2,3-Dioxabicyclo[2.2.2]oct-5-ene: A Pyramidalized Olefin Whose Facial Selectivity Does Not Parallel Its Pyramidalization

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The HF/3-21G-optimized geometry of 2,3-dioxabicyclo[2.2.2]oct-5-ene (1) shows that its olefinic hydrogens are bent in the syn direction (with respect to the dioxy bridge) by 2.1°, thus giving rise to anti pyramidalization of the doubly-bonded carbon atoms. However, diazomethane, 2-diazopropane, 3,4-dihydroisoquinoline N-oxide, and several nitrile oxides (i.e., bulky nitrile oxides and nitrile oxides with a low dipole moment) reacted with 1 to afford the syn adduct as the dominant product. That is, the preferred approach of these 1,3-dipoles to 1 takes place from the direction opposite to that of its ground-state pyramidalization. The syn preference of these reactions is explained as a result of higher steric interactions in the anti than in the syn attack. Steric effects, which favor the syn attack, overcome electrostatic interactions and factors related to pyramidalization, which favor the anti. This conclusion is discussed on the basis of ab initio (STO-3G) and semiempirical (AM1) calculations of the syn and anti transition structures of the reactions of diazomethane and some nitrile oxides with 1. In particular, these calculations show that (i) pyramidalization of the trigonal centers of 1 is higher in anti TSs than in their syn counterparts, thus paralleling the ground-state anti pyramidalization of 1, and (ii) a more inclined trajectory of approach to 1 is followed by the 1,3-dipole in the anti than in the syn attack in order to lessen steric interactions. Transition structures also offer some explanation of the unexpected anti selectivity of the reaction of trimethylacetonitrile oxide with 1.

Introduction

Over the last two decades, theoretical and experimental studies have repeatedly shown that the trigonal centers of a double bond often pyramidalize significantly when put in an unsymmetrical environment.[1-4] This finding has raised the question of what, if any, is the relationship between pyramidalization of trigonal centers and their reactivity. Recently, Seebach et al.[3,4] have suggested that the steric course of attack on a trigonal center can be predicted from the direction of its pyramidalization; that is, the reaction will occur preferentially from the direction into which the center is pyramidalized.

However, there is some controversy about the role of pyramidalization in determining facial selectivity, even in the case of substantially pyramidalized alkenes, e.g., norbornene (Figure 1),[2] whose facial selectivity is in accord with Seebach's suggestion. Several years ago, Houk clearly stated that ground-state pyramidalization parallels reactivity and diastereoselectivity but does not cause it.[5] He argued that the ground-state anti (with respect to the methano bridge) distortion of the olefinic hydrogens[6] of norbornene (syn pyramidalization[6] of the doubly-bonded carbon atoms) is caused by relief of torsional strain (i.e., between the olefinic and bridgehead hydrogens and between the π bond and the methano bridge), just as the syn transition state of the reactions of this olefin is more stable than its anti counterpart (a lower torsional strain is present in the former, in particular, a more favorable staggering between the bonds being formed and the allylic σ bonds[5]) (Figure 1). Thus, in Houk's opinion, staggering between the incipient bonds and the allylic σ bonds is the dominant factor in controlling facial selectivity in norbornene reactions. In contrast, Gleiter and Morokuma advocate ground-state syn pyramidalization and the related more facile anti than syn deformability of the olefinic hydrogens as the principal origin of the high syn selectivity of norbornene reactions.[7,8]

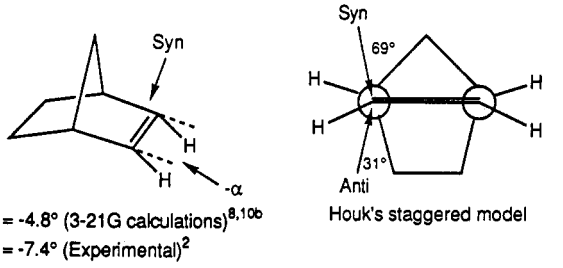

Figure 1. Pyramidalization of norbornene and staggering between the forming bonds and allylic σ bonds in norbornene reactions. An angle of 102° (typical for 1,3-dipolar cycloadditions) between the forming bonds and the π bond is assumed.

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(1) (a) Houk, K. N. *Stereochemistry and reactivity of systems containing π electrons*; Watson, W. H., Ed.; Verlag Chemie International: Deerfield Beach, 1983; pp 1–40. (b) Borden, W. T. *Chem. Rev.* **1989**, *89*, 1095. (c) Haddon, R. C. *J. Am. Chem. Soc.* **1991**, *113*, 1781.

(2) (a) Ermer, O.; Bell, P.; Mason, S. A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1239 and references cited therein. (b) The value of 7.4° was not evaluated for norbornene itself but for a norbornenedicarboxylic anhydride.

(3) Seebach, D.; Zimmermann, J.; Gysel, U.; Zieglert, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763.

(4) Seebach, D.; Maetzeke, T.; Petter, W.; Klotzer, B.; Plettner, A. *J. Am. Chem. Soc.* **1991**, *113*, 1781 and references cited therein.

(5) Houk, K. N.; Rondan, N. G.; Brown, F. K. *Isr. J. Chem.* **1983**, *23*, 3 and references cited therein.

(6) Syn pyramidalization of the doubly bonded carbon atoms corresponds to anti bending of the olefinic hydrogens and *vice versa*.

(7) Spanget-Larsen, J.; Gleiter, R. *Tetrahedron* **1983**, *39*, 3345.

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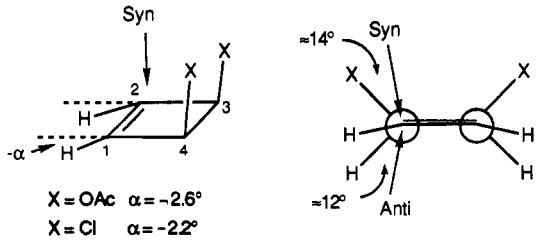


Figure 2. Pyramidalization and staggering for cyclobutenes. An angle of 102° between the forming bonds and the π bond is assumed.

We also have addressed this problem and have found that the tendency to maximize σ–π hyperconjugation, which induces ground-state pyramidalization of norbornene,[9a,b] is paralleled in the TS of its reactions by the tendency to maximize delocalization between the forming bonds and the allylic σ bonds.[10b,c,11]

The norbornene problem makes it clear that the link between facial selectivity and pyramidalization can be overshadowed by the presence of staggering effects; i.e., both factors can often convincingly explain the same stereochemical outcome. Only a few examples have been reported in which factors controlling facial selectivity can unambiguously be related to factors which promote ground-state pyramidalization.[3,4] One convincing example of this relationship, not compounded by staggering effects, is provided by the dominance of syn attack (disfavored by steric and electrostatic interactions) in the reactions of several 1,3-dipoles[12a,b] and osmium tetraoxide[12c] with cis-3,4-disubstituted cyclobutenes bearing electron-attracting open-chain substituents (i.e., dialkoxy, diacetoxy, dimesyloxy, and dichlorocyclobutene). In these reactions, staggering between the incipient bonds and the allylic bonds during a syn attack is similar to that during an anti attack (Figure 2). Moreover, we have shown[10a–c,12b] that factors such as Hehre's electrostatic effect[13] or Cieplak's effect (i.e., antiperiplanar interactions between σ^* orbitals of the forming bonds and the σ orbitals of the allylic bonds)[14] cannot explain the observed selectivity. On the other hand, these cyclobutenes exhibit a small but significant syn (with respect to heteroatoms) pyramidalization of the trigonal carbon atoms (i.e., the olefinic hydrogens are anti bent by 2–3°, Figure 2)[9a,12b,15] and a related more facile anti than syn deformability of the olefinic hydrogens (it takes less energy by ≈2 kcal mol^{-1} to bend these hydrogens in the anti direction by 20° than in the syn direction by the same amount, i.e., $E_{+20°(syn)} - E_{-20°(anti)} = 1.2–2.9$ kcal mol^{-1}).[12b] Syn pyramidalization and the more facile anti deformability of the olefinic hydrogens (both were traced back by us to the tendency of the system to maximize vicinal delocalization between the σ-AOs of the allylic C–X bonds and the π-AOs of the double bond)[9a] are the only factors that adequately parallel the observed syn selectivity.

Analysis of the activation energy of the HF/3-21G syn and anti transition structures of the reactions of dichlorocyclobutene with diazomethane[10a] and formonitrile oxide[10b,c] has shown that the intrinsic facial bias of this cyclobutene is reflected, at the transition state, in the deformation energy of both cyclobutene and the 1,3-dipole and in the interaction energy between them. Analysis of intramolecular interactions in these transition structures has indicated that the strong synperiplanar vicinal delocalizations between the incipient bonds and the C–Cl bonds are a major factor in determining the higher stability of the syn transition structure relative to its anti counterpart.[10c] Thus, in the reactions of these cis-3,4-disubstituted cyclobutenes factors related to their ground-state pyramidalization win over steric and electrostatic effects in controlling facial selectivity.

In the context of our systematic study of facial selectivity in 1,3-dipolar cycloadditions, we now report the reaction of 1,3-dipoles with the pyramidalized 2,3-dioxabicyclo[2.2.2]oct-5-ene (1). As in the case of cyclobutenes, staggering between the incipient bonds and allylic σ bonds should not be important in differentiating the two faces of 1, but in contrast with cyclobutenes, it will be shown that the facial selectivity of 1,3-dipolar cycloadditions of this dipolarophile does not parallel its pyramidalization: it represents an exception to the rule suggested by Seebach.[3]

Only the reactions of 1 with diimide (syn/anti = 66/34)[16a] and *m*-chloroperbenzoic acid (syn/anti = 45/55)[16b] have previously been reported.

HF/3-21G Geometry of 2,3-Dioxabicyclo[2.2.2]oct-5-ene. HF/3-21G[17] geometry of bicyclo[2.2.2]oct-2-ene exhibits a planar double bond with the olefinic hydrogens eclipsed with the bridgehead hydrogens (Figure 3). On the other hand, the HF/3-21G full optimization of the geometry of 2,3-dioxabicyclo[2.2.2]oct-5-ene (1) led to a structure of C_s symmetry in which the olefinic hydrogens are bent out-of-plane in the syn[18] direction by a small but significant amount ($\alpha = +2.1°$) (Figure 3).[19] Noteworthy, this anti (with respect to the allylic oxygen atoms) pyramidalization of the doubly-bonded carbon atoms of

(8) Koga, N.; Ozawa, T.; Morukuma, K. *J. Phys. Org. Chem.* **1990**, *3*, 519.

(9) (a) Rastelli, A.; Burdisso, M.; Gandolfi, R. *J. Phys. Org. Chem.* **1990**, *3*, 159. (b) Rastelli, A.; Cocchi, M.; Schiatti, E.; Gandolfi, R.; Burdisso, M. *J. Chem. Soc., Faraday Trans.* **1990**, *86*, 783.

(10) (a) Bagatti, M.; Ori, A.; Rastelli, A.; Burdisso, M.; Gandolfi, R. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1657. (b) Bagatti, M.; Rastelli, A.; Burdisso, M.; Gandolfi, R. *J. Phys. Org. Chem.* **1992**, *5*, 819. (c) Bagatti, M.; Ori, A.; Rastelli, A.; Burdisso, M.; Gandolfi, R. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 29. (d) Rastelli, A.; Bagatti, M.; Gandolfi, R. *Ibid.*, in press.

