

but only one shoulder at 296 cm^{-1} is well defined. The 184-cm^{-1} and 218-cm^{-1} bands are broad and certainly contain several components. A comparison of the low frequency resonance Raman spectrum of oxytyrosinase with those of *Limulus polyphemus* and *Busycon canaliculatum* oxyhemocyanin is shown in Figure 2. A tabulation of these data and those from two other arthropods is given in Table I. The vibrations enhanced for oxytyrosinase correspond quite closely to those for the oxyhemocyanins, both in energies of vibrations and intensity patterns. These vibrations are most likely metal-ligand stretches and bends but the absence of any shift upon $^{18}\text{O}_2$ substitution precludes the assignment of the Cu-O vibrations. Imidazoles have frequently been suggested as protein ligands. Model studies¹² confirm that copper-imidazole vibrations occur at these energies and the observed bands are tentatively assigned as such in Table I.

The energy of the 755-cm^{-1} band indicates that the oxygen is bound as peroxide and the shift to lower frequency of 41 cm^{-1} upon $^{18}\text{O}_2$ incorporation (Figure 1) further confirms this assignment as it is close to the calculated shift of 43 cm^{-1} for a pure O-O stretch. Similarly, the 744-cm^{-1} band of *Cancer* oxyhemocyanin shifts by 40 to 704 cm^{-1} upon isotope substitution.⁷ The O-O stretch for *Neurospora* tyrosinase is higher than that found for any hemocyanin, but, considering the range of frequencies found for the hemocyanins in Table I, the difference is not significant.

The results of these studies establish that the coordinated oxygen in oxytyrosinase exists as peroxide and strongly suggest that the copper atoms in this derivative are in the divalent state, the lack of an EPR signal being attributable to antiferromagnetic coupling between the Cu(II) ions (cf. ref 13). It has been determined¹⁴ that one oxygen molecule binds per two coppers in *Neurospora* oxytyrosinase, just as in hemocyanin. The correspondence of the peroxide stretch and the metal-ligand vibrations demonstrate that the active sites of oxyhemocyanin and oxytyrosinase are very similar. Since peroxide complexes are known¹⁵ to oxygenate substrates under relatively mild conditions, our results would indicate that the increased reactivity of tyrosinase is due to the details of the substrate-active site interactions rather than the relative activation of the oxygen.

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References and Notes

- (1) (a) R. Malkin and B. G. Malmstrom, *Adv. Enzymol.*, **33**, 177 (1970); (b) J. A. Fee, *Struct. Bonding*, (Berlin), **23**, 1 (1975).
- (2) K. E. Van Holde and E. F. J. van Bruggen in "Subunits in Biological Systems," Part A, S. N. Timasheff and G. D. Fasman, Ed., Marcel Dekker, New York, 1971, pp 1-53.
- (3) W. H. Vanneste and A. Zuberbuhler in "Molecular Mechanisms of Oxygen Activation", O. Hayaishi, Ed., Academic Press, New York, 1974, pp 374-394.
- (4) (a) R. L. Jolley, Jr., L. H. Evans, and H. S. Mason, *Biochem. Biophys. Res. Commun.*, **46**, 878 (1972); (b) R. L. Jolley, Jr., L. H. Evans, N. Makino, and H. S. Mason, *J. Biol. Chem.*, **249**, 335 (1974).
- (5) S. Gutteridge and D. Robb, *Eur. J. Biochem.*, **54**, 107 (1975).
- (6) K. Lerch, *FEBS Lett.*, **69**, 157 (1976).
- (7) (a) J. S. Loehr, T. B. Freedman, and T. M. Loehr, *Biochem. Biophys. Res. Commun.*, **56**, 510 (1975); (b) T. B. Freedman, J. S. Loehr, and T. M. Loehr, *J. Am. Chem. Soc.*, **98**, 2809 (1976).
- (8) J. A. Larrabee, T. G. Spiro, N. S. Ferris, W. H. Woodruff, W. A. Maltese, and M. S. Kerr, *J. Am. Chem. Soc.*, **99**, 1979 (1977).
- (9) K. Lerch, unpublished work.
- (10) D. M. Kurtz, Jr., D. F. Shriver, and I. M. Klotz, *J. Am. Chem. Soc.*, **98**, 5033 (1976).
- (11) T. J. Thamann, J. S. Loehr, and T. M. Loehr, *J. Am. Chem. Soc.*, **99**, 4187 (1977).
- (12) J. A. Larrabee and T. G. Spiro, *J. Am. Chem. Soc.*, submitted for publication.
- (13) R. S. Himmelwright, N. C. Eickman, and E. I. Solomon, *J. Am. Chem. Soc.*, submitted for publication.
- (14) K. Lerch, unpublished results.
- (15) V. J. Choy and C. J. O'Connor, *Coord. Chem. Rev.*, **9**, 145 (1972/73), and references therein.

