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# STEREOSELECTIVITIES OF MESITONITRILE OXIDE CYCLOADDITIONS TO 7-SUBSTITUTED NORBORNADIENES

Lorenzo Dal Bo[1a], Marco De Amici[1a], Carlo De Micheli*[1a†], Remo Gandolfi*[1b], and K. N. Houk*[1c]

Istituto Chimico Farmaceutico dell´Universita di Milano,
Viale Abruzzi 42, 20121 Milano, Italy

Istituto di Chimica Organica, Universita di Pavia
Viale Taramelli 10, 27100 Pavia, Italy

Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, California 90024, U.S.A.

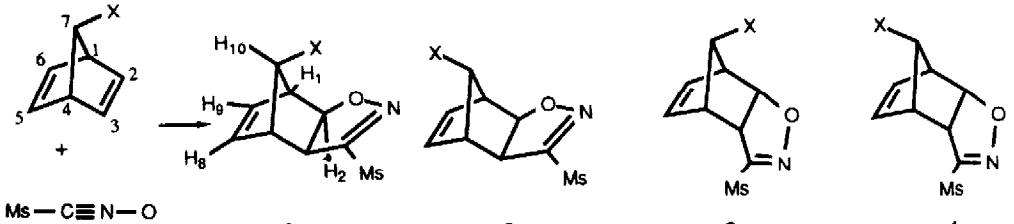
Summary: The stereochemistries of cycloadditions of mesitonitrile oxide to norbornadiene and nine 7-substituted derivatives have been investigated. The stereoselectivities are controlled primarily by torsional effects which are altered by 7-substituents.

There has been much recent interest in the stereochemistry of cycloadditions to 7-substituted norbornadienes.[2] Aside from mechanistic and theoretical interest, such reactions have been of value in synthesis.[3] Wilt's report of a reinvestigation of the cycloadditions of diazoalkanes to 7-chloronorbornadiene,[4] as well as considerations of earlier reports of hexachlorocyclopentadiene,[2,5] dihalocarbene,[6] dichloroketene,[7] and benzoylnitrile oxide cycloadditions[8] to 7-substituted norbornadienes, have led us to seek a general explanation for stereoselectivity in such systems. In particular, we have focused upon the interactions between forming bonds and allylic bonds, and the alterations of these interactions by the electronegativity of the 7-substituents.[2] We wish to report the stereochemistries of cycloadditions of mesitonitrile oxide to a series of 7-substituted norbornadienes. These results parallel in some respects those obtained with other electrophiles.

The reactions of mesitonitrile oxide with the norbornadienes were performed in ether solution at room temperature with a 1,3-dipole:dipolarophile ratio of 1:30, in order to avoid the formation of bis-adducts. The adduct percentages reported in Table 1 were obtained by analysis of the reaction mixtures by HPLC, using a column of Porasil and n-hexane:isopropanol as eluent. The endo isomers have two maxima at 220nm and 254nm, respectively, whereas the exo derivatives show a single maximum at 220nm. The values of $\varepsilon$ at 220nm are the same for all the isomers of a series. The 220nm band was chosen for the analytical determinations in order to

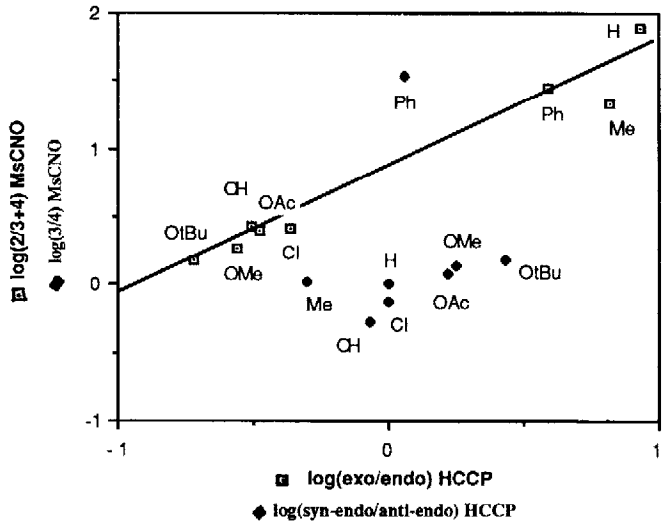
avoid the introduction of correction factors. All the adducts were separated and purified by column chromatography and were characterized by 1H-NMR analysis; the structures of adducts **d-j** were also correlated through standard transformations of **1i-4i**.[9] The differentiation of the exo adducts (**1** and **2**) from the endo isomers (**3** and **4**) is based upon the value of the coupling constant between protons H-1 and H-2. This coupling is approximately 1-2Hz in the first group and 4Hz in the second set of compounds.[10] The identification of syn ( **1** and **3**) and anti (**2** and **4**) structures is based upon the presence of a W coupling constant between the anti H-10 and H-2(2Hz) in **1** and between the syn H-10 and H-8 or H-9 (1Hz) in **4**.[11] The dipolarophiles listed in Table 1 have been prepared following previously reported procedures or from the hydroxy derivatives (**i**) by standard methods.[2,5]