(11) (a) These hyperconjugative interactions are evaluated by using an orthogonalized hybrid atomic orbital basis set.[9,10c,d,34] It should be stressed that in our model[34] all the interactions between bonds, and consequently also those between the incipient bonds and the allylic σ bonds even when they bear either a synperiplanar or a synclinal relationship, are stabilizing because they give rise to delocalization. In contrast, in Houk's model the interactions between eclipsed bonds (synperiplanar interactions) are considered destabilizing.[5]

(12) (a) Burdisso, M.; Gandolfi, R.; Lucchi, M.; Rastelli, A. *J. Org. Chem.* **1988**, *53*, 2123. (b) Burdisso, M.; Gamba, A.; Gandolfi, R.; Toma, L.; Rastelli, A.; Schiatti, E. *J. Org. Chem.* **1990**, *55*, 3311 and references cited therein. (c) Burdisso, M.; Gandolfi, R.; Rastelli, A. *Tetrahedron Lett.* **1991**, *32*, 2659.

(13) (a) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650. (b) Kahn, S. D.; Hehre, W. J. *Ibid.* **1987**, *109*, 663.

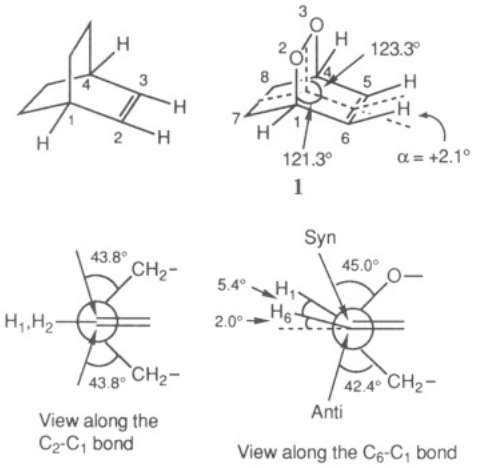
(14) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

(15) (a) Hake, H.; Landen, H.; Martin, H. D.; Mayer, B.; Steigel, A.; Distefano, G.; Modelli, A. *Tetrahedron Lett.* **1988**, *29*, 6601. (b) For difluorocyclobutene see: Caramella, P.; Marinone Albini, F.; Vitali, D.; Rondan, N. G.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 1875.

(16) (a) Bloodworth, A. J.; Eggelte, H. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 2069. (b) Abkulut, N.; Balci, M. *J. Org. Chem.* **1988**, *53*, 3338.

(17) Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavacari, K.; Binkley, J. S.; Gonzales, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. GAUSSIAN 88, Gaussian, Pittsburgh, PA, 1988.

(18) Throughout we will use the syn descriptor for attack on the double bond of 1 (and for substituents in the adducts) near the dioxy bridge. The same system of descriptors will be used for out-of-plane bending of the olefinic hydrogens, e.g., in syn bending these hydrogens bend toward the dioxy bridge and the bending angle α is given a plus sign.



Bond lengths (Å) and bond angles (°) of **1**.

C_1-O_2 = 1.476	C_1-H_1 = 1.077
O_2-O_3 = 1.475	C_5-H_5 = 1.070
C_1-C_6 = 1.505	C_1-C_6-C_5 = 113.0
C_1-C_7 = 1.536	C_1-C_6-H_6 = 121.9
C_5-C_6 = 1.317	H_1-C_1-C_6 = 114.0
C_7-C_8 = 1.559	H_5-C_5-C_6 = 125.1

Total energy of **1** = -379.34988 hartree

Figure 3. Geometry details of the HF/3-21G ground-state structures of bicyclo[2.2.2]oct-2-ene and of 2,3-dioxabicyclo-[2.2.2]oct-5-ene. Staggering between the forming bonds and allylic σ bonds for attacks on these two dipolarophiles.

1 is similar in magnitude to that calculated for dichloro- and dialkoxycyclobutenes (see Figure 2), but it takes place in the direction opposite to the syn pyramidalization of these cyclobutenes.

Moreover, in contrast to what is observed in norbornene, the syn out-of-plane bending of the olefinic hydrogens in the ground state of 1 brings about a decrease of the torsion angle (i.e., an increase in torsional interactions) between these hydrogens and the bridgehead hydrogens relative to that in a planar or in an anti bent geometry. Thus, geometries of bicyclooctene derivatives (see also the discussion about the deformed molecules below) do not provide any evidence that correlates with the effectiveness of torsional repulsions between olefinic and bridgehead hydrogens.

We also calculated (HF/3-21G) the energy of model molecules in which an out-of-plane bending of the olefinic hydrogens by +20° (syn) and −20° (anti), respectively, was imposed on the otherwise frozen equilibrium geometry of 1. In the anti bent molecule, the dihedral angle between the olefinic and bridgehead hydrogens ($H_1C_1C_6H_6$ = 26.1°) is much higher than that in the syn bent form ($H_1C_1C_6H_6$ = −11.2°). However, the syn bent molecule was found to be more stable than the anti bent, i.e., $E_{+20°(syn)} - E_{-20°(anti)}$ = −1.6 kcal mol^{-1}. This energy bias, which once again is similar in magnitude but opposite in sign to that calculated for dialkoxy and bis(mesyloxy)cyclobutenes, etc.,[9b] suggests that ground-state effects should be reflected in the transition state and should favor an anti attack over a syn attack on 1.

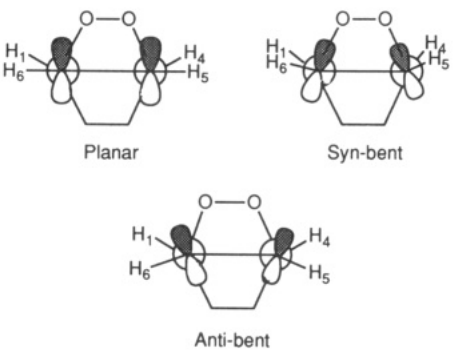


Figure 4. Hyperconjugative interactions between the π bond and the allylic σ bonds in the planar, syn-bent, and anti-bent forms of 1.

The ground-state deformation of 1 and the more facile syn than anti deformability of its olefinic hydrogens can be explained if one assumes that (i) there is a tendency to maximize delocalization between bonds, in particular that between the π-bond and the allylic σ bonds, and (ii) that vicinal delocalizations between the σ-AOs of the C–O bonds and the π-AOs of the double bond are more stabilizing than those involving the σ-AOs of the C–C bonds. As shown in Figure 4, syn bending of the olefinic hydrogens gives rise to a tilting of the π-AOs that strengthens the π-σ_{CO} interaction while weakening the π-σ_{CC} delocalization; the opposite is true for anti bending.

As for staggering between the incipient bonds and the allylic σ bonds (exemplified in Figure 3; an angle of 102° between the forming bonds and the double bond is assumed), it should be similar in the two diastereotopic attacks on 1.

On the basis of the structural data for 1, one can anticipate that (i) anti attack should be favored by its anti pyramidalization, (ii) steric effects should favor syn attack since a methylene group is sterically more demanding than an oxygen atom (v = 0.52 and 0.36 for Me and OMe, respectively),[20] and (iii) electrostatic repulsions between the terminal heteroatom of the 1,3-dipole and the oxygen atoms of the dipolarophile should discourage syn attack (dipole moment of 1: μ = 3.1 D, MNDO[21] calculations).

Results and Discussion

It is well known that bicyclo[2.2.2]oct-2-ene is very reluctant to enter cycloaddition with 1,3-dipoles, in particular diazoalkanes.[22,23] However, the presence of two oxygen atoms highly enhances the reactivity of 1 toward diazoalkanes. Thus, high yields of syn/anti[18] mixtures could be isolated from the reactions of 1 with excess diazoalkane, i.e., diazomethane and 2-diazopropane (Scheme I). The syn adduct (i.e., 2) is prevalent in both reactions, and a significant increase in syn selectivity parallels the increase in steric requirements upon passing from the former to the latter 1,3-dipole.

(19) We have recently observed (STO-3G calculations) that also in the norbornene series (i.e., norbornene, 7-oxanorbornene, and 5,6-dioxanorbornene) replacement of a carbon atom by an oxygen atom results in a change in pyramidalization which parallels that found for bicyclooctenes, i.e., a decrease in the 7-oxa derivative and an increase in the 5,6-dioxa derivative as compared to norbornene.[9b] At the same time Houk reported (3-21G calculations) that an electron-withdrawing group at position 7 brings about a decrease of norbornadiene pyramidalization: Houk, K. N.; Wu, Y.-D.; Mueller, P. H.; Caramella, P.; Paddon-Row, M. N.; Nagase, S.; Mazzocchi, P. H. *Tetrahedron Lett.* **1990**, *31*, 7289. Houk had also previously shown (STO-3G calculations) that pyramidalization of acyclic alkenes is influenced by the electronegativity of the allylic substituent.[5]

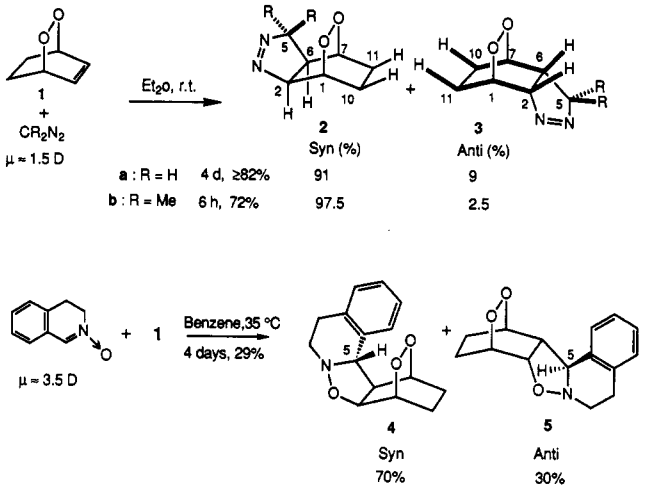
(20) Charton, M. *Top. Curr. Chem.* **1983**, *114*, 57.

(21) Dewar, M. J. S.; Thei, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 4899. The standard version of MNDO as implemented in the MOPAC package of computer programs was used.

(22) Huisgen, R. *Pure. Appl. Chem.* **1981**, *53*, 171.

(23) Burdisso, M.; Gandolfi, R. *Tetrahedron* **1991**, *47*, 7699.

Scheme I



We then investigated the reaction of 3,4-dihydroisoquinoline *N*-oxide, which is characterized by a higher dipole moment (≈3.5 D)[24] than diazoalkanes (1.5 D for diazomethane),[24a] with 1 (Scheme I). This reaction was very sluggish, and a decrease in syn selectivity, relative to the reaction of diazoalkanes, was observed. However, here again, the syn addition was clearly dominant over its anti counterpart. Only two (i.e., *exo-syn*-**4** and *exo-anti*-**5**) of the four possible diastereoisomers were isolated. Insurmountable steric interactions between the ethano and dioxy bridge, respectively, and an attacking endo-oriented dihydroisoquinoline *N*-oxide are responsible for the absence of endo-anti and endo-syn adducts.

Syn/anti ratios were evaluated by ^{1}H NMR, and all of the adducts were fully characterized. Even at first sight it is quite evident that syn adducts of 1,3-dipoles to 1 should exhibit substantially higher dipole moments than those of the related anti adducts. This qualitative prediction was substantiated by MNDO calculations; for example, the dipole moment of **2a** (4.7 D) exceeds that of **3a** (2.0 D) by 2.7 D.[25,26] This difference makes syn adducts move more slowly than anti adducts on thin-layer and column chromatography, thus allowing not only an easy separation of facial isomers but also a fast reliable distinction between them. Further diagnostic features for definitive structural assignments were provided by ^{1}H NMR data (see Experimental Section): (i) The signals of H-2 (H-6) in anti adducts displayed a long-range (^4J) coupling constant of 1.0–2.0 Hz owing to the presence of a *W* coupling path between H-2 (H-6) and H-10-syn (H-11-syn) (Scheme I). A coupling path of this type and the related coupling constant were missing in syn adducts. (ii) $J_{1,2}$ and $J_{6,7}$ are higher by ≥2.0 Hz in anti ($J_{1,2}$ and $J_{6,7}$ ≈ 4.0–5.0 Hz) than in syn adducts ($J_{1,2}$ and $J_{6,7}$ ≈ 2.0–3.0 Hz) as a result of the fact that the dihedral angles $H_1C_1C_2H_2$ and $H_6C_6C_7H_7$ are smaller by ≈10° in anti adducts than in syn isomers (50° and 53°, respectively, in anti **3a** and 63° and 66°, respectively, in syn **2a**; MNDO geometries).[25,26] (iii) Protons H-2 and H-6 in anti adducts resonated at lower fields by ≥0.4 ppm (in $CDCl_3$) than the same protons in syn adducts as a consequence of a deshielding effect by the lone pairs of the oxygen atoms. Consistently, the same protons experienced a lower ASIS [aromatic solvent induced shift, $\Delta\delta = \delta(CDCl_3) - \delta(C_6D_6)$; see Experimental Section]; namely, they displayed an upfield shift less by 0.3–0.4 ppm in anti than in syn adducts upon passing from chloroform to benzene. The high electron density next to the oxygen atoms prevents efficient solvation by benzene molecules on the side syn to the dioxy bridge.

