

Our data support this interpretation. Burmeister has suggested that thiocyanate acts as a donor in second- and third-row transition metal complexes in high oxidation states.⁸

Despite numerous electron-transfer studies, it was only recently that the first definitive evidence for adjacent attack on a polyatomic ligand was obtained by Shea and Haim.⁹ They found that reduction of $\text{Co}(\text{NH}_3)_5\text{SCN}^{2+}$ by Cr^{2+} and $\text{Co}(\text{CN})_5^{3-}$ involved adjacent attack at sulfur. The rates of adjacent and remote attack by Cr^{2+} were comparable. Haim cited arguments¹⁰ which suggest that formation of CrSCN^{2+} (which is unstable) should be *ca.* 10^3 times slower than the formation of CrNCS^{2+} from $\text{Co}(\text{NH}_3)_5\text{SCN}^{2+}$. Therefore, adjacent attack at sulfur is unusually rapid. The great facility of the adjacent mode of attack was attributed to the high electron-mediating ability of sulfur when bound to an oxidizing center such as cobalt(III). Further unpublished studies by Shea and Haim¹¹ indicate that the rate of reduction by $\text{Co}(\text{CN})_5^{3-}$ of $\text{Co}(\text{NH}_3)_5\text{SCN}^{2+}$ is *ca.* 10^3 times that of $\text{Co}(\text{NH}_3)_5\text{NCS}^{2+}$.

Complexes of the type $\text{LCo}(\text{DH})_2\text{SCN}$ and $\text{LCo}(\text{DH})_2\text{NCS}$ are of comparable stability in nitrobenzene.³ Reasoning from Haim's results, one would predict that *adjacent* attack would be a very favorable pathway. Our results lend support to previous conclusions by Haim and Sutin.¹² We are presently studying the effects of ligands on the reaction rates in these systems, as well as extending our studies on the effect of the trans ligand on bonding mode.

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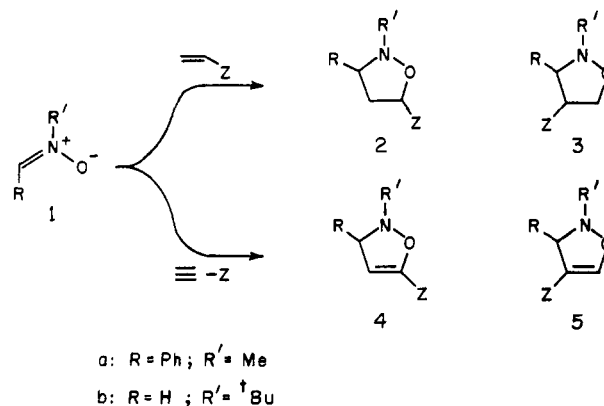
Reversal of Nitron Cycloaddition Regioselectivity with Electron-Deficient Dipolarophiles

Sir:

A solution to the vexing problem of regioselectivity in concerted cycloadditions¹ has been proposed recently.²⁻⁴ According to the frontier orbital treatment of 1,3-dipolar cycloadditions,²⁻⁵ the unidirectional addition of many 1,3 dipoles to both electron-rich and electron-deficient monosubstituted dipolarophiles should no longer be observed when the dipolarophile is

made highly electron deficient.⁴ We wish to report confirmations of this prediction.

The reactions of *C*-phenyl-*N*-methylnitron, **1a**, and other disubstituted nitrones to monosubstituted alkenes give only the 5-substituted isoxazolidines, **2**.⁶⁻¹⁰ Reactions of the parent nitron, a tautomer of formaldoxime, with acrylonitrile or acrylic esters,¹¹ as well as the reaction of *N*-(1-ethylcyclohexyl)nitron with styrene gave the 5-substituted adducts, **2**.¹² To verify the unimportance of steric hindrance at the nitron carbon in producing regioselectivity, we have studied the reactions of *N*-*tert*-butylnitron with a variety of monosubstituted alkenes and alkynes, including enamines, enol ethers, alkylethylenes, styrene, acrylonitrile, and



methyl acrylate. These reactions gave only the 5-substituted adducts, **2**. With methyl propiolate, Huisgen, *et al.*, observed diminished regioselectivity.^{13,14} Nitron **1a** gave a 42:58 mixture of **4a**- CO_2Me and **5a**- CO_2Me with methyl propiolate in DMF at 85° ,¹³ while 3,4-dihydroisoquinoline *N*-oxide and isoquinoline *N*-oxide reacted with methyl propiolate to give only the 4-substituted isomers, **5**.^{13,14} Low regioselectivity was also observed in reactions of diphenylnitrimine and benzonitrile oxide with methyl propiolate.^{15,16}