**Table 1**: Percentages of Adducts Obtained from the Mesitonitrile Oxide Cycloadditions.




| | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| **a** | X = H | 98.7 | | 1.3 | |
| **b** | X = Me | -- | 95.5 | 2.3 | 2.2 |
| **c** | X = Ph | -- | 96.5 | 3.4 | 0.1 |
| **d** | X = OBut | 8.9 | 54.8 | 21.8 | 14.5 |
| **e** | X = OMe | 10.9 | 57.7 | 18.2 | 13.2 |
| **f** | X = $OCOCH_3$ | 13.3 | 61.9 | 13.6 | 11.2 |
| **g** | X = $OCO_2CH_3$ | 3.2 | 64.7 | 15.8 | 16.3 |
| **h** | X = $OCOCF_3$ | 7.2 | 62.5 | 12.8 | 17.5 |
| **i** | X = OH | 49.6 | 36.6 | 4.8 | 9.0 |
| **j** | X = Cl | < 0.1 | 72.0 | 12.0 | 16.0 |

In order to compare these results with the stereochemistries of other electrophilic cycloadditions to norbornadienes, the Figure on the next page shows a plot of the logarithms of the ratio of exo (**2**) to total endo(**3** + **4**) cycloadditions for the reactions reported here versus the same exo/endo ratio for the additions of hexachlorocyclopentadiene to the same norbornadienes.[2,5] This comparison excludes **1**, since steric repulsions or attractive interactions with X will influence this rate. Also shown is a comparison of the ratio of endo-syn (**3**) to endo-anti (**4**) products for the two reactions.




For the exo/endo ratio, the only significant difference is the sensitivity of the ratios for different electrophilic 7-substituents.[2,5] We can apply the interpretation made for the other cases to these new results. An electron-withdrawing group at the 7-position decreases the rate of exo attack by electrophilic species. The origin of this effect is the electron-withdrawal from the 1,2-, 2,3-, 3,4-, and 4,5-$\sigma$ bonds. When these bonds are electron-rich, exo attack is facilitated. Electron-rich $\sigma$ bonds facilitate exo attack because they are anti to the electron-deficient partial bonds in the transition state. The effect is smaller, but the same as that which accelerates exo-2-norbornyl solvolysis. Electron-withdrawal by a 7-substituent decreases the rate of electrophilic attack in any fashion, but more at the exo face than at the endo.

For hexachlorocyclopentadiene cycloadditions, 7-alkoxy substituents also facilitate syn-endo over anti-endo attack by a through-space effect. The oxygen located on the back-side of a double bond facilitates the attack of electrophiles on the opposite side, through orbital mixing with the $\pi$ bond of the alkene or through an electrostatic effect.[2] This is not observed with MsCNO, which gives about equal amounts of **3** and **4** in every case except that of phenyl. The origin of this difference is under investigation.

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9. Compound **1j** was synthesized from **1i** by reaction with $SOCl_2$; a HPLC analysis (detection limit: 0.1%) did not show the presence of this adduct in the reaction mixture. **1d** could not be separated from **2d** by conventional column chromatography: the synthesis of **1d** was accomplished by reacting **1i** with isobutylene in the presence of con. $H_2SO_4$ by the method previously reported by H. C. Beyerman and J. S. Boutekoe, *Rec. Trav. Chim.*, **81**, 691 (1962).
10. A further differentiation of **2** from the other three adducts is based on the value of the chemical shift of H-10. The proximity of the isoxazoline ring to this proton in **2** produces a significant deshielding effect (e.g., see note 11).
11. **1d**: (m.p. 113-5°C), δ ($CDCl_3$) 2.98 (bs, H-7), 3.35 (bs, H-1), 3.52 (bd, H-6, $J_{2,6}$= 9.0 Hz), 3.80 (bs, H-10), 5.20 (dt, H-2, $J_{1,2} + J_2$, 10 = 1.0 Hz and $J_{2,6}$ = 9.0 Hz), 6.13 (m, H-8 and H-9).

**2d**: (m.p. 122-3°C), δ. ($CDCl_3$) 2.82 (bs, H-7), 3.32 (bs, H-1), 3.45 (bd, H-6, $J_{2,6}$ = 9.5 Hz), 4.65 (bs, H-10), 4.97 (dd, H-2, J1,2 = 1.0 Hz and $J_{2,6}$ = 9.5 Hz), 6.15 (m, H-8 and H-9).

**3d**: (viscous oil), δ ($CDCl_3$) 2.71 (bs, H-7), 3.16 (bs, H-1), 3.67 (bs, H-10), 4.43 (dd, H-6, $J_{6,7}$ = 4.0 Hz and $J_{2,6}$ = 9.0 Hz), 5.52 (dd, H-2, $J_{1,2}$ = 4.0 Hz and $J_{2,6}$ = 9.0 Hz), 6.03 (ddd, H-8, $J_{1,8}$ = 1.0 Hz, $J_{7,8}$ = 3.2 Hz and $J_{8,9}$ = 6.5 Hz), 6.12 (m, H-9).

**4d**: (m.p. 137-8°C), δ ($CDCl_3$) 2.81 (bs, H-7), 3.34 (bs, H-1), 3.71 (bs, H-10), 4.09 (dd, H-6, $J_{6,7}$ = 4.0 Hz and $J_{2,6}$ = 10.0 Hz), 5.24 (dd, H-2, $J_{1,2}$ = 4.0 Hz and $J_{2,6}$ = 10.0 Hz), 6.08 (ddt, H-8, $J_{1,8}$ = $J_{8,10}$ = 1.1 Hz, $J_{7,8}$ = 3.2 Hz and $J_{8,9}$ = 6.6 Hz), 6.21 (m, H-9).

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