The negative value of the ASIS effect for H-5 in **4** and the fact that this proton in **5** experienced an ASIS effect similar or even lower than that of the other protons testifies to its being inside (i.e., a structure resulting from an exo TS).

It is quite evident that, at variance with Seebach's suggestion[3] and the above cited results in the cyclobutene field, the preferred approach of diazoalkanes and nitrones to 1 is from the direction opposite to that into which its trigonal centers are pyramidalized. The syn preference in the reaction with diazomethane can be easily explained by higher steric interactions in the anti than syn approach.[27] This rationalization is supported by the enhancement in the syn preference observed for the reaction of sterically more encumbered 2-diazopropane.[28]

The lesser syn selectivity in the reaction of dihydroisoquinoline *N*-oxide compared to diazomethane can be attributed to repulsive electrostatic interactions between the negatively charged oxygen atom of this 1,3-dipole and those of 1 in the syn attack.[28]

In order to substantiate the role of steric and electrostatic interactions, we decided to investigate the reactions of 1 with a large number of nitrile oxides whose size and dipole

(24) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, pp 28–29. (b) Breur, E. In *Nitrones, Nitronates and Nitroxides*; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: New York, 1989; p 142.

(25) (a) It is well known that AM1 and MNDO methods underestimate the length of O–O bonds by ca. 0.15 Å.[26] MNDO calculations predicted 1.30 Å for the O–O bond length in 1 in contrast to 1.47 Å calculated by the HF/3-21G method. The MNDO errors in O–O bond length are of little significance as far as dipole moments and relative energies of the two diastereoisomers are concerned. In fact, changes by less than 0.1 D in the dipole moments and by less than 0.1 kcal mol^{-1} in the relative energies were observed on passing from full optimized geometries (relative energies of **2a** vs **3a** and of **71** vs **81** are reported in ref 27) to geometries in which a O–O bond length of 1.47 Å was imposed. Imposing this O–O bond length led to the following values for the $H_1C_1C_2H_2$ and $H_6C_6C_7H_7$ dihedral angles in **2a** and **3a**: 52° and 55°, respectively, in anti **3a** and 61° and 64°, respectively, in syn **2a**. (b) This observation can be explained on the basis of the well-known steep decrease (Karplus relationship) in the ^3J values as the dihedral angle between the involved protons changes from 20° to 70°. Moreover, also the electronegativity effect of the oxygen atoms should give rise to smaller $J_{1,2}$ and $J_{6,7}$ in syn adducts as compared to anti adducts. In syn adducts the oxygen atoms at position 9 and 8, respectively, bear an antiperiplanar relationship to H-2 and H-6, i.e., the arrangement in which they can exhibit their maximum lowering effect on vicinal coupling constants. Günther, H. *NMR Spectroscopy*; Wiley and Sons: New York, 1980; pp 106–113.

(26) (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. P.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Dewar, M. J. S.; Hwang, J. C.; Khun, D. R. *J. Am. Chem. Soc.* **1991**, *113*, 735.

(27) The steric effect of the ethano bridge can also be held responsible for the lower stability of anti than syn adducts. Given that electrostatic interactions destabilize syn adducts as compared to the related anti adducts, the higher stability of the former (e.g., **2a** is more stable than **3a** by 3.0 kcal mol^{-1} and **71** than **81** by 2.2 kcal mol^{-1}, MNDO calculations)[25] is certainly the result of their significantly lower steric congestion.

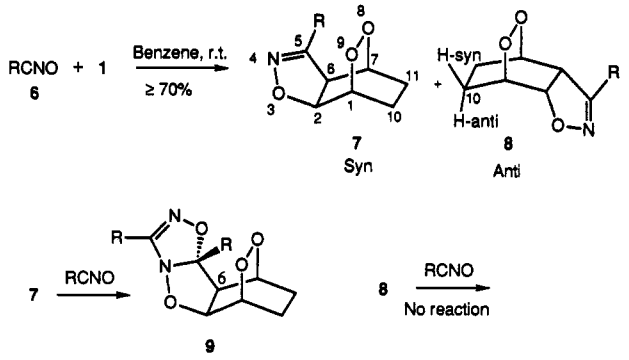
(28) (a) The selectivity observed in the reactions of these mildly nucleophilic 1,3-dipoles is in contrast with predictions based on Hehre's electrostatic model. In fact, this model predicts that attack by a nucleophile should occur as anti with respect to lone pair containing substituents. Anyway, in discussing facial selectivity of the reaction between butadiene and 3-benzoyl-6-(methoxycarbonyl)-2,3-oxazabicyclo-[2.2.2]oct-5-ene Hehre has already suggested that in diheterobicyclooctenes steric factors may play a dominant role overshadowing stereoelectronic effects.[13a] (b) The observed selectivity is in accord with predictions based on Cieplak's effect. In fact, the dominant attack occurs as anti with respect to the more electron-rich allylic σ bonds,[14] i.e., the σ_{CC} bonds. However, we have shown that, in contrast with Cieplak's assumption, delocalization involving the incipient bonds and the allylic σ_{CO} bonds is more important than that involving the σ_{CC} bonds both for antiperiplanar and synclinal orientations.[10d,33]

Table I. Syn/Anti Ratios, Evaluated by ^{1}H NMR, for the Reactions of Nitrile Oxides with 1

dipole moment of RCNO (D)	R	relative yields 7 (syn), %	8 (anti), %
4.58[a]	a: *p*-MeC_6H_4	30	70
	b: *p*-$MeOC_6H_4$	35	65
4.00[a]	c: C_6H_5	36	64
2.62[a]	d: *p*-ClC_6H_4	40	60
≈0[b]	e: *p*-$NO_2C_6H_4$	45	55
	f: EtO_2C	57	43
	g: C_6H_5CO	64	36
	h: MeCO	73	27
5.48[b]	i: 2,6-$Cl_2C_6H_3$	43	57
4.38[a]	j: 2,4,6-$Me_3C_6H_2$	82	18
3.90[b]	k: 3,5-Cl_2-2,4,6-Me_3C_6	87.5	12.5
4.50[a]	l: Me	36	64
c	m: Br	54	46
	n: t-Bu	18	82

[a] Experimental. [b] Calculated by the vectorial additive method. [c] The dipole moment of bromonitrile oxide is certainly significantly lower than that of acetonitrile oxide.

Scheme II



a - n see Table I

moment[29] varied over a wide range. The reactions were carried out in benzene at room temperature, and the nitrile oxide was slowly generated in situ from the related hydroximic acid chloride with solid sodium bicarbonate, with the exception of stable nitrile oxides that were used as such. Syn/anti ratios, which were easily evaluated from ^{1}H NMR spectra of the crude reaction mixtures, are gathered in Table I. Syn and anti adducts, i.e., **7** and **8** (Scheme II), could be obtained in a pure state by silica gel column chromatography (see Experimental Section). Careful monitoring of the reaction mixtures by TLC from the outset clearly showed that the syn/anti ratio did not appreciably change during the reaction time. Moreover, control experiments demonstrated that adducts are stable under the reaction conditions. Small amounts of a bis-adduct, i.e., **9**, were detected in the reactions of **1** with benzonitrile oxide (**6c**) and its *p*-methyl and *p*-methoxy derivatives, i.e., **6a** and **6b**. Formation of this compound could be suppressed by using an excess of **1**. The bis-adduct **9b** was isolated and fully characterized; it is the product of the reaction of a second molecule of the nitrile oxide with the carbon–nitrogen double bond of the isoxazoline moiety of the syn adduct. In fact, **9b** was obtained in low yield by the reaction of nitrile oxide **6b** with **7b**. In contrast, anti adduct **8b** proved unreactive when treated with an excess of *p*-methoxybenzonitrile oxide. The ^{1}H NMR spectrum of **9b** displayed the signal of H-6 at higher field than that of the same proton in **7b** where it is deshielded by the carbon–nitrogen double bond.

The structure assignments of the isoxazoline derivatives rest firmly on chromatographic behavior [R = Me, μ = 4.85 and 2.00 D for syn **7** and anti **8**, respectively (MNDO calculations)][25,26] and ^{1}H NMR spectra which exhibited the very same diagnostic features (see Experimental Section) described above for the pyrazoline and isoxazolidine derivatives. The ^{1}H NMR absorption pattern of the protons of the ethano bridge provided a further diagnostic characteristic for a distinction between syn adducts **7** and anti adducts **8**. In syn adducts, these protons gave rise to two well-separated multiplets, each representing two protons, with the lower field signal corresponding to protons H-10-syn and H-11-syn, deshielded by the dioxy bridge. In anti adducts, the signal at higher field accounted for only one proton, i.e., H-11-anti, while the other anti proton, i.e., H-10-anti, deshielded by the oxygen atom of the heterocyclic ring, resonated at a chemical shift very similar to that of H-10-syn and H-11-syn.

The role of electrostatic effects emerges from the facial preference observed for the series of para-substituted benzonitrile oxides (entries a-e, Table I) and for other pairs of nitrile oxides (entries j,k and entries l,m, Table I), i.e., for nitrile oxides with exactly the same or with very similar steric encumbrance but with varying dipole moment.[29] The presence of electron-attracting substituents, which give rise to a decrease in the dipole moment of the nitrile oxide as well as in the electron density on its oxygen atom, brings about a small but not negligible increase in the preference for the syn attack. Thus, we may conclude that electrostatic interactions disfavor the attack on the side of the dioxy bridge of **1**. This leads us to believe that the reversal in facial selectivity on passing from para-substituted benzonitrile oxides (entries a-e, prevalence of anti addition) to acyl nitrile oxides (entries f-h, dominance of syn addition) is mostly the consequence of a reduction in electrostatic interactions in the reactions of these latter 1,3-dipoles as compared to the former ones.

Upon passing from benzonitrile oxide to ortho,ortho-disubstituted derivatives (entries i-k, Table I), there is certainly a large increase in the bulkiness of the nitrile oxide, which is paralleled by a clear-cut enhancement of syn selectivity. The obvious straightforward explanation for this finding is that steric interactions counteract the effect of electrostatic interactions (and of pyramidalization), and for sterically very encumbered nitrile oxides, the former interactions prevail, leading to a dominance of attack syn to the sterically less demanding allylic substituent, i.e., the dioxy bridge.