Since steric effects appeared to be little different in the acrylate and propiolate, we suggested that the loss or reversal of regioselectivity resulted from the lower HO orbital energy of the propiolate (IP = 11.15 eV)¹⁷ than that of the acrylate (IP = 10.72 eV)¹⁸ so that interaction of the dipole HO orbital with the dipolarophile LU orbital (which favors 4-substituted adducts) was of greater importance with the propiolate than with the acrylate.⁴

Ethyl propiolate reacts rapidly and exothermically

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with *N*-*tert*-butylnitrone, **1b**, at 25° in CCl₄ to give a mixture of isoxazolines **4b**-CO₂Et and **5b**-CO₂Et, which were separated by thick-layer chromatography and purified by short-path vacuum distillation. The separated isomers showed no tendency to interconvert in solution. The "normal" adduct **4b**-CO₂Et (ir(film) 5.78, 6.11 μ ; nmr (CCl₄) δ 4.00, d, J = 2.5 Hz (H₂CN), 5.60, t, J = 2.5 Hz (HC=)) and the reversed adduct **5b**-CO₂Et (ir(film) 5.83, 6.08 μ ; nmr (CCl₄) δ 4.00, d, J = 2.0 Hz (H₂CN), 7.11, t, J = 2.0 Hz (HC=)) were formed in a ratio of 70:30.^{19, 20}

Cyanoacetylene (IP = 11.81 eV),²¹ a more electron-deficient dipolarophile than propiolic ester, showed a greater tendency to form "reversed" regioisomers. Thus, *C*-phenyl-*N*-methylnitrone and cyanoacetylene reacted at 25° in benzene to form only **5a**-CN (ir(film) 4.50 μ ; nmr (CCl₄) δ 4.78 d, J = 2.0 Hz (PhCH), 7.10, d, J = 2.0 Hz (=CH)), while *N*-*tert*-butylnitrone reacted exothermically to form a 50:50 mixture of **4b**-CN (ir(film) 4.45 μ ; nmr (CCl₄) δ 4.05, d, J = 3.0 Hz (CH₂N) 5.62, t, J = 3.0 Hz (HC=)) and **5b**-CN (ir(film) 4.50; nmr (CCl₄) δ 4.05, d, J = 2.0 Hz (CH₂N), 7.10, t, J = 2.0 Hz (=CH)).

Since the reversal of regioselectivity in these acetylenes as compared to the corresponding alkenes was attributable to the lower orbital energies of the former, a similar effect was expected with alkenes substituted by one or more powerful electron-withdrawing groups. Thus, nitroethylene reacted at 60° with **1a** to give a mixture of the *cis* and *trans* 4-substituted isomers **3a**-NO₂. The major isomer in solution was *cis*-**3a**-NO₂ (nmr (CDCl₃) δ 3.87, d, J = 8.0 Hz (CHPh), ABX octet 4.34, dd, J = 8.0, 10.5 Hz (OCHCNO₂-*trans*), 4.62, dd, J = 5.5 Hz, J = 10.5 Hz (OCHCNO₂-*cis*), 5.46, ddd, J = 5.5, 8.0, 8.0 Hz), while silica gel or added base caused total isomerization to the more stable *trans*-**3a**-NO₂ (ir(film) 6.40 μ ; nmr (CCl₄) δ 3.95, d, J = 6.0 Hz (CHPh), ABX-octet 4.15, dd, J = 6.7, J = 10.5 Hz (OCHCNO₂-*trans*), 4.44, dd, J = 3.0, 10.5 Hz (OCHCNO₂-*cis*), 4.95, ddd, J = 3.0, 6.0, 6.7 Hz (CHNO₂)). Nitroethylene and *N*-*tert*-butylnitrone reacted rapidly at 25°, but the unstable "normal" adduct **2b**-NO₂ was not isolated (nmr (CCl₄) δ 1.13, s (*t*-Bu), 2.6–3.2, m (–CH₂CH₂–), 5.4–5.6, m (OCHNO₂)).

