

REGIOSELECTIVITY OF NITRILE OXIDE CYCLOADDITIONS
TO ELECTRON-DEFICIENT DIPOLAROPHILES.

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Nitrile oxides give predominantly 5-substituted isoxazolines even with very electron-deficient alkene dipolarophiles, but very electron-deficient alkyne dipolarophiles give substantial amounts of 4-substituted isoxazoles. The contrast between nitrones and nitrile oxides, and between alkenes and alkynes, can be explained on the basis of orbital energies and changes in orbital energies upon molecular distortions in the cycloaddition transition states.

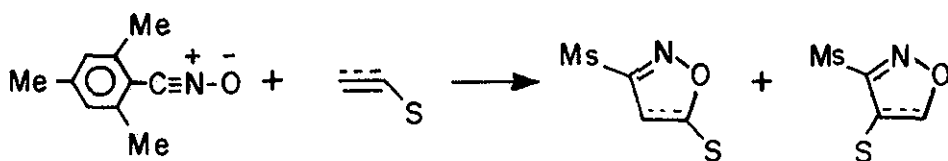
Nitrones, which normally react with monosubstituted alkenes and alkynes to give the 5-substituted isoxazolidines and isoxazolines, respectively,^{2,3} give, instead, 4-substituted products when the nitrone is made sufficiently electron-rich and the

dipolarophile is made sufficiently electron-deficient.^{4,5} This change in regioselectivity signals a switch from nitrene LUMO-dipolarophile HOMO control of regioselectivity to nitrene HOMO-dipolarophile LUMO control.

We have rationalized the formation of significant quantities of the 4-substituted adducts with various nitrile oxides and alkyl propiolates on a similar basis,⁶ and also predicted that the same type of behavior would be observed in reactions of nitrile oxides with other electron-deficient dipolarophiles.³ We wish to report that this prediction is marginally followed experimentally, and that the extent of "reversal" of regioselectivity is far less for nitrile oxides than was expected on the basis of our experience with nitrenes.

Figure 1 gives the experimental regioselectivities, determined by nmr spectroscopy, for the cycloadditions of mesito-nitrile oxide to a variety of electron-deficient alkenes and alkynes.^{6,7}

Figure 1. Regioselectivities of Mesitonitrile Oxide Cycloadditions (CCl₄, 25°) to Electron-Deficient Dipolarophiles.



Acrylonitrile	<98	:	<2
Methyl acrylate ^a	93	:	7

Nitroethylene	~100	:	~0
Phenyl vinyl sulfone	96	:	4
Methyl vinyl sulfone	94	:	6
Ethyl propiolate	34	:	66
Methyl propiolate ^a	28	:	72
Cyanoacetylene	57	:	43
Trifluoropropyne	57	:	43

a) In ether; Reference 6.

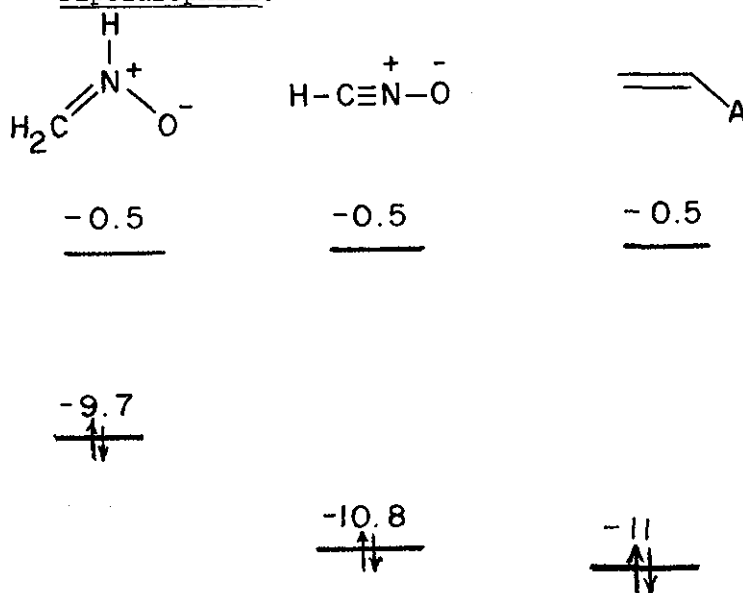
Mesitronitrile oxide (MNO) gives more of the 4-substituted adducts than less electron-rich nitrile oxides such as *p*-nitrobenzonitrile oxide (NBNO) and benzonitrile oxide (BNO). All of the alkenes listed above give only 5-substituted adducts with these 1,3-dipoles, except methyl acrylate, which gives 4% of the 4-adduct with BNO.⁹ With methyl propiolate and cyanoacetylene, BNO gives 28%⁶ and 18%, respectively, of the 4-adducts, while with NBNO, 30%⁶ and 2% of the 4-adducts are formed, respectively. The larger amounts of 4-substituted adducts with mesitronitrile oxide are compatible with the concept that nitrile oxide HOMO-dipolarophile LUMO interactions, which favor formation of these adducts, are greatest with the more electron-rich mesitronitrile oxide.⁵ A similar trend is found for reactions of methyl propiolate with an extensive series of nitrile oxides.⁶