In an attempt to further document the effect of an increase in steric requirements of the 1,3-dipole, we extended our study to aliphatic nitrile oxides, i.e., acetonitrile oxide and trimethylacetonitrile oxide. The result (entries l and n, Table I) was surprising and quite disturbing: there was not the expected significant increase in syn selectivity on passing from the former to the latter 1,3-dipole, but in striking contrast to what was found for aromatic nitrile oxides, the opposite was observed, i.e., a lower syn selectivity for the bulkier 1,3-dipole. We do not have a definite explanation for this observation. It is quite evident that the phenyl ring of aromatic nitrile oxides can adapt itself, through conformational isomerism, to minimize steric interactions with **1**, whereas this is not a

(29) Grundmann, Ch.; Grünanger, P. *The Nitrile Oxides*; Springer-Verlag: Berlin–Heidelberg–New York, 1971; p 21.

possibility for the symmetrical *tert*-butyl group. This is only to say that on passing from acetonitrile oxide to trimethylacetonitrile oxide the relative increase in steric interactions in the two TSs may be different from that characterizing the replacement of a phenyl by a 2,4,6-trimethylphenyl group. The problem of trimethylacetonitrile oxide will be discussed again (see below) on the basis of MO calculations. This anomalous result makes it clear that the balance of steric effects on the face selectivity of 1 is delicate in spite of its rigid and simple structure.

But, what about the relationship between pyramidalization and stereochemical outcome? Even if in the reactions of nitrile oxides there are several examples of dominant anti attack on 1, i.e., in agreement with its pyramidalization, there is not any unambiguous evidence that, in these examples, factors related to anti pyramidalization are the dominant factors that control facial selectivity. Thus, taking into account all of the above data, one is forced to maintain that 1 represents an exception to the rule advanced by Seebach.[3]

This does not mean that pyramidalization (or more properly factors that induce pyramidalization) does not play any role in determining facial selectivity in the reactions of 1 but only that this role does not emerge clearly because it is overridden by steric interactions. In fact, one could well argue that if 1 were not anti pyramidalized either we would have obtained only syn adducts (e.g., in the reactions of diazoalkanes and of hindered aromatic nitrile oxides) or syn addition would have been dominant (e.g., in the case of benzo and acetonitrile oxide). Our calculations on the isolated molecule of 1, which provide evidence that syn deformability of the olefinic hydrogens is more facile than anti, support this reasoning.

At this point, the question arises as to how steric and electrostatic interactions between the attacking 1,3-dipole and 1 as well as ground-state pyramidalization of 1 are reflected in the geometry of the syn and anti transition states. In particular, one may be interested to know whether the attacking 1,3-dipole tends to avoid steric interactions by elongation of the forming bonds or by an increase in the inclination (with respect to a perpendicular trajectory) of its trajectory of approach to 1 and whether the out-of-plane bending of the olefinic hydrogens is the same or not in the diastereoisomeric syn and anti transition states. As a first attempt to answer these questions, we have carried out ab initio minimal basis set (RHF/STO-3G) calculations[17] of the syn and anti transition structures (TS)[30,31] of the reactions of diazomethane, formonitrile oxide, and acetonitrile oxide with 1 (Figure 5 and Table II). Moreover, to gain an idea how to explain the

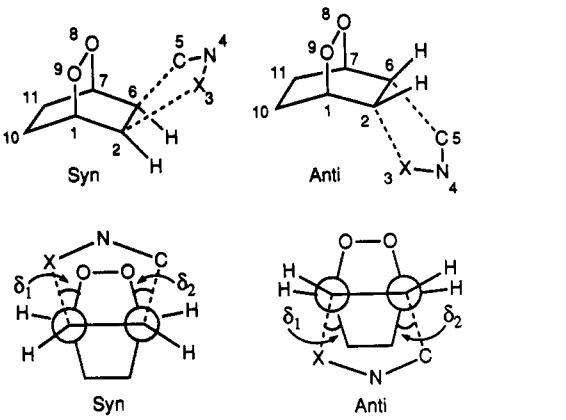


Figure 5. Schematic view of syn and anti TSs with the numbering used in Table II and Table III.

Table II. Activation Energies, Bond Lengths (Å), and Bond and Dihedral Angles (deg) for the RHF/STO-3G-Optimized Geometries of Transition Structures of the Reaction of Diazomethane, Formonitrile Oxide, and Acetonitrile Oxide with 1[a-e]

	diazomethane		HCNO		MeCNO	
	syn	anti	syn	anti	syn	anti
E_{act} (kcal mol^{-1})	21.6	24.8	18.7	20.3	18.1	19.6
C_2–C_6	1.345	1.348	1.340	1.342	1.341	1.343
N_4–X_3	1.183	1.185	1.295	1.297	1.306	1.308
C_5–N_4	1.352	1.353	1.185	1.185	1.184	1.184
C_5–N_4–X_3	145.2	145.0	144.0	144.0	144.1	144.0
C_2---X_3	2.296	2.304	2.161	2.189	2.122	2.149
C_5---C_6	2.318	2.336	2.404	2.402	2.433	2.425
α_2[d]	−16.9	23.0	−17.3	21.5	−18.8	22.9
α_6[d]	−22.5	27.3	−17.1	22.5	−17.1	22.5
$\beta(C_1$–C_2–C_6–$C_7)$	2.3	−0.2	1.7	−0.3	1.6	0.4
γ_1 (X_3–C_2–C_6–C_1)	−101.7	110.0	−103.2	109.1	−103.7	109.0
γ_2 (C_5–C_6–C_2–C_7)	105.4	−114.8	102.2	−113.0	101.9	−112.5
δ_1[e]	50.7	49.8	54.4	51.7	55.2	51.8
δ_2[e]	51.9	53.5	46.4	48.3	45.8	48.4

[a] For numbering see Figure 5. [b] The total energies of diazomethane, HCNO, MeCNO, and 1 are −145.920 61, −165.392 21, −203.988 75, and −376.738 69 hartree. Double bond length in 1: 1.311 Å. C_5–N_4 bond length in diazomethane, HCNO, and MeCNO: 1.282, 1.155, and 1.156 Å, respectively. N_4–X_3 bond length in diazomethane, HCNO, and MeCNO: 1.190, 1.293, and 1.306 Å, respectively. C_5–N_4–X_3 = 180° for all three dipoles. The complete set of data is available on request. [c] Dihedral angles between the olefinic and bridgehead hydrogens (i.e., H_2–C_2–C_1–H_1 and H_6–C_6–C_7–H_7) are larger by ≈7–11° in syn than in related anti TSs. [d] α_2 and α_6 give the out-of-plane bending of the olefinic hydrogens H_2 and H_6. α_2 (α_6) is the difference between 180° and the absolute value of the improper dihedral (torsion) angle H_2–C_2–C_6–C_1 (H_6–C_6–C_2–C_7). α_2 (α_6) is given a positive sign when H_2 (H_6) is bent in the syn direction and a negative sign when H_2 (H_6) is bent in the anti direction with respect to the dioxy bridge. [e] See Figure 5.

"anomalous" behavior of trimethylacetonitrile oxide, the AM1 transition structures[32] of its reaction with 1 have been compared to AM1 transition structures of the reactions of formonitrile oxide, acetonitrile oxide and pyruvonitrile oxide with the same dipolarophile (Figure 5 and Table III). The choice of the semiempirical MO model and of the very modest ab initio model is imposed by the size of the molecules under study and by the need to have comparable results for several reactions. However, we feel that these types of calculations are reliable enough (in particular, geometrical details that are shared by the two types of calculations) for our limited purpose, i.e., to answer the above questions and to provide some compu-

(30) Transition structures were calculated using the RHF/STO-3G method and gradient techniques with optimization of all variables. Critical points were characterized by diagonalizing the Hessian matrices of the optimized structures; transition structures have only one negative eigenvalue (first-order saddle points), the corresponding eigenvectors involving the expected concerted formation of the two new bonds.

(31) For previous ab initio calculations on transition structures of 1,3-dipolar cycloaddition, see: (a) McDouall, J. J.; Robb, M. A.; Niazi, U.; Bernardi, F.; Schlegel, H. B. *J. Am. Chem. Soc.* **1987**, *109*, 4642 and references cited therein. (b) Brown, F. K.; Chandra Singh, U.; Kollman, P. A.; Raimondi, L.; Houk, K. N.; Bock, C. W. *J. Org. Chem.* **1992**, *57*, 4862. (c) Brown, F. K.; Raimondi, L.; Wu, Y.-D.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4405. (d) Raimondi, L.; Wu, Y.-D.; Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4409. (e) Reference 11. (f) Sustmann, R.; Sicking, W. *J. Org. Chem.* **1993**, *58*, 82. (g) Semiempirical MO calculations on TSs of 1,3-dipolar cycloadditions have been reported in ref 31f and in: Sustmann, R.; Sicking, W.; Felderhoff, M. *Tetrahedron*, **1990**, *46*, 783.

(32) The version of AM1 as implemented in the GAUSSIAN 88 package of programs was used.[17]

Table III. Activation Energies, Bond Lengths (Å), and Bond and Dihedral Angles (deg) for the AM1-Optimized Geometries of Transition Structures of the Reaction of Formonitrile Oxide, Acetonitrile Oxide, Trimethylacetonitrile Oxide, and Pyruvonitrile Oxide with 1[a-c]

	HCNO		MeCNO		t-BuCNO		MeCOCNO	
	syn	anti	syn	anti	syn	anti	syn	anti
E_{act} (kcal mol^{-1})	70.4	70.9	59.7	60.2	48.0	47.7	31.0	32.0
C_2–C_6	1.392	1.391	1.393	1.394	1.396	1.395	1.388	1.388
N_4–O_3	1.197	1.196	1.199	1.199	1.200	1.200	1.186	1.186
C_5–N_4	1.243	1.246	1.251	1.255	1.251	1.254	1.264	1.264
C_5–N_4–O_3	132.8	132.6	131.5	131.0	132.0	131.6	131.3	131.2
C_2---O_3	2.175	2.251	2.105	2.169	2.060	2.119	2.215	2.295
C_5---C_6	2.079	2.050	2.119	2.085	2.155	2.121	2.076	2.055
α_2[d]	−11.7	12.7	−14.1	15.6	−15.6	17.8	−9.8	10.9
α_6[d]	−25.3	29.5	−25.2	29.4	−25.6	29.4	−24.9	28.9
β (C_1–C_2–C_6–C_7)	4.0	−2.0	3.6	−1.8	3.5	−0.7	3.1	−1.3
γ_1 (O_3–C_2–C_6–C_1)	−103.3	109.7	−103.4	109.5	−102.5	109.5	−102.2	109.4
γ_2 (C_5–C_6–C_2–C_7)	106.7	−113.0	107.9	−113.4	111.0	−114.4	108.3	−114.6
δ_1[e]	53.7	48.2	53.8	48.3	53.7	47.8	52.0	47.0
δ_2[e]	51.0	49.9	51.5	50.1	52.1	51.3	52.7	51.2

[a] For numbering see Figure 5. [b] The heats of formation of HCNO, MeCNO, t-BuCNO, and MeCOCNO and 1 are 0.014 96, 0.063 65, 0.047 86, 0.028 90, and 0.004 03 hartree, respectively. Double bond length in 1: 1.346 Å. C_5–N_4 bond length in HCNO, MeCNO, t-BuCNO, and MeCOCNO: 1.168, 1.169, 1.168, and 1.172 Å, respectively. N_4–O_3 bond length in HCNO, MeCNO, t-BuCNO, and MeCOCNO: 1.180, 1.180, 1.181, and 1.173 Å, respectively. The complete set of data is available on request. [c] In the case of pyruvonitrile oxide the reported values refer to TSs with an s-trans conformation of the C=O and C=N moieties. The related syn and anti TSs with an s-cis conformations exhibit a higher activation energy by ≈2.4 and 1.7 kcal mol^{-1}, respectively. [d] For definitions of α_2 and α_6 see Table II. [e] See Figure 5.

tational support to the above qualitative rationalization of the experimental trends.

There are relevant differences in the transition structures obtained by the ab initio and semiempirical methods not only so far as activation energies are concerned, but also in geometry details. With respect to the latter, for example, asynchronicity of forming bond length tends to be reversed on passing from RHF/STO-3G (Table II) to AM1 (Table III) calculations. In fact, C_5---C_6 bond length is higher than C_2---O_3 bond length in STO-3G syn and anti transition structures of the reactions of formonitrile oxide with 1, whereas the opposite holds in related AM1 transition structures.