Finally, phenyl vinyl sulfone reacted rapidly with **1b** in chloroform at 25° to give a 70:30 mixture of the "normal" adduct, **2b**-SO₂Ph (ir (CCl₄) 7.60, 8.69 μ ; nmr (CDCl₃) δ 2.4–3.2, m (–CH₂CH₂–), 4.7–5.1, m (HCSO₂)), and the "reversed" adduct, **3b**-SO₂Ph (nmr (CDCl₃) δ 3.0–3.4, m (CH₂N), 3.8–4.4, m (OCH₂-CHSO₂Ph)). The "normal" adduct, **2b**-SO₂Ph, mp 91–93°, was isolated in a pure form, while the "reversed" adduct **3b**-SO₂Ph was isolated in an impure state contaminated by **2b**-SO₂Ph.

Phenyl vinyl sulfone reacted with **1a** at 80° to give the normal adduct, **2a**-SO₂Ph, as a *cis*,*trans* mixture (32%) and the reversed adduct, *trans*-**3a**-SO₂Ph (68%). While the epimeric mixture of normal adducts **2a**-SO₂Ph (nmr (CDCl₃) δ 5.02, dd, J = 3.0, 8.3 Hz (OCH-SO₂Ph)) did not undergo deuterium exchange in Na-

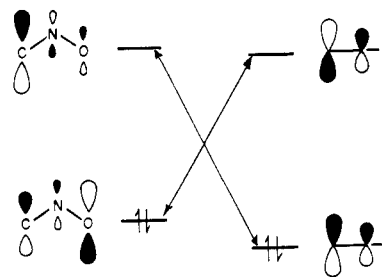


Figure 1. Interaction of frontier orbitals of a nitrone with the frontier orbitals of an electron-deficient dipolarophile.

OEt-EtOD, the reversed isomer, *trans*-**3a**-SO₂Ph underwent deuterium exchange in KOH-D₂O-THF without epimerization. Whereas the nmr spectrum of the undeuterated material has a complex multiplet at 3.6–4.7 ppm for the four ring protons, the deuterated molecule has an AB quartet (δ_A 4.25, δ_B 4.47, J_{AB} = 9.5 Hz) and a singlet for the benzylic proton at δ 3.87.

The thermal rearrangement of the 4-substituted Δ^4 -oxazolines²² occurred readily at 85°, while the corresponding 5-substituted Δ^4 -isoxazolines, **4b**-CN, **4a**-CN, and **4b**-CO₂Et, were stable under these conditions, providing further confirmation of the regiochemical assignments.

Table I summarizes the regiochemical observations

Table I. Adduct Ratios²⁰ from Nitrone Cycloadditions to Electron-Deficient Dipolarophiles

Nitrone	Dipolarophile	2 or 4 (5 sub- stituted)	3 or 5 (4 sub- stituted)
C-Ph, N-Me	Methyl propiolate ¹⁸	42	58
N- <i>t</i> -Bu	Ethyl propiolate	70	30
C-Ph, N-Me	Cyanoacetylene	0	100
N- <i>t</i> -Bu	Cyanoacetylene	50	50
C-Ph, N-Me	Nitroethylene	0	100
N- <i>t</i> -Bu	Nitroethylene	100	0
C-Ph, N-Me	Phenyl vinyl sulfone	32	68
N- <i>t</i> -Bu	Phenyl vinyl sulfone	70	30

made here. In every case, the amount of "reversal" to form 4-substituted adducts is greater with **1a** than **1b**. These results are readily explicable, and were predicted, by frontier orbital considerations.^{3, 4} The dipole LU-dipolarophile HO interaction strongly favors formation of the 5-substituted adduct with all dipolarophiles, whereas the dipole HO-dipolarophile LU interaction only weakly favors formation of the 4-substituted adducts (Figure 1).⁴ As a result, not until the latter interaction is much stronger than the former will reversal of regioselectivity occur. Once the dipole LU interaction is sufficiently small, Coulombic or dipole-dipole interactions, which favor formation of the 4-substituted isomers, may become dominant. From the results reported here, monosubstituted alkenes of IP \lesssim 11.2 eV should show partial or total reversal of regioselectivity with nitrones, as well as with nitrile oxides and nitrile imines. Although the ionization potentials of the nitroethylene and phenyl vinyl sulfone have not been measured, the greater

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(20) Adduct ratios determined from isolated products or nmr integration of reaction mixtures closely agreed.