However, in all cases, only small amounts of the 4-substituted isoxazolines are formed in the reactions of mesitronitrile oxide with electron-deficient alkenes, while substantial 4-adducts are formed with the electron-deficient alkynes. A similar

discontinuity between alkene and alkyne regioselectivities is observed for nitrones,⁵ but in all cases, mesitonitrile oxide gives far less of the 4-substituted adducts than are formed in the reactions of a variety of nitrones.

One reason for the greater tendency of nitrones than nitrile oxides to give 4-substituted adducts with a given electron-deficient dipolarophile is immediately obvious from the frontier molecular orbital theory in its simplest form. As shown schematically in Figure 2,¹⁰ nitrones are considerably more electron-rich than nitrile oxides, and since the dipole HOMO-dipolarophile LUMO frontier orbital interaction favors formation of the 4-substituted adduct, nitrones give more "reversal" of regioselectivity than nitrile oxides.

Figure 2. Frontier Orbital Energies (eV) of Parent Nitron and Nitrile Oxide and of a Typical Electron-Deficient Dipolarophile.



Two other factors are less immediately obvious, but are probably of similar importance in causing nitrile oxides to resist reversal of regioselectivity. In our recent calculations on fulminic acid and other simple 1,3-dipoles,^{10,11} we found that the HCN angle of fulminic acid can bend with little expenditure of energy, and if it does so sufficiently, the carbon terminus becomes the most nucleophilic. Thus, as bending of the RCN angle occurs in the transition state of the reaction,¹² the oxygen of a nitrile oxide is only slightly more nucleophilic than that of the carbon.¹¹ The nitron HCN angle is bent with greater difficulty, and the reversal of the most nucleophilic terminus does not accompany this distortion.

The discontinuity between alkenes and alkynes, and the greater reactivity of the latter towards nucleophiles, can be explained on a similar basis.¹³ Although alkynes and alkenes with the same substituent have similar electron affinities and would, on this basis, be expected to be similar in reactivities toward nucleophilic species, it takes less energy to bend the HCC angle at one terminus of alkynes than to bend the HCC angle of alkenes. This, in itself, indicates that alkynes should distort more easily than alkenes toward product, and thus react more readily. Of even greater significance is the drastic drop in alkyne LUMO energy with HCC bending, as compared to the modest drop in alkene LUMO energy upon similar bending, a result of efficient $\pi^*_{CC} - \sigma^*_{CC}$ mixing for small distortions in alkynes. This rapid drop in LUMO energy with small distortions along the reaction coordinate indicates that alkynes will be consid-

erably more nucleophilic than alkenes with similar LUMO energies. In other words, alkyne LUMO-nucleophile HOMO interactions are much stronger in the transition state than alkene LUMO-nucleophile HOMO interactions, even for alkynes and alkenes of similar LUMO energies in the isolated molecules. This role of alkyne bending is supported by Poppinger's transition state calculations, which indicate considerably greater HCC out-of-plane bending in the transition state for the reaction of acetylene (16-19°) than of ethylene (5-10°) with fulminic acid.¹²

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