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# NITRONE IONIZATION POTENTIALS AND CYCLOADDITION REGIOSELECTIVITIES.

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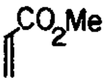
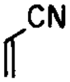
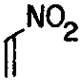
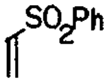
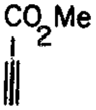
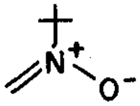
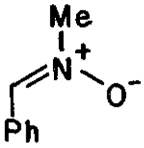
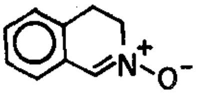
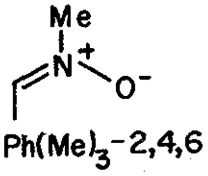
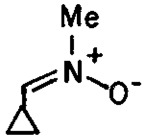
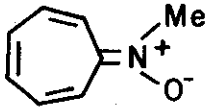
In agreement with theoretical predictions, the "normal" preference for formation of 5-substituted isoxazolines in 1,3-dipolar cycloadditions of nitrones to substituted alkenes changes to a preference for the 4-substituted adduct as the ionization potential of the nitrone decreases, or that of the alkene increases.

The exclusive formation of 5-substituted isoxazolidine and isoxazoline adducts in the reactions of both electron-rich and electron-deficient alkenes or alkynes with nitrones was long an unexplained phenomenon.[2] In 1973, we proposed that nitrones would give "reversed" (4-substituted) adducts with very electron-deficient alkenes and alkynes,[3] and this prediction was soon proven experimentally.[4] We now wish to report that the extent of "reversal" of regioselectivity in cycloadditions of nitrones regularly increases as the nitrone ionization potential (IP) decreases, in accord with the frontier orbital model of 1,3-dipolar cycloaddition regioselectivity.[3,5]

Table I shows the experimental regioselectivities observed with six nitrones and six electron-deficient alkenes and alkynes. The data on N-tert-butylnitrone and C-phenyl-N-methyl nitrone were reported earlier,[4] the data on C-mesityl-N-methylnitrone are available in one of our dissertations,[6] while the remaining data are reported here for the first time. C-Cyclopropyl-N-methylnitrone[7] and N-methyl cycloheptatrienylidene nitrone[8] have not been reported previously. The structures of all adducts and adduct ratios have been determined by nmr spectroscopy, so that the adduct ratios are accurate to ±5%.[4,6,8]

Table I. Ratios of 5-Substituted : 4-Substituted Adducts From Nitrone Cycloadditions of Electron-Deficient Dipolarophiles.

| |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
|  | 100:0 | 100:0 | 100:0 | 70:30 | 70:30 | 50:50 |
|  | 100:0[a] | 100:0[a] | 0:100 | 32:68 | 42:58[a] | 0:100 |
|  | 100:0[b] | 20:80 | | | 0:100[c] | 0:100 |
|  | 50:50 | 15:85 | 0:100 | 0:100 | 0:100 | 0:100 |

| | | |
|---|---|---|
|  | ≈70:30[7] | ≈50:50[7] |
|  | | 0:100 [10 + 2]adduct[8] |

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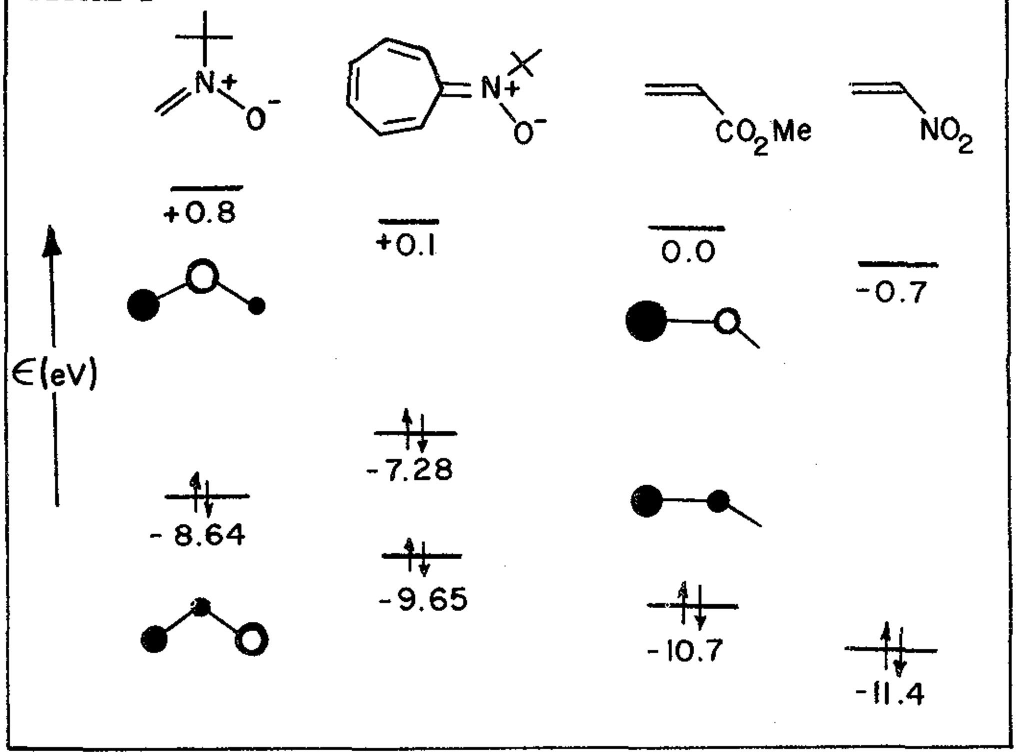
As we have noted earlier, and since explained theoretically,[9,10] alkynes with a given electron-withdrawing substituent show decidedly more "reversal" of regioselectivity than is shown by an alkene with the same substituent. This arises not from a higher electron affinity (lower LUMO energy) in the isolated alkyne, but from the drastic stabilization of the alkyne LUMO upon bending of the terminal groups out of linearity.[9]

