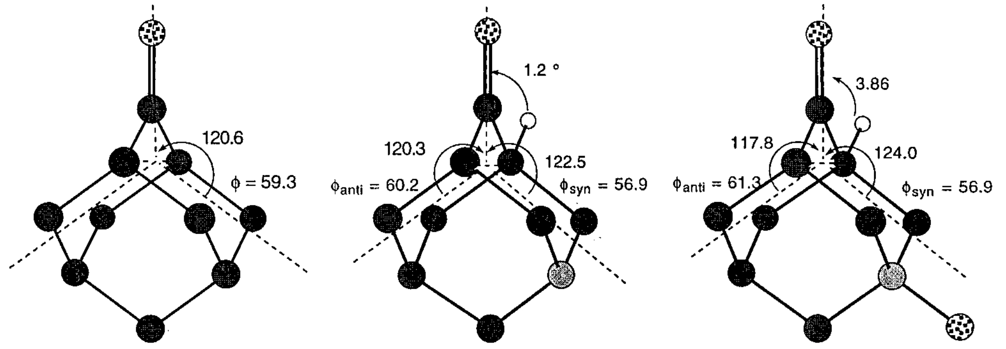
[19] (a) Mukherjee, D.; Wu, Y-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110,* 3328. (b) Wu, Y-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109,* 908.



(b) Bond angles (°)



(c) Dihedral angles (°)



1 **2** **3**

Figure 2. Optimized (6-31G*) structure of adamantanone (**1**), 5-azaadamantanone (**2**), and 5-azaadamantanone *N*-oxide (**3**).

features, selected (a) bond lengths, (b) bond angles, and (c) dihedral angles are listed along with the structures in Figure 2.

A. Distortion of 5-Azaadamantanone (2) and Its *N*-Oxide (3). Adamantanone (**1**) has a C_{2v} symmetry with the *C*2 axis oriented along the carbonyl C=O bond. Using the aforementioned definition of the endocyclic dihedral angle ϕ, it is obvious that the structures of the 5-azaadmantanone (**2**) and its *N*-oxide (**3**) are distorted from the C_{2v} structure of **1**, Figure 2. The degree of distortion is much greater for the *N*-oxide **3** than for the amine **2**. This is significant since the observed π-facial selectivity was much greater for **3** than for **2**.[2]

To the best of our knowledge, there are no experimental parameters on the structures of 5-azaadamantanone (**2**) and its *N*-oxide (**3**).[20] To search for experimental parameters for comparison to our calculation, we have carefully reviewed the three articles previously referred to by le Noble.[10-12] The first was a report on the crystal structure of 4-α-(*p*-chlorobenzoyloxy)-1-azaadamantane hydrochloride (**4**, Chart 1) by Galvez.[10] The sentence "each ring is a nearly perfect chair" was used, and quoted by le Noble.[2] However, if one carefully reads the whole sentence, it is clear that a distorted crystal structure, rather than a symmetrical one, was described. The following is the original sentence shown in its entirety:

"Therefore, each ring is a nearly perfect chair, but the C5 atom is more deviated from the plane through C4, C6, C8, C9, (0.743(5) Å), than from the plane through C3, C4, C6, C7, (0.688(5) Å), as a consequence of the *p*-chlorobenzoyloxy position on the C5 atom, the substituted cyclohexane and piperidine rings, in endo and exo positions respectively, having the largest deviation."[10]

Thus, the distortion observed in the crystal of **4** is in the same direction as in the calculated structure of **3**: the piperidine ring is flatter than the cyclohexane ring. Galvez has attributed the distortion to the substituent *p*-chlorobenzoyloxy. Although a direct comparison cannot be made to support the current calculations because the crystal structure is not a ketone, the claim of a nondistorted **3** with reference to **4** is inaccurate.