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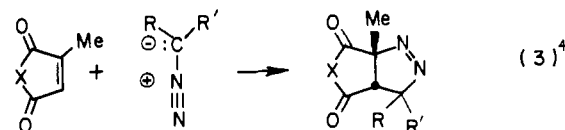
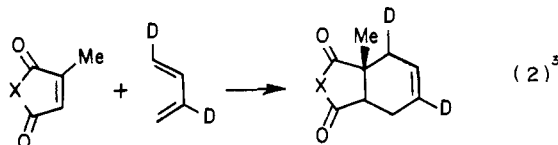
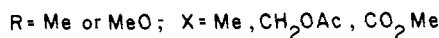
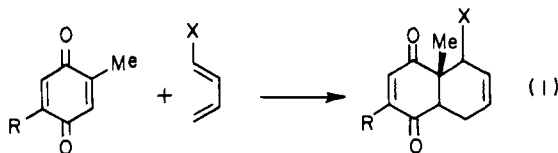
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Schizophrenic Substituents: The Origin of Anomalous Substituent Effects on Cycloaddition Regioselectivity

Sir:

The frontier molecular orbital (FMO) method has proven valuable in the rationalization and prediction of cycloaddition regioselectivity.¹ However, it is surprising that, in some cases, small difference in sizes of terminal FMO coefficients nevertheless lead to high regioselectivity; in a few other cases, predictions of FMO theory are clearly at odds with experiment. We report here model calculations which reveal two important general refinements of the FMO method, and also provide explanations of anomalous regioselectivities observed in a large class of cycloadditions.

Bohlmann and co-workers recently reported several Diels-Alder reactions of substituted benzoquinones (eq 1) and pointed out that the regioselectivities of these Diels-Alder reactions could not be understood on the basis of frontier molecular orbital (FMO) theory.² Numerous other reactions, summarized in eq 2 and 3,^{3,4} are of a specific type which has not been treated explicitly by frontier MO theory:¹ the electron-deficient partner in the cycloaddition is made unsymmetrical by substitution of a methyl group, which is usually thought of as a monolithic donor group. Our previous generalizations suggest that donors, including methyl, cause the π^* LUMO of an otherwise symmetrical alkene to be polarized in such a fashion that the larger LUMO coefficient will be possessed by the donor-substituted carbon.^{1a,5} Bohlmann's HOMO calculations on the quinones used in his studies verify



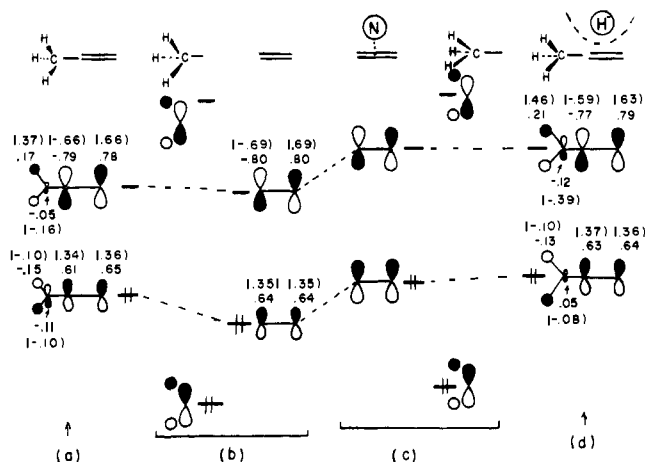


Figure 1. π molecular orbitals of (a) propene, (b) methyl and ethylene fragments, (c) ethylene-nucleophile polarization complex and methyl fragments, and (d) propene-nucleophile polarization complex. The coefficients are from STO-3G or (in parentheses) 4-31G. For the latter, coefficients of the outer part of the 2p orbitals are shown.¹⁴

this generalization.² Thus, in all of the cases summarized in eq 1-3, frontier MO theory, based on MO's of isolated reactants, predicts formation of the wrong product,⁸ since the terminus with the larger HOMO coefficient would be predicted to attack the methyl-substituted carbon. We will show here that the small LUMO polarization in such cases can be reversed by the approach of a reagent, and that secondary orbital interactions can override the alkene LUMO polarization. These effects are likely to be of general importance in influencing reactivity and regioselectivity in additions to alkenes.