Figure 1 shows the π frontier orbital energies of N-t-butylnitrone and N-methylcycloheptatrienylidene nitrone, determined by photoelectron spectroscopy in the case of occupied orbitals,[8,12] and calculated as electron affinities in the case of vacant orbitals.[12] The frontier orbital energies of methyl acrylate and nitroethylene, two extremes of the compounds studied here, are also shown.

For all of the nitrones and electron-deficient dipolarophiles, the gap between the nitrone HOMO and the dipolarophile LUMO is smaller than the opposite frontier orbital interaction. As we have discussed earlier, the rates of reactions of nitrones increase as the dipolarophile is made more electron-deficient, but with only moderately electron-deficient dipolarophiles, the

FIGURE 1



nitrone LUMO-dipolarophile HOMO interaction has the greatest influence on regioselectivity due to the large difference in nitrone LUMO terminal coefficients. However, as the nitrone is made more electron-rich, the nitrone HOMO-dipolarophile LUMO interaction increases, and this not only accelerates the reaction, but increases the amount of 4-substituted adduct formed, since the nitrone has the largest terminal coefficient at oxygen, and the dipolarophiles at the unsubstituted carbon.[3,12]

It can be seen (Table I) that a decrease in nitrone IP (top to bottom), or an increase in dipolarophile EA (left to right), leads to an increase in the amount of the 4-substituted regioisomer formed. Table II gives the lowest π ionization potentials of the nitrones, and the weighted average of the first two IP's for conjugated nitrones.[7,8,11] The weighted average is used, since the first IP of the nitrone will not be an accurate reactivity or regioselectivity index when these molecules are compared to non-conjugated derivatives.[11] The choice of 70% $IP_1$ + 30% $IP_2$ is qualitatively similar to the calculated percentages of orbital electron density on the nitrone moiety in the HOMO and SHOMO, respectively.

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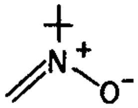
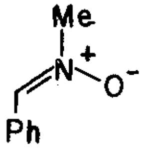
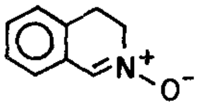
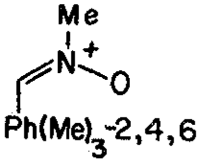
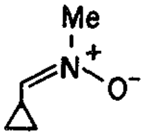
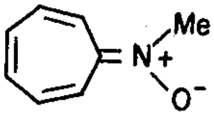
Table II. $\pi$ Ionization Potentials (eV) of Nitrones.

| | IP's | $0.7IP^1 + 0.3IP^2$ |
|---|---|---|
|  | 8.64 | 8.64 |
|  | 8.01, 9.91 | 8.58 |
|  | 7.81, 9.99 | 8.46 |
|  | 8.08, 9.1 | 8.39 |
|  | 8.30 | 8.30 |

|  |  |  |
|---|---|---|
|  | 7.28, 9.65 | 7.99 |

An electron-donor on the nitrone has a second effect which will also favor "reversal" of regioselectivity: donors increase the oxygen nucleophilicity relative to that of the carbon terminus. The HOMO and LUMO of N-<u>tert</u>-butylnitrone are shown in Figure 1. A donor group will not only mix in an antibonding fashion with, and destabilize, the nitrone HOMO, but will cause the nitrone LUMO to mix into the nitrone HOMO in an antibonding fashion at the site of donor substitution.[12b] This will decrease the carbon coefficient and increase that of oxygen in the HOMO. Thus, both the increase in HOMO energy, and the increased polarization of the HOMO towards oxygen causes increased formation of the 4-substituted isoxazolidines and isoxazolines as better donors are attached to the nitrone carbon. This effect is, of course, related to the concept of partial charges in the transition state,[2] but is not obviously related to diradical models of regioselectivity.[13]

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3 K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, J. Am. Chem. Soc., 1973, **95**, 7301.

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