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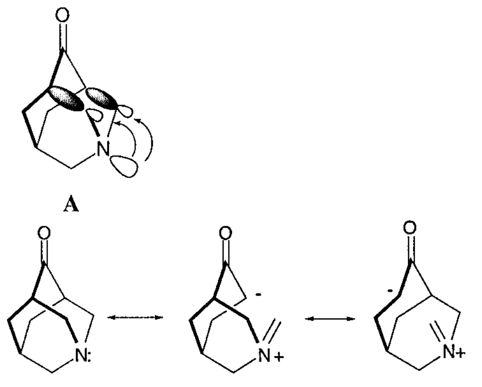
[20] There is an early report of a crystal structure of adamantanone in the plastic phase. Unfortunately, the crystal was orientationally disordered and the X-ray diffraction data were interpreted with assumptions leading to obvious error. Amoureux, J. P.; Bee, M. *J. Phys. C* **1980**, *13*, 3577–83.

Chart 2



A

a **b** **c**

The other two references previously given in support of a symmetric **3** are reports on the crystal structure of 5,7-diphenyl-1,3-diazaadamantanone, **5**, Chart 1.[11,12] It is interesting to point out that **5** has a C_{2v} symmetry, just like the parent compound adamantanone (**1**), while **2** and **3** have no symmetry axis along the carbonyl group. Because of the distinct difference in symmetry between **3** and **5**, it is inappropriate to use the crystal structure of **5** to exclude a possible distortion in **3**.

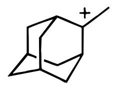
The piperidinedione ring in **3** is considerably flatter than the opposing cyclohexanone ring. This can be seen from the endocyclic dihedral angles ϕ and the torsional angle $\tau_{OCC\alpha C\beta}$, Figure 2. The endocyclic dihedral angle ϕ is 59.3° in adamantanone. Using it as a standard, the ϕ in the piperidinedione ring of **3** (56.9°) is smaller, therefore, flatter than the cyclohexanone in **1**. On the other hand, the ϕ in the cyclohexanone ring of **3** (61.3°) is larger, therefore, more puckered. The torsional angle $\tau_{OCC\alpha C\beta}$ in adamantanone **1** is 120.6°. Again this can be used as a standard to judge the symmetry in the azaadamantanones. $\tau_{OCC\alpha C\beta}$ is 124.0° in the piperidinedione ring of **3** and 117.8° in the cyclohexanone ring of **3**, indicating a serious distortion, Figure 2. The carbonyl group is pyramidalized and bends away from the nitrogen-containing ring. The dihedral angle τ_{OCCH} is 0° in adamantanone and 3.86° in **3** at the SCF level of theory using the 6-31* basis set. At the 6-31+G* level, the pyramidalization is even greater ($\tau_{OCCH} = 4.04°$).

The structure of **2** is not as distorted as **3**. However, the phenomenon of negative hyperconjugation appears to be present in **2**. The C−N bond distances in **2** (1.457 Å) are considerably shorter than that in **3** (1.484 Å). This is consistent with the well known effect of negative hyperconjugation.[21] An attractive two-electron interaction between the lone pair of the nitrogen atom and the C−C σ^* orbital is present in the amine **2**, structure **A**, Chart 2. Negative hyperconjugation has been demonstrated theoretically for many molecular systems, including anions and neutral molecules.[21] Recent NMR experiments have confirmed that a high energy barrier exists in the inversion-rotation in compounds, such as FCH_2-NR_2.[22] This is because the large negative hyperconjugation effect in FCH_2-NR_2 due to the small energy difference between the lone pair orbital and the σ^*_{C-F} orbital. In the azaadamantanone system, the energy difference between the lone pair and the σ^*_{C-C} orbital is expected to be large. Therefore the hyperconjugative interaction in **2** is expected to be small. This interaction can be depicted either in terms of the molecular orbital diagram **A** or in terms of the classical double bond/no bond format (**a**, **b**, **c**, Chart 2).

The result of such interaction is the shortening of the C−N bond and the lengthening of the $C_\alpha-C_\beta$ bonds. By comparing the bond distances and angles with that of **3** (Figure 2), the structural parameters of **2** in Table 2 are consistent with the structures depicted in Chart 2. It is worth noting that even though the C−N bond length in **2** is shorter than that in **3**, the ϕ of **2** is identical to that of **3**. This is probably because that the bond angle $\angle_{CNC}$ in **2** (110.0°) is larger than that in **3** (109.3°), another indication of negative hyperconjugation.