In the STO-3G data (Table II), calculated activation energies correctly predict dominance of syn attack in the case of diazomethane and a decrease in syn selectivity on passing from diazomethane to nitrile oxides, but they fail in predicting the prevalence of anti attack in the reactions of these latter 1,3-dipoles.

Very interesting are the figures for γ_1 and γ_2 (Table II), that is, for the improper dihedral (torsion) angles that we use to describe the slant of the incipient bonds. The larger these angles, the more inclined is the trajectory of attack by the 1,3-dipole with respect to a perpendicular (i.e., $\gamma = \pm 90°$) attack on the double bond of 1. Actually, γ_1 and γ_2 are always remarkably larger (i.e., γ_1 by 5–8° and γ_2 by ≈10°) in the anti TS than in its syn counterpart. This trend in STO-3G results is corroborated by AM1 data (Table III). It is quite evident that owing to the higher steric requirement of the ethano bridge the 1,3-dipole is forced to follow a more inclined approach in the anti than in the syn attack in order to minimize steric interactions.

Moreover, γ_2, i.e., the slant of the incipient C_5---C_6 bond, is slightly larger (by 2–3°) in both TSs of the diazomethane reaction than in the related TSs of nitrile oxide reactions, suggesting a higher or at least a comparable steric effect for the CH_2 group of the former 1,3-dipole relative to that of the RC moiety of formonitrile oxide and acetonitrile oxide. Diazomethane is a small 1,3-dipole, certainly smaller in size, for example, than acetonitrile oxide. However, one of the methylene hydrogens of diazomethane is pointing inside, giving rise to a steric interaction not present in the case of nitrile oxides [see, for example, structure 2 (Scheme I) as compared to 7 (Scheme II)]. In contrast to γ_2, γ_1 (the inclination of the C_2---X_3 bond) is slightly larger (by 2°) in the syn TS of nitrile oxide cycloaddition than in the syn TS of diazomethane reaction, while being very similar in the anti TS for both types of 1,3-dipoles. This is clearly a reflection of the higher electrostatic repulsion between the oxygen atom of the nitrile oxides and the oxygen atom at position 9 of the dipolarophile as compared to that involving the nitrogen atom of diazomethane.

The electrostatic repulsion between the terminal heteroatom of the 1,3-dipole and the "inside" oxygen atom at position 9 (Figure 5) also brings about an increase in staggering between the incipient C_2---X_3 bond and the C_1–O_9 bond in the syn TS, as compared to that between the incipient C_2---X_3 bond and the C_1–C_{10} bond in the anti TS. In fact, in STO-3G calculations, δ_1 is larger in the syn than in the anti TS whereas the opposite holds for δ_2 (Figure 5 and Table II). In the case of AM1 calculations, on passing from the anti to the syn TS, the increase in δ_1 is larger than that in δ_2 (Table III).

Thus, the geometries of TSs provide support for the notions concerning the steric effect of the ethano bridge and the electrostatic effect of the dioxy moiety.

Another noteworthy feature of the STO-3G syn and anti TSs is that the out-of-plane bending of the olefinic hydrogens, as described by the improper dihedral angles α_2 and α_6 (Table II), is always larger (by 4–6°) in the anti than in the syn approach. That is, pyramidalization of the doubly-bonded carbon atoms of 1 is higher in that one of the two diastereoisomeric TSs in which it takes place in the direction of ground-state pyramidalization. This trend is confirmed by AM1 calculations even if absolute values for α_2 and α_6 are quite different from those of ab initio calculations. This finding suggests that factors involved in ground-state pyramidalization also are at work in determining facial selectivity of the reactions of 1. In fact, an analysis of electron delocalizations in these TSs shows that synclinal interactions between the incipient bonds (C_2---X_3 and C_5---C_6) and the allylic σ bonds are less stabilizing than related antiperiplanar interactions

and that interactions involving allylic σ_{CO} bonds are more important than those involving allylic σ_{CC} bonds.[10d] As a result, the anti attack, which entails antiperiplanar interactions between allylic σ_{CO} bonds and incipient bonds (Figure 5), is favored over the syn attack by this effect even if hyperconjugative interactions cannot overpower steric interactions. This observation confirms that the tendency to maximize $\sigma-\pi$ hyperconjugation, which drives ground-state pyramidalization, is superseded at the transition state by the tendency to maximize delocalization between allylic σ bonds and incipient bonds.[9a,b,10,33,34]

Finally, as for the trimethylacetonitrile oxide problem, inspection of Table III[35] shows that along the series HCNO, MeCNO, and t-BuCNO there is a progressive elongation of the incipient C_5---C_6 bond (≈0.08 Å) paralleled by a shortening of the incipient C_2---O_3 bond (≈0.12 Å) both in the syn and (to a very similar extent) in the anti TS. The decrease in C_2---O_3 bond length is accompanied by the expected increase (4–5°) in out-of-plane bending of H-2 (i.e., α_2), whereas elongation of the C_5---C_6 bond does not result in the expected decrease in α_6. Evidently, as far as α_6 is concerned, the enhanced repulsion between R and H-6 on passing from R = H to R = t-Bu counterbalances the C_5---C_6 bond lengthening effect. The effect of the increase in the steric requirements of R is similar in both diasteroisomeric TSs and is accommodated mostly through elongation of the C_5---C_6 bond while the consequent weakening in bonding is compensated by a strengthening of the C_2---O_3 bond.

As for the trajectory of attack, the slant of the C_2---O_3 bond (i.e., γ_1) is the same in the anti TSs and very similar in the syn TSs of all four nitrile oxides studied. The inclination of the C_5---C_6 bond (i.e., γ_2) in the anti TS undergoes a negligible enhancement (by 1°) on passing from HCNO to t-BuCNO, whereas the related increase in γ_2 in the syn approach is slightly larger (4°), thus suggesting a slightly larger increase in steric congestion in the syn than in the anti attack.

In short, all of these geometrical details point to a similar or even slightly larger increase in steric interactions along the series HCNO, MeCNO, and t-BuCNO in the syn transition state compared to its anti counterpart. It is gratifying that this conclusion is not in contrast with the observed decrease in syn selectivity on passing from MeCNO to t-BuCNO. Moreover, our calculations also demonstrate that the increase in steric interactions felt by both TSs is actually lower (see, in particular, the very small increase in inclination of the trajectory of approach) than that one would have predicted on the basis of the very large change in bulkiness of the R group (υ(Me) – υ(H) = 0.52 and υ(t-Bu) – υ(Me) = 0.71).[20]

Conclusion

2,3-Dioxabicyclo[2.2.2]oct-5-ene (1) is anti pyramidalized with respect to the dioxy bridge by a small but not negligible amount as shown by its ab initio optimized geometry. However, most of the 1,3-dipoles investigated prefer to attack the syn face of 1. Thus, this bicyclic olefin represents the first unambiguously documented example of a ground-state pyramidalized olefin whose facial selectivity does not parallel, as a rule, its pyramidalization. Steric factors, which favor syn attack, often overcome electrostatic interactions and factors related to pyramidalization that favor anti attack. However, MO calculations on 1 as well as on transition structures of its 1,3-dipolar cycloadditions suggest that delocalizations involving σ-allylic bonds are responsible for ground-state pyramidalization (delocalizations involving σ-allylic bonds and π bond) and play a non-negligible role in favoring anti attack on 1 (delocalizations involving σ-allylic bonds and forming bonds), thus counteracting, at least in part, steric effects.

Experimental Section

Melting points were uncorrected. Elemental analyses were made on a Carlo Erba CHN analyzer, Model 1106. Infrared spectra were recorded as either Nujol suspensions or films on a Perkin-Elmer 157 spectrophotometer. NMR spectra were recorded on a Bruker AE 300 (at 300 MHz) spectrometer with tetramethylsilane as internal standard. The chemical shifts of aromatic protons will not be reported. For several adducts also the aromatic solvent-induced shift [(ASIS, $\Delta\delta = \delta(CDCl_3) - \delta(C_6D_6)$] was determined. Protons were correlated by decoupling and COSY experiments. ^{1}H NMR spectra were evaluated as first-order spectra, and only the most relevant vicinal J (i.e., $J_{1,2}$, $J_{6,7}$, and $J_{2,6}$) and ^4J (i.e., $J_{2,10\text{-syn}}$ and $J_{6,11\text{-syn}}$) will be, as a rule, reported. In particular, the coupling constants involving only the protons of the ethano bridge will not be reported. In all of the adducts there was a coupling betwen H-1 and H-7 on the order of ≈2.5 Hz (see the values reported below for **2a**, **3a**, **2b**, and 8c). Thin-layer chromatograms were done on plates precoated with silica gel 60 GF_{254} (Merck). Spots were visualized either by spraying with 3% chromic oxide in sulfuric acid (50%) followed by heating at 120 °C or under UV light. All of the anti adducts exhibited a significantly higher R_f as compared to the related syn adducts. Column chromatography was performed with silica gel 60 (70–230 mesh, Merck) eluting with cyclohexane/ethyl acetate mixtures. 2,3-Dioxabicyclo[2.2.2]oct-5-ene (1)[36] [mp 80–82 °C (lit.[36] mp 82–84 °C); ^{1}H NMR, ($CDCl_3$) δ 1.49 (m, H-7-anti and H-8 anti), 2.29 (m, H-7-syn and H-8-syn), 4.67 (m, H-1 and H-7), 6.69 (m, H-5 and H-6)], diazoalkanes,[37] 3,4-dihydroisoquinoline *N*-oxide,[38] nitrile oxides, and their precursors[29,39] were prepared according to literature procedures.

Reaction of Diazoalkanes with 2,3-Dioxabicyclo[2.2.2]oct-5-ene (1). The reaction of diazomethane with 1 (246 mg, 2.20 mmol) was carried out in ethyl ether at room temperature (≈20–23 °C) by using a large excess of a concentrated solution of the 1,3-dipole. After 4 days the dipolarophile had totally been consumed (as judged by TLC). The solvent was evaporated and the syn/anti ratio (90:10) in the crude reaction product (325 mg) evaluated by ^{1}H NMR. The reaction was very clean, and only adducts **2a** and **3a**, aside from trace amounts of 1, were detected. The two diastereoisomers were separated by column chromatography (cyclohexane/ethyl acetate = 1/1).

2a: 250 mg (74%), colorless crystals, mp 54–56 °C; IR 1549 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.77 (m, H-11-anti), 1.01 (m, H-10-anti), 1.08 (m, H-6, $J_{2,6}$ = 10.7 Hz, $J_{5\text{-endo},6}$ = 5.2 Hz, $J_{5\text{-exo},6}$ = 10.0 Hz, and $J_{6,7}$ = 2.2 Hz), 1.77 (m, H-11-syn), 1.83 (m, H-10-syn), 3.12 (m, H-7, $J_{1,7}$ = 2.2 Hz, $J_{7,11\text{-syn}}$ = 2.2 Hz, and $J_{7,11\text{-anti}}$ = 1.0 Hz), 4.08 (H-2, $J_{1,2}$ = 2.2 Hz, $J_{2,5\text{-endo}}$ = 3.0 Hz, and $J_{2,5\text{-exo}}$ = 1.3 Hz),

(33) The hyperconjugative effect calculated by us reflects all the delocalizations between the involved bonds (e.g., the incipient bonds and the allylic σ bonds).[9,10c,d,34] Thus, it is quite evident that it is different from Cieplak's effect (based on bond orbital interactions) which only takes into account antiperiplanar hyperconjugative interactions between the occupied $\sigma_{\text{anti allylic bond}}$ and the vacant $\sigma^*_{\text{forming bond}}$.[14]

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(35) The AM1 relative syn and anti activation energies (absolute values cannot be reliable) are consistent with formation of mixtures for all the four nitrile oxides and with dominance of syn attack in the reaction of pyruvonitrile oxide. However, they are wrong in predicting the syn attack as prevalent also in the reactions of the other three nitrile oxides.