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electron-withdrawing power of the nitro or sulfonyl groups than cyano or ester groups, as measured by σ values,^{23,23a} indicates the frontier orbitals of the former will be at lower energy than those of the latter.

The results reported here are in variance with those predicted by a postulated diradical mechanism,²⁴ and, furthermore, incursion of a dipolar intermediate mechanism seems unlikely in light of the negligible effect of solvent polarity changes on the rates of these reactions,²⁵ and the increase, rather than decrease, of 5-substituted adducts with increasing solvent polarity in the closely related nitrile oxide-methyl propiolate reactions.²⁶

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Minimum Chain Length Required for the Observation of a Temperature-Sensitive, Salt-Sensitive, Positive Circular Dichroism Band in Derivatives of L-Alanine¹

Sir:

The conformational properties of ionized homopolymers in aqueous solvents are highly dependent upon ionic strength.² Certain salts can also alter the stability of the ordered conformations formed by proteins.³ The effects upon the conformational properties of proteins are not due simply to alterations in ionic strength because the result observed depends upon the type of salt used³ and similar results can be observed in homopolypeptides which do not contain ionizable side chains.⁴

Fully ionized homopolypeptides, which have been widely used as models for polypeptides in a random coil conformation,⁵ exhibit a small positive circular dichroism band near 216 nm⁶ whose intensity is de-

creased by increasing either salt concentration or temperature.^{4,7-9} This observation has been the basis for proposing the existence of a new ordered structure, the "extended helix," which is presumed to be stabilized by electrostatic interaction of the charged side chains.⁷⁻¹¹ According to this proposal,⁷⁻¹¹ the random coil exhibits only negative circular dichroism above 200 nm, and the small positive band observed near 216 nm arises from the "extended helix." Evidence against the existence of an ordered structure stabilized by the electrostatic interaction of charged side chains has been provided by comparison of the optical activity^{4,12} and unperturbed dimensions¹³ of ionized poly(L-glutamic acid) and an un-ionized random-coil derivative, poly(*N*⁵- ω -hydroxyethyl-L-glutamine).

The effects of solvent composition and temperature upon the circular dichroism exhibited by a variety of low molecular weight derivatives of L-alanine are being investigated in order to clarify the mechanism of the interaction of polypeptides with salts. A few of the significant characteristics observed with several of these compounds are presented here. The circular dichroism spectra were obtained using a Jasco J-20 spectropolarimeter calibrated with *d*-10-camphorsulfonic acid.¹⁴ The results for the small derivatives of L-alanine are presented as the mean ellipticity per carbonyl group¹⁵ in order to facilitate comparison to the mean residue ellipticity reported for polypeptides.

The circular dichroism of Ac-Ala-OMe, Ac-Ala-Ala-OMe, and Ac-Ala-Ala-Ala-OMe¹⁶ in water at 15°, shown in Figure 1, exhibit an extremely small negative band at 231-234 nm, a weak positive band at 208-214 nm, and a strong negative band at or below 190 nm. Increasing the chain length through this series increases the intensity of the negative circular dichroism observed below 200 nm and produces a slight decrease in intensity and red shift for the maximum positive circular dichroism. The final member of this series would be random-coil poly(L-alanine) of high molecular weight, which cannot be studied in water due to its insolubility.¹⁷ A useful substitute with a -CH₂R side chain is poly(*N*⁵- ω -hydroxyethyl-L-glutamine), an un-ionized polypeptide which assumes a random coil conformation in water.^{13,18} Extension of the trends observed, in water, in the circular dichroism of the series Ac-Ala-OMe, Ac-Ala-Ala-OMe, Ac-Ala-Ala-Ala-OMe leads to the circular dichroism pattern observed in this solvent with poly(*N*⁵- ω -hydroxyethyl-L-glutamine).^{4,12}

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