B. It Is Energetically More Favorable for an sp^2 Carbon to Adopt a Pyramidalized Form in the Distorted Adamantanone System. The calculated endocyclic dihedral angle ϕ is 59.3° for adamantanone **1**, which is about 10 ° greater than the ϕ in cyclohexanone ($\phi = 49.1°$).[14] The ϕ in **2** and **3** are also larger than their corresponding free six-membered ketones by ~12°. Therefore, the six-membered rings in adamantanone system are considerably more puckered than free cyclohexanone and piperidinedione ($\phi = 45.8°$).[14] This indicates that the cage structure of adamantanone system is not strain free. One easily identifiable source of strain is the mutual constraint at the α carbons of the carbonyl group by the two rings. Thus the bond angle $\angle_{C\alpha COC\alpha'}$ (112.0° in **2** and 111.7° in **3**) is smaller than that in cyclohexanone (115.4 °) or that in 4-piperidinedione oxide (114.6°). On the other hand, adamantane ($\phi = 60°$) has only a minimal amount of strain compared to cyclohexane ($\phi = 55°$).[23] This is because all carbon atoms in adamantane are sp^3 hybridized. Adamantanone, on the other hand, contains a trigonal planar sp^2 carbon atom, which prefers 120° bond angle. The bond angle $\angle_{C\alpha COC\alpha'}$ in **1, 2**, and **3** is much smaller than a normal sp^2-hybridized atom angle. The ideal 120° bond angle of a sp^2 carbon atom can only be achieved when a six-membered ring is planar, such as in the benzene ring. The adamantanone system has two six-membered rings joined at C2, C4, and C6, which does not allow the flattening of either chair conformation.

Therefore, a strain due to the compressed angle ($\angle_{C\alpha COC\alpha'}$) exists in adamantanone derivatives. To relieve some of this strain, the carbonyl carbon of the adamantanones prefers to adopt a pyramidalized configuration whenever symmetry allows. This conclusion is based on the current calculations and on several reports in the literature. First, the $SbCl_5$-complexed 5-phenyl-2-adamantanone is distorted according to a X-ray structure analysis by Laube.[5] Secondly, there are mounting evidence that the tertiary carbocation **6** is pyramidalized.[24] It appears to be energetically more favorable for the normally planar sp^2 carbon to adopt a pyramidalized form in the distorted adamantanone system.



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C. Implications on Diastereofacial Selectivity. The reduction of **2** and **3** with $NaBH_4$ in methanol has been studied by le Noble.[2] The result is 95% syn attack on **3** and 62% syn attack on **2**. Here we suggest that the

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[21] For theoretical studies, see: (a) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371. (b) Dill, J. D.; Schleyer, P. v. P.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 1663. (c) Schleyer, P. v. P.; Kos, A. J. *Tetrahedron*, **1983**, *39*, 1141. (d) Bingham, R. C. *J. Am. Chem. Soc.* **1975**, *97*, 6743. (e) Hoffmann, R.; Radom, L.; Pople, J. A.; Schleyer, P. v. P.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1972**, *94*, 6221.

[22] For an experimental study, see: (f) Rahman, M. M.; Lemal, D. M.; Dailey, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 1964.

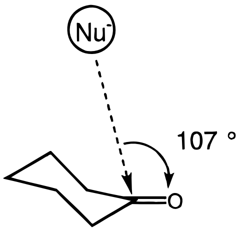

Figure 3. Illustration of the Burgi–Dunitz trajectory. The angle $\angle_{\mathrm{NuCO}}$ is 107 ± 5°.

observed diastereofacial selectivity can be accounted for by the distorted azaadmantanone structure. The steric effect related to the Burgi-Dunitz trajectory is considered.[25a]

Through the study of the X-ray structures of amino ketones, Burgi and Dunitz proposed that the optimal trajectory for nucleophilic addition to carbonyl compounds should be around 107°, Figure 3.[25a] This was later confirmed by theoretical calculations.[25b] 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.[26] Anh has concluded that the Felkin model for nucleophilic addition to α-chiral ketones works best when the Burgi–Dunitz trajectory is considered.[18]

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.[27] Thus a nucleophile with high HOMO energy would have greater attacking angle than one with lower HOMO. The importance of the Burgi–Dunitz trajectory theory was further highlighted by Heathcock through a study of Lewis acid-mediated additions of enol silanes to chiral aldehydes.[28] 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, we see that the attack on the two faces of 5-azaadmantanone oxide (**3**) shows significant differences in steric interactions, Figure 4.