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4.18 (ddd, H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18.3 Hz), 4.37 (m, H-1, $J_{1,10\text{-syn}}$ = 4.1 Hz and $J_{1,10\text{-anti}}$ = 2.2 Hz), 4.58 (ddd, H-5-endo); $\Delta\delta$ = $\delta(CDCl_3) - \delta(C_6D_6)$ 0.91 (H-11-anti), 0.81 (H-10-anti), 1.16 (H-6), 0.57 (H-11-syn), 0.57 (H-10-syn), 0.85 (H-7), 0.77 (H-2), 0.59 (H-5-exo), 0.48 (H-1), 0.27 (H-5-endo). Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.35; H, 6.43; N, 18.32.

3a: 28 mg (8%), colorless glassy solid; IR 1550 cm^{-1}; ^1H NMR (C_6D_6) δ 0.63 (m, H-11-anti), 1.05 (m, H-10-anti), 1.42 (m, H-11-syn), 1.66 (m, H-10-syn), 2.03 (m, H-6, $J_{2,6}$ = 10.0 Hz, $J_{5\text{-endo},6}$ = 3.3 Hz, $J_{5\text{-exo},6}$ = 9.8 Hz, $J_{6,7}$ = 4.0 Hz, and $J_{6,11\text{-syn}}$ = 1.9 Hz), 3.25 (m, H-7, $J_{1,7}$ = 2.8 Hz, $J_{7,11\text{-syn}}$ = 3.6 Hz, and $J_{7,11\text{-anti}}$ = 1.2 Hz), 3.68 (ddd, H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18.4 Hz and $J_{2,5\text{-exo}}$ = 2.3 Hz), 3.88 (ddd, H-5-endo, $J_{2,5\text{-endo}}$ = 3.3 Hz), 4.54 (m, H-1, $J_{1,2}$ = 4.0 Hz, $J_{1,10\text{-syn}}$ = 4.0 Hz, and $J_{1,10\text{-anti}}$ = 2.5 Hz), 4.62 (m, H-2, $J_{2,10\text{-syn}}$ = 2.0 Hz); $\Delta\delta$ 0.67 (H-11-anti), 0.35 (H-10-anti), 0.55 (H-11-syn), 0.38 (H-10-syn), 0.75 (H-6), 0.79 (H-7), 0.88 (H-5-exo), 0.80 (H-5-endo), 0.46 (H-1), 0.50 (H-2). Anal. Found: C, 54.45; H, 6.53; N, 18.14.

To a solution of compound 1 (150 mg, 1.34 mmol) in ethyl ether was added an excess of an ethereal solution of 2-diazopropane. The reaction mixture was kept at room temperature for 6 h, the solvent was then evaporated, and all the residue (180 mg) was dissolved in deuteriochloroform to evaluate the syn/anti ratio (97.5:2.5). Chromatographic separation of the two adducts was performed with cyclohexane/ethyl acetate (4:1) as eluant.

2b: 170 mg (70%), colorless platelets from ethyl ether, mp 145–148 °C dec; IR 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, Me), 1.72 (s, Me), 1.73 (m, H-10-anti and H-11-anti), 1.77 (dd, H-6, $J_{2,6}$ = 9.8 Hz and $J_{6,7}$ = 1.4 Hz), 2.28 (m, H-11-syn), 2.38 (m, H-10-syn), 4.09 (m, H-7, $J_{1,7}$ = 2.7 Hz, $J_{7,11\text{-syn}}$ = 3.5 Hz, and $J_{7,11\text{-anti}}$ = 1.7 Hz), 4.82 (dd, H-2, $J_{1,2}$ = 3.2 Hz), 5.08 (m, H-1, $J_{1,10\text{-syn}}$ = 5.2 Hz and $J_{1,10\text{-anti}}$ = 1.5 Hz); $\Delta\delta$ 0.35 (Me), 0.18 (Me), 0.82 (H-10-anti and H-11-anti), 0.88 (H-6), 0.50 (H-11-syn), 0.53 (H-10-syn), 0.71 (H-7), 0.80 (H-2), 0.46 (H-1). Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.55; H, 7.63; N, 15.52.

3b: 4 mg (1.5%), colorless glassy solid; IR 1550 cm^{-1}; ^1H NMR (C_6D_6) δ 0.64 (s, Me), 0.81 (m, H-10-anti and H-11-anti), 1.12 (s, Me), 1.51 (m, H-11-syn), 1.75 (m, H-10-syn), 1.95 (ddd, H-6, $J_{2,6}$ = 7.5 Hz, $J_{6,7}$ = 3.2 Hz, and $J_{6,11\text{-syn}}$ = 1.8 Hz), 3.39 (m, H-7), 4.48 (ddd, H-2, $J_{1,2}$ = 6.7 Hz and $J_{2,10\text{-syn}}$ = 1.9 Hz), 4.55 (m, H-1); $\Delta\delta$ 0.53 (Me), 0.39 (H-10-anti and H-11-anti), 0.56 (Me), 0.30 (H-10-syn), 0.53 (H-11-syn), 0.50 (H-6), 0.60 (H-7), 0.54 (H-2), 0.47 (H-1). Anal. Found: C, 59.60; H, 7.79; N, 15.42.

Compounds **2** and **3** are stable under reaction conditions whereas some decomposition took place during column chromatography. A fast elution kept this drawback at a minimum.

Reaction of 3,4-Dihydroisoquinoline *N*-Oxide with 1. A solution of 3,4-dihydroisoquinoline *N*-oxide (145 mg, 0.99 mmol) and of 1 (105 mg, 0.94 mmol) in benzene (3 mL) was kept at 35 °C for 4 days. TLC analysis clearly showed that the syn/anti ratio was ≈2:1. Then the reaction mixture was diluted with benzene/cyclohexane (1:1) (10 mL) and washed repeatedly with water to remove most of the unreacted 1,3-dipole. The organic phase was dried with anhydrous sodium sulfate and after evaporation of the solvent the slightly yellow residue was analyzed by ^1H NMR (syn/anti = 70/30) and column chromatographed with cyclohexane/ethyl acetate (4:1) as eluant.

4: 49 mg (20%), colorless crystals, mp 114–115 °C dec; ^1H NMR ($CDCl_3$) δ 1.51 (m, H-11-anti), 1.72 (m, H-10-anti), 2.40 (m, H-10-syn and H-11-syn), 2.71 (ddd, H-6, $J_{2,6}$ = 10.2 Hz, $J_{5,6}$ = 9.2 Hz, and $J_{6,7}$ = 2.7 Hz), 2.88, 3.02, 3.24, and 3.42 (four m, the four protons of the ethano moiety of the tetrahydroisoquinoline system), 4.22 (m, H-1, $J_{1,2}$ = 1.9 Hz), 4.42 (m, H-7), 4.50 (dd, H-2), 4.90 (d, H-5); $\Delta\delta$ = $\delta(CDCl_3) - \delta(C_6D_6)$ 0.77 (H-11-anti), 0.81 (H-10-anti), 0.50 (H-10-syn and H-11-syn), 0.79 (H-6), 0.46, 0.37, 0.17 and 0.10 (the four protons of the ethano moiety of the tetrahydroisoquinoline system), 0.35 (H-1), 0.55 (H-7), 0.69 (H-2), −0.24 (H-5). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.55; H, 6.43; N, 5.52.

5: 21 mg (9%), colorless prisms from cyclohexane, mp 80–81 °C dec; ^1H NMR ($CDCl_3$) δ 2.15 (m, H-10-anti and H-11-anti), 2.25 (m, H-10-syn and H-11-syn), 2.92, 3.05, 3.18, and 3.38 (four m, the four protons of the ethano moiety of the tetrahydroisoquinoline system), 3.22 (dddd, H-6, $J_{2,6}$ = 9.2 Hz, $J_{5,6}$ = 7.8 Hz, $J_{6,7}$ = 4.8 Hz, and $J_{6,11\text{-syn}}$ = 1.1 Hz), 4.30 (m, H-1, $J_{1,2}$ = 5.0 Hz), 4.38 (d, H-5), 4.48 (m, H-7), 4.78 (ddd, H-2, $J_{2,10\text{-syn}}$ = 1.0 Hz); $\Delta\delta$ 0.54 (H-11-anti), 0.30 (H-10-anti), 0.40 (H-11-syn), 0.30 (H-10-syn), 0.42, 0.30, 0.43 and 0.26 (the four protons of the ethano moiety of the tetrahydroisoquinoline system), 0.34 (H-6), 0.37 (H-1), 0.36 (H-5), 0.55 (H-7), 0.27 (H-2). Anal. Found: C, 69.65; H, 6.53; N, 5.32.

Reactions of Nitrile Oxides with 1. The nitrile oxides **6a–6h**, **6l**, and **6n** were prepared in situ from the corresponding hydroximic acid chloride and **6m** from the corresponding hydroximic acid bromide. Thus, a solution of the hydroximic acid chloride or bromide (1.00 mmol) and of excess 1 (1.2 mmol) in anhydrous benzene (15 mL) was stirred at room temperature (≈21 °C) for 3–4 days in the presence of a high excess of solid sodium bicarbonate (4.00 mmol). After that time TLC analysis of the reaction mixture showed the presence of unreacted 1, of the dimer of the nitrile oxide, and of syn and anti adducts in a ratio which qualitatively corresponded to that successively evaluated by ^1H NMR analysis. The inorganic salts were filtered off, the solvent evaporated, and the crude residue analyzed by ^1H NMR to evaluate the syn/anti ratios gathered in Table I. The syn/anti ratios so obtained were found to be highly reproducible, and the results reported in Table I are the average of two runs. The syn and anti adducts were isolated by column chromatography by using cyclohexane/ethyl acetate mixtures (from 8:2 to 2:8) as eluant. In the case of low soluble adducts (e.g., **7e** and **8e**) a mixture cyclohexane/ethyl acetate/dichloromethane (6:2:2) was used. The syn adducts always exhibited a lower R_f as compared to that of the related anti adducts. We used excess 1 in order to avoid formation of bis-adducts of the type **9**. The presence of small amounts of this compound was detected in the reactions of **6a–6c** when equimolar amounts of the 1,3-dipole and of the dipolarophile were used. The R_f of the bis-adduct was slightly higher than that of the syn monoadduct, and in the ^1H NMR of the crude reaction mixture its presence was revealed by a double doublet ($J \approx 1.0$ and 9.0 Hz) at $\delta \approx 3.2$ attributable to H-6. Both syn and anti adducts proved stable in benzene solution in the presence of sodium bicarbonate as well as in the solid state at room temperature for 2 weeks. Some decomposition took place during column chromatography as shown by the development, in several instances, of a brown yellow color as soon as adducts are absorbed on silica gel. This decomposition is higher for syn adducts which move more slowly on chromatography. However, this behavior did not prevent isolation of adducts (and syn/anti ratios were qualitatively similar to spectroscopic syn/anti ratios) by this technique, and total yields of isolated pure adducts varied in the range 70–85%.

The reaction of trimethylacetonitrile oxide with 1 was also carried out in nitromethane (8 d at rt). A slight increase in the syn/anti ratio (22:78) as compared to benzene (18:82) was observed.

In the case of stable nitrile oxides, i.e., **6i–6k**, the reaction was carried out in anhydrous benzene for 8–10 days at 30 °C by using equimolar amounts of the 1,3-dipole and of 1 as there is no danger of bis-addition. Workup, evaluation of syn/anti ratios, and isolation of the adducts were performed as described above.

7a: colorless prisms from methanol, mp 141–143 °C dec; ^1H NMR ($CDCl_3$) δ 1.76 (m, H-10-anti and H-11-anti), 2.38 (m, H-10-syn and H-11-syn), 2.38 (s, Me), 3.96 (dd, H-6, $J_{2,6}$ = 12.2 Hz and $J_{6,7}$ = 2.3 Hz), 4.30 (m, H-1), 4.40 (m, H-7), 4.88 (dd, H-2, $J_{1,2}$ = 2.5 Hz); $\Delta\delta$ = $\delta(CDCl_3) - \delta(C_6D_6)$ 0.98 (H-10-anti and H-11-anti), 0.67 (H-10-syn and H-11-syn), 0.34 (Me), 0.99 (H-6), 0.51 (H-1), 0.54 (H-7), 0.76 (H-2). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.75; H, 6.33; N, 5.52.

8a: colorless needles from methanol, mp 118–121 °C; ^1H NMR ($CDCl_3$) δ 1.52 (m, H-11-anti), 2.01 (m, H-11-syn), 2.11 (m, H-10-anti and H-10-syn), 2.38 (s, Me), 4.39 (ddd, H-6, $J_{2,6}$ = 11.2 Hz, $J_{6,7}$ = 4.7 Hz, and $J_{6,11\text{-syn}}$ = 1.7 Hz), 4.39 (m, H-1), 4.52 (m, H-7), 5.21 (ddd, H-2, $J_{1,2}$ = 5.4 Hz and $J_{2,10\text{-syn}}$ = 1.4 Hz); $\Delta\delta$ = $\delta(CDCl_3) - \delta(C_6D_6)$ 0.33 (H-11-anti), 0.46 (H-11-syn), 0.42 (H-10-syn), 0.26 (H-10-anti), 0.32 (Me), 0.60 (H-6), 0.41 (H-1), 0.50 (H-7), 0.35 (H-2). Anal. Found: C, 68.63; H, 6.25; N, 5.62.

7b: colorless crystals from methanol, mp 145–148 °C dec; ^1H NMR ($CDCl_3$) δ 1.77 (m, H-10-anti and H-11-anti), 2.39 (m, H-10-syn and H-11-syn), 3.85 (s, OMe), 3.95 (dd, H-6, $J_{2,6}$ = 12.2 Hz and $J_{6,7}$ = 2.2 Hz), 4.32 (m, H-1), 4.41 (m, H-7), 4.89 (dd, H-2,

$J_{1,2}$ = 2.7 Hz); $\Delta\delta$ 0.99 (H-10-anti and H-11-anti), 0.65 (H-10-syn and H-11-syn), 0.63 (OMe), 1.00 (H-6), 0.51 (H-1), 0.58 (H-7), 0.75 (H-2). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.55; H, 5.63; N, 5.52.

8b: colorless needles from ethanol, mp 104–105 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (m, H-11-anti), 2.02 (m, H-11-syn), 2.12 (m, H-10-anti and H-10-syn), 3.85 (s, OMe), 4.38 (ddd, H-6, $J_{2,6}$ = 11.2 Hz, $J_{6,7}$ = 4.6 Hz, and $J_{6,11\text{-syn}}$ = 1.8 Hz), 4.40 (m, H-1), 4.51 (m, H-7), 5.20 (ddd, H-2, $J_{1,2}$ = 5.2 Hz and $J_{2,10\text{-syn}}$ = 0.8 Hz); $\Delta\delta$ 0.32 (H-11-anti), 0.44 (H-11-syn), 0.40 (H-10-syn), 0.24 (H-10-anti), 0.63 (OMe), 0.58 (H-6), 0.52 (H-1), 0.47 (H-7), 0.33 (H-2). Anal. Found: C, 64.27; H, 5.84; N, 5.48.

7c: colorless prisms from methanol, mp 137–139 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (m, H-10-anti and H-11-anti), 2.39 (m, H-10-syn and H-11-syn), 3.98 (dd, H-6, $J_{2,6}$ = 12.4 Hz and $J_{6,7}$ = 2.4 Hz), 4.33 (m, H-1), 4.43 (m, H-7), 4.92 (dd, H-2, $J_{1,2}$ = 2.6 Hz); $\Delta\delta$ 1.04 (H-10-anti and H-11-anti), 0.67 (H-10-syn and H-11-syn), 1.09 (H-6), 0.55 (H-1), 0.65 (H-7), 0.81 (H-2). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.35; H, 5.43; N, 5.87.

8c: colorless prisms from methanol, mp 107–110 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (m, H-11-anti), 2.02 (m, H-11-syn), 2.12 (m, H-10-anti and H-10-syn), 4.41 (ddd, H-6, $J_{2,6}$ = 11.3 Hz, $J_{6,7}$ = 4.6 Hz, and $J_{6,11\text{-syn}}$ = 1.7 Hz), 4.41 (m, H-1, $J_{1,7}$ = 2.7 Hz), 4.52 (m, H-7), 5.23 (ddd, H-2, $J_{1,2}$ = 5.4 Hz and $J_{2,10\text{-syn}}$ = 1.4 Hz); $\Delta\delta$ 0.43 (H-11-anti), 0.52 (H-11-syn), 0.47 (H-10-syn), 0.32 (H-10-anti), 0.69 (H-6), 0.57 (H-1), 0.57 (H-7), 0.41 (H-2). Found: C, 67.59; H, 5.53; N, 5.92.

7d: colorless prisms from benzene/petroleum ether, mp 153–155 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.77 (m, H-10-anti and H-11-anti), 2.39 (m, H-10-syn and H-11-syn), 3.93 (dd, H-6, $J_{2,6}$ = 12.3 Hz and $J_{6,7}$ = 2.2 Hz), 4.32 (m, H-1), 4.38 (m, H-7), 4.92 (dd, H-2, $J_{1,2}$ = 2.6 Hz). Anal. Calcd for $C_{13}H_{12}ClNO_3$: C, 58.76; H, 4.55; N, 5.27. Found: C, 58.90; H, 4.43; N, 5.39.

8d: colorless prisms from benzene/petroleum ether, mp 133–135 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.49 (m, H-11-anti), 2.05 (m, H-11-syn), 2.11 (m, H-10-anti and H-10-syn), 4.38 (ddd, H-6, $J_{2,6}$ = 11.2 Hz, $J_{6,7}$ = 4.6 Hz, and $J_{6,11\text{-syn}}$ = 1.8 Hz), 4.38 (m, H-1), 4.49 (m, H-7), 5.23 (ddd, H-2, $J_{1,2}$ = 5.5 Hz and $J_{2,10\text{-syn}}$ = 1.0 Hz). Anal. Found: C, 58.87; H, 4.55; N, 5.30.

7e: colorless prisms from ethanol/dichloromethane, mp 178–179 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.80 (m, H-10-anti and H-11-anti), 2.42 (m, H-10-syn and H-11-syn), 4.01 (dd, H-6, $J_{2,6}$ = 12.3 Hz and $J_{6,7}$ = 2.4 Hz), 4.36 (m, H-1), 4.41 (m, H-7), 5.02 (dd, H-2, $J_{1,2}$ = 2.5 Hz). Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.58; H, 4.43; N, 10.05.

8e: slightly yellow prisms from ethyl ether/*n*-hexane, mp 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (m, H-11-anti), 2.11 (m, H-10-anti, H-10-syn and H-11-syn)), 4.41 (ddd, H-6, $J_{2,6}$ = 11.3 Hz, $J_{6,7}$ = 4.6 Hz, and $J_{6,11\text{-syn}}$ = 1.8 Hz), 4.43 (m, H-1), 4.52 (m, H-7), 5.31 (ddd, H-2, $J_{1,2}$ = 5.4 Hz and $J_{2,10\text{-syn}}$ = 1.1 Hz). Anal. Found: C, 56.50; H, 4.53; N, 10.32.

7f: colorless crystals from methanol, mp 89–92 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, Me), 1.71 (m, H-10-anti and H-11-anti), 2.38 (m, H-10-syn and H-11-syn), 3.73 (dd, H-6, $J_{2,6}$ = 12.4 Hz and $J_{6,7}$ = 2.6 Hz), 4.28 (m, H-1), 4.35 (q, CH_2), 4.63 (m, H-7), 4.93 (dd, H-2, $J_{1,2}$ = 2.3 Hz). Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17. Found: C, 53.06; H, 5.89; N, 6.03.

8f: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.39 (m, Me), 1.51 (m, H-11-anti), 1.98 (m, H-10-anti), 2.15 (m, H-10-syn and H-11-syn), 4.17 (ddd, H-6, $J_{2,6}$ = 11.8 Hz, $J_{6,7}$ = 4.9 Hz, and $J_{6,11\text{-syn}}$ = 1.5 Hz), 4.37 (m, H-1), 4.48 (m, CH_2), 4.62 (m, H-7), 5.26 (ddd, H-2, $J_{1,2}$ = 5.2 Hz and $J_{2,10\text{-syn}}$ = 1.3 Hz). Anal. Found: C, 52.68; H, 5.81; N, 6.04.

7g: colorless prisms from methanol, mp 131–134 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.74 (m, H-10-anti and H-11-anti), 2.38 (m, H-10-syn and H-11-syn), 4.01 (dd, H-6, $J_{2,6}$ = 12.3 Hz and $J_{6,7}$ = 2.7 Hz), 4.33 (m, H-1), 4.65 (m, H-7), 4.95 (dd, H-2, $J_{1,2}$ = 2.4 Hz); $\Delta\delta$ 1.06 (H-10-anti and H-11-anti), 0.76 (H-10-syn and H-11-syn), 0.73 (H-6), 0.70 (H-1), 0.37 (H-7), 0.96 (H-2). Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.75; H, 5.05; N, 5.52.

8g: glassy solid; ^{1}H NMR ($CDCl_3$) δ 1.55 (m, H-11-anti), 1.98 (m, H-10-anti), 2.15 (m, H-10-syn and H-11-syn), 4.33 (ddd, H-6, $J_{2,6}$ = 11.6 Hz, $J_{6,7}$ = 5.0 Hz, and $J_{6,11\text{-syn}}$ = 1.5 Hz), 4.37 (m, H-1), 4.81 (m, H-7), 5.26 (ddd, H-2, $J_{1,2}$ = 5.4 Hz and $J_{2,10\text{-syn}}$ = 1.4 Hz); $\Delta\delta$ 0.52 (H-11-anti), 0.40 (H-10-anti), 0.50 (H-11-syn and H-11-anti), 0.60 (H-6), 0.56 (H-1), 0.20 (H-7), 0.57 (H-2). Found: C, 64.72; H, 5.09; N, 5.29.

7h: colorless crystals from *n*-hexane/ethyl ether, mp 99–102 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.71 (m, H-10-anti and H-11-anti), 2.35 (m, H-10-syn and H-11-syn), 2.58 (s, Me), 3.71 (dd, H-6, $J_{2,6}$ = 12.3 Hz and $J_{6,7}$ = 2.7 Hz), 4.28 (m, H-1), 4.59 (m, H-7), 4.92 (dd, H-2, $J_{1,2}$ = 2.4 Hz). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.95; H, 5.84; N, 7.07.

8h: colorless prisms from *n*-hexane/ethyl ether, mp 69–71 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (m, H-11-anti), 1.92 (m, H-10-anti), 2.12 (m, H-10-syn and H-11-syn), 2.52 (s, Me), 4.11 (ddd, H-6, $J_{2,6}$ = 11.6 Hz, $J_{6,7}$ = 4.8 Hz, and $J_{6,11\text{-syn}}$ = 1.5 Hz), 4.33 (m, H-1), 4.64 (m, H-7), 5.24 (ddd, H-2, $J_{1,2}$ = 5.2 Hz and $J_{2,10\text{-syn}}$ = 1.3 Hz). Found: C, 54.72; H, 5.71; N, 7.28.