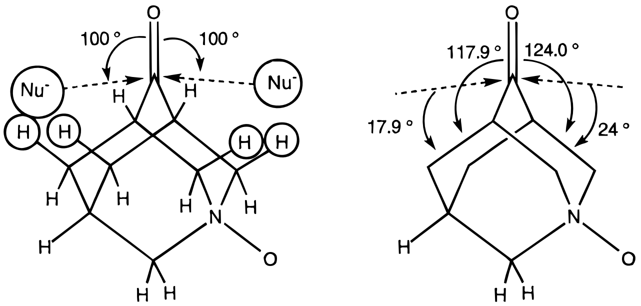

Figure 4. Differences in steric interactions for syn and anti attack on 5-azaadmantanone *N*-oxide (**3**).

An attack angle of 100° is depicted to illustrate the difference in steric interactions resulted from the distortion of the azaadmantanone skeleton. It can be seen that the cyclohexanone part (opposite to the ring containing the nitrogen atom) of the ring of **3** 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 $\sim$60/40 (syn:anti).[1,3] These results of modest diastereofacial selectivity has been rationalized in terms of either the hyperconjugative model[1,2,6] or electrostatic effect.[3,7–9] However, a selectivity of 96:4 (syn:anti) was observed for 5-azaadamantanone *N*-oxide (**3**).[2] le Noble has shown the absence of electrostatic effects in the additions to **3** by changing the reaction media. We agree that polar effects alone are probably not accountable for such a dramatic increase in π-facial selectivity. However, we also doubt that hyperconjugative effects alone could 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-azaadmantanone oxide (**3**).

Conclusions

The calculated structures of 5-azaadamantanone (**2**) and its *N*-oxide (**3**) show different degree of distortion. The structure of **3** is considerably more distorted than that of **2**. The direction of the distortion is the bending of the carbonyl group toward the cyclohexanone ring and away from the piperidinedione ring. The piperidinedione ring is flatter than the cyclohexanone ring. Due to the compressed bond angle ($C_\alpha C(=O)C_\alpha$) in the adamantanone system, it is energetically more favorable for the sp^2 carbon to adopt a pyramidalized configuration. For the calculated azaadamantanones **2** and **3**, both the degree and the direction of the distortion are consistent with the previously observed π-facial selectivity in the reduction of **2** and **3** with $NaBH_4$. The observed diastereofacial selectivity can be easily understood in terms of steric effect related to the Burgi–Dunitz trajectory. Therefore, the structural effect must be counted before invoking other electronic effects. Based on most reported π-facial selection in the adamantanone system ($\sim$60/40),[1,3] the high ratio (96/4) observed for **3** is most likely due to structure distortion according to this study.

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(23) Shen, M.; Schaefer, H. F., III; Liang, C.; Lii, J. H.; Allinger, N. L.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1992**, *114*, 497.

(24) Kelly, D. P.; Aherne, K.; Delgado, F.; Giansiracusa, J. J.; Jensen, W. A.; Karavokiros, R. A.; Mantello, R. A.; Reum, M. E. *J. Am. Chem. Soc.* **1993**, *115*, 12010.

(25) (a) Burgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Burgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956–1957.

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

(27) Liotta, C. L.; Burgess, E. M.; Eberhardt, W. H. *J. Am. Chem. Soc.* **1984**, *106*, 4849–4852.

(28) (a) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 7199. (b) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819.

(29) Pross, A.; Radom, L.; Riggs, N. V. *J. Am. Chem. Soc.* **1980**, *102*, 2253–2259.