7i: colorless prisms from methanol, mp 184–187 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.70 (m, H-10-anti and H-11-anti), 2.38 (m, H-10-syn and H-11-syn), 4.08 (m, H-7), 4.15 (dd, H-6, $J_{2,6}$ = 12.2 Hz and $J_{6,7}$ = 2.2 Hz), 4.38 (m, H-1), 4.97 (dd, *H*-2, $J_{1,2}$ = 2.5 Hz). Anal. Calcd for $C_{13}H_{11}Cl_2NO_3$: C, 52.02; H, 3.70; N, 4.67. Found: C, 52.07; H, 3.55; N, 4.77.

8i: colorless prisms from cyclohexane, mp 137–140 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (m, H-11-anti), 2.20 (m, H-10-anti, H-10-syn and H-11-syn), 4.19 (m, H-7), 4.49 (m, H-1), 4.64 (ddd, H-6, $J_{2,6}$ = 11.3 Hz, $J_{6,7}$ = 4.4 Hz, and $J_{6,11\text{-syn}}$ = 1.0 Hz), 5.29 (ddd, H-2, $J_{1,2}$ = 5.4 Hz and $J_{2,10\text{-syn}}$ = 0.8 Hz). Anal. Found: C, 52.08; H, 3.73; N, 4.54.

7j: colorless needles from benzene, mp 153–155 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, H-11-anti), 1.74 (m, H-10-anti), 2.28 (s, 3 H, Me), 2.30 (m, H-11-syn), 2.32 (s, 6 H, Me), 2.34 (m, H-10-syn), 3.81 (dd, H-6, $J_{2,6}$ = 12.3 Hz and $J_{6,7}$ = 2.4 Hz), 4.01 (m, H-7), 4.35 (m, H-1), 4.86 (dd, H-2, $J_{1,2}$ = 2.5 Hz); $\Delta\delta$ 1.04 (H-11-anti), 0.96 (H-10-anti), 0.18 (Me), 0.71 (H-11-syn), –0.05 (Me), 0.58 (H-10-syn), 0.65 (H-6), 0.73 (H-7), 0.54 (H-1), 0.74 (H-2). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.01; H, 7.00; N, 5.22.

8j: colorless prisms from methanol, mp 124–127 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.73 (m, H-11-anti), 2.08 (m, H-11-syn), 2.18 (m, H-10-anti and H-10-syn), 2.28 (s, 3 H, Me), 2.37 (s, 6 H, Me), 4.09 (m, H-7), 4.39 (ddd, H-6, $J_{2,6}$ = 11.3 Hz, $J_{6,7}$ = 4.5 Hz, and $J_{6,11\text{-syn}}$ = 1.7 Hz), 4.45 (m, H-1), 5.19 (ddd, H-2, $J_{1,2}$ = 5.3 Hz and $J_{2,10\text{-syn}}$ = 1.0 Hz); $\Delta\delta$ 0.29 (H-11-anti), 0.45 (H-11-syn), 0.40 (H-10-syn), 0.23 (H-10-anti), 0.25 (Me), 0.29 (Me), 0.64 (H-7), 0.34 (H-6), 0.53 (H-1), 0.30 (H-2). Found: C, 70.59; H, 7.16; N, 5.27.

7k: colorless prisms from benzene, mp 178–181 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.51 (m, H-11-anti), 1.73 (m, H-10-anti), 2.30 (bs, 3 H, Me), 2.37 (m, H-10-syn and H-11-syn), 2.40 (bs, 3 H, Me), 2.53 (s, 3H, Me), 3.70 (dd, H-6, $J_{2,6}$ = 12.4 Hz and $J_{6,7}$ = 2.3 Hz), 3.99 (m, H-7), 4.37 (m, H-1), 4.91 (dd, H-2, $J_{1,2}$ = 2.5 Hz); $\Delta\delta$ 1.01 (H-11-anti), 1.01 (H-10-anti), 0.22 (Me), ≈0.81 (H-11-syn), ≈0.65 (H-10-syn), –0.32 (Me), 0.09 (Me), 0.86 (H-6), 0.95 (H-7), 0.61 (H-1), 0.88 (H-2). Anal. Calcd for $C_{16}H_{17}Cl_2NO_3$: C, 56.15; H, 5.01; N, 4.09. Found: C, 56.25; H, 5.11; N, 3.99.

8k: colorless glassy solid; ^{1}H NMR ($CDCl_3$) δ 1.65 (m, H-11-anti), 2.40 (m, H-11-syn, H-10-anti and H-10-syn), 2.41 (s, Me), 2.55 (s, 6 H, Me), 4.04 (m, H-7), 4.19 (ddd, H-6, $J_{2,6}$ = 11.2 Hz, $J_{6,7}$ = 4.0 Hz, and $J_{6,11\text{-syn}}$ = 1.0 Hz), 4.49 (m, H-1), 5.21 (ddd, H-2, $J_{1,2}$ = 5.6 Hz and $J_{2,10\text{-syn}}$ = 0.7 Hz). Found: C, 56.34; H, 5.14; N, 4.26.

7l: colorless needles from benzene/petroleum ether, mp 100–102 °C; ^{1}H NMR ($CDCl_3$) δ 1.68 (m, H-10-anti and H-11-anti), 2.02 (d, Me, $J_{Me,H\text{-}6}$ = 1.2 Hz), 2.39 (m, H-10-syn and H-11-syn), 3.41 (ddq, H-6, $J_{2,6}$ = 12.2 Hz and $J_{6,7}$ = 2.7 Hz), 4.19 (m, H-1), 4.30 (m, H-7), 4.70 (dd, H-2, $J_{1,2}$ = 2.3 Hz); $\Delta\delta$ 1.01 (H-11-anti), 0.90 (H-10-anti), 0.32 (Me), 0.65 (H-11-syn), 0.60 (H-10-syn), 1.09 (H-6), 0.47 (H-1), 0.93 (H-7), 0.70 (H-2). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.90; H, 6.43; N, 8.52.

8l: colorless needles from petroleum ether, mp 66–68 °C; ^{1}H NMR (C_6D_6) δ 0.98 (m, H-11-anti), 1.23 (d, Me, $J_{Me,H\text{-}6}$ = 1.0 Hz), 1.59 (m, H-11-syn), 1.69 (m, H-10-syn), 1.79 (m, H-10-anti), 3.06 (dddq, H-6, $J_{2,6}$ = 11.3 Hz, $J_{6,7}$ = 4.9 Hz, and $J_{6,11\text{-syn}}$ = 1.7 Hz), 3.48 (m, H-7), 3.79 (m, H-1), 4.68 (dd, H-2, $J_{1,2}$ = 5.2 Hz and $J_{2,10\text{-syn}}$ = 1.2 Hz); $\Delta\delta$ 0.58 (H-11-anti), 0.74 (Me), 0.50 (H-11-syn), 0.40 (H-10-syn), 0.30 (H-10-anti), 0.77 (H-6), 0.86 (H-7), 0.51 (H-1), 0.34 (H-2). Anal. Found: C, 56.70; H, 6.66; N, 8.31.

7m: colorless prisms *n*-hexane/ethyl ether, mp 85–86 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.72 (m, H-10-anti and H-11-anti), 2.39 (m, H-10-syn and H-11-syn), 3.64 (dd, H-6, $J_{2,6}$ = 12.2 Hz and $J_{6,7}$ = 2.6 Hz), 4.27 (m, H-1), 4.40 (m, H-7), 4.87 (dd, H-2, $J_{1,2}$ = 2.4 Hz); $\Delta\delta$ 0.98 (H-10-anti and H-11-anti), 0.71 (H-10-syn and H-11-syn), 1.04 (H-6), 0.58 (H-1), 0.71 (H-7), 0.85 (H-2). Anal. Calcd for $C_7H_8BrNO_3$: C, 35.92; H, 3.45; N, 5.99. Found: C, 35.77; H, 3.53; N, 5.88.

8m: colorless prisms from *n*-hexane, mp 62–65 °C; ^{1}H NMR ($CDCl_3$) δ 1.71 (m, H-11-anti), 2.12 (m, H-10-anti, H-10-syn and H-11-syn), 4.03 (ddd, H-6, $J_{2,6}$ = 11.4 Hz, $J_{6,7}$ = 4.7, and $J_{6,11\text{-syn}}$ = 1.6 Hz), 4.33 (m, H-1), 4.41 (m, H-7), 5.17 (ddd, H-2, $J_{1,2}$ = 5.4 Hz and $J_{2,10\text{-syn}}$ = 1.4 Hz); $\Delta\delta$ 0.54 (H-11-anti), 0.56 (H-10-anti, H-10-syn and H-11-syn), 0.89 (H-6), 0.72 (H-1), 0.80 (H-7), 0.65 (H-2). Anal. Found: C, 35.67; H, 3.54; N, 6.10.

7n: colorless prisms from *n*-hexane, mp 139–142 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, t-Bu), 1.69 (m, H-10-anti and H-11-anti), 2.36 (m, H-10-syn and H-11-syn), 3.53 (dd, H-6, $J_{2,6}$ = 12.3 Hz and $J_{6,7}$ = 2.4 Hz), 4.23 (m, H-1), 4.46 (m, H-7), 4.70 (dd, H-2, $J_{1,2}$ = 2.4 Hz); $\Delta\delta$ 0.10 (t-Bu), 0.97 (H-11-anti), 0.87 (H-10-anti), 0.64 (H-11-syn), 0.58 (H-10-syn), 0.81 (H-6), 0.47 (H-1), 0.65 (H-7), 0.67 (H-2). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.34; H, 8.13; N, 6.52.

8n: colorless prisms from methanol, mp 68–72 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, t-Bu), 1.52 (m, H-11-anti), 2.12 (m, H-10-anti, H-10-syn and H-11-syn), 3.91 (ddd, H-6, $J_{2,6}$ = 11.0 Hz, $J_{6,7}$ = 4.0 Hz, and $J_{6,11\text{-syn}}$ = 1.6 Hz), 4.49 (m, 2 H, H-1 and H-7), 4.98 (ddd, H-2, $J_{1,2}$ = 5.7 Hz and $J_{2,10\text{-syn}}$ = 0.9 Hz); $\Delta\delta$ 0.34 (t-Bu), 0.20 (H-11-anti), 0.31 (H-10-syn), 0.41 (H-11-syn), 0.21 (H-10-anti), 0.39 (H-6), 0.56 (H-1 and H-7), 0.26 (H-2). Found: C, 62.39; H, 8.17; N, 6.56.

Reaction of 6b with 7b and 8b. A solution of **7b** (0.30 mmol) and of *p*-methoxybenzohydroximic acid chloride (0.50 mmol) in benzene (5 mL) was stirred at room temperature for 4 days in the presence of excess solid sodium bicarbonate. Then the inorganic salts were filtered off and the solvent evaporated to give a slightly yellow residue. Column chromatography (cyclohexane/ethyl acetate (7:3) as eluant) of this residue afforded pure **9b** (20%) aside from the nitrile oxide dimer and unreacted **7b**.

9b: colorless crystals from ethanol, mp 165–167 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (m, H-10-anti), 1.68 (H-11-anti), 2.19 (m, H-11-syn), 2.30 (H-10-syn), 3.21 (dd, H-6, $J_{2,6}$ = 9.0 Hz and $J_{6,7}$ = 0.8 Hz), 3.80 and 3.86 (two s, OMe), 3.86 (m, H-7), 4.29 (m, H-1), 4.58 (dd, H-2, $J_{1,2}$ = 3.5 Hz); $\Delta\delta$ 0.99 (H-10-anti), 0.97 (H-11-anti), 0.57 (H-11-syn), 0.58 (H-10-syn), 0.33 and 0.36 (OMe), 0.48 (H-6), 0.28 (H-7), 0.57 (H-1), 0.58 (H-2). Anal. Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.55; H, 5.48; N, 6.80.

Under the very same conditions the reaction of excess **6b** with **8b** did not produce any bis-adduct as shown by TLC and ^{1}H NMR analysis of the reaction mixture.

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