The normal small LUMO polarization toward the methyl group results from the dominance of the methyl donor effect (via the π_{CH_3} orbital) over the acceptor effect (via the $\pi^*_{\text{CH}_3}$ orbital).^{7,9} However, the polarization of the LUMO can be reversed upon approach of a nucleophilic reagent to a methyl-substituted double bond; that is, the LUMO polarization is dominated by the acceptor nature of the methyl group (via the $\pi^*_{\text{CH}_3}$ orbital) upon approach of an electron-rich reagent. The methyl group still deactivates the double bond toward nucleophilic attack,²⁻⁴ even while directing nucleophilic attack to the remote carbon of the double bond. Thus, the methyl exhibits schizophrenic tendencies, deactivating the molecule toward reaction with nucleophiles, as expected of a donor, but directing attack to the remote alkene terminus, as expected of an acceptor.

A number of other anomalies observed in cycloaddition regioselectivities can be explained similarly. Thus, unsaturated electron-withdrawing groups (e.g., cyano and carbonyl groups) also behave in some circumstances as donors, while donors with moderately low-lying acceptor orbitals (e.g., Cl, Br, and SR) act as both donors and acceptors.¹⁰

Figure 1 outlines a perturbation rationale of the schizophrenic behavior of the methyl substituent in the cycloadditions mentioned. The methyl group acts as a hyperconjugative donor through the influence of the filled π_{CH_3} orbital, while, in principle, the methyl can also be a hyperconjugative acceptor through the influence of the vacant π_{CH_3} orbital. Computations,^{6,7} and experimental measurements of ionization potentials¹¹ and electron affinities,¹² indicate that the π_{CH_3} donor effect normally dominates. In isolated alkenes, both the π and π^* orbitals are raised upon methyl substitution. The alkene π^* LUMO is affected less than the π HOMO, but the LUMO is both raised and polarized in the fashion expected for a donor substituent (Figure 1a). That is, the donor π_{CH_3} orbital causes some of the π to be mixed in a bonding fashion into the π^* orbital. However, when an electron-rich diene or 1,3 dipole ap-

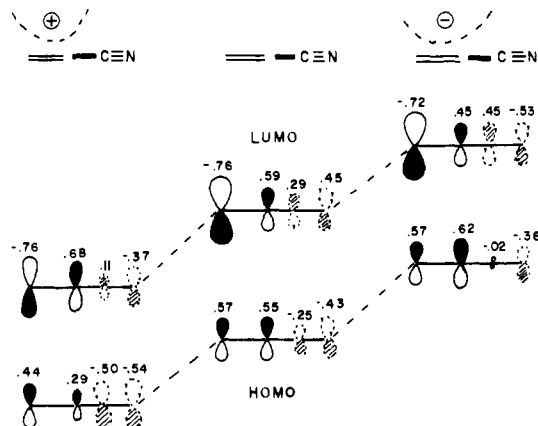


Figure 2. Polarization of the frontier molecular orbitals of acrylonitrile by a proton (which serves as a model electrophile) and hydride ion (which serves as a model nucleophile).

proaches the double bond, both electrostatic interactions and charge transfer will raise the π and π^* energies (Figure 1c), so that the π^* orbital will drift up in energy, where it will be influenced more by the $\pi^*_{\text{CH}_3}$ acceptor orbital than by the π_{CH_3} donor orbital. The $\pi^*_{\text{CH}_3}$ orbital causes some of the π orbital to be mixed into the π^* in an antibonding fashion, thus diminishing the LUMO coefficient at the site of substitution and increasing the remote LUMO coefficient (Figure 1d).⁹

A computational test of this hypothesis was carried out by ab initio STO-3G and 4-31G calculations^{13,14} on a propene-hydride "polarization complex", in which hydride was placed symmetrically between the sp^2 carbons of an alkene distorted slightly toward sp^3 , and at a distance of 1.15 Å from the center of the double bond. No overlap between the two fragment orbitals was allowed.¹⁵ As shown in Figure 1, the LUMO polarization, although small, is reversed in the polarization complex as compared to isolated propene. The change in methyl orbital coefficients supports the idea that this change in polarization results from an increased contribution of the $\pi^*_{\text{CH}_3}$ orbital of the LUMO. Nevertheless, the methyl group deactivates the molecule toward attack by nucleophilic reagents by the net elevation of the propene LUMO energy and by the increased closed-shell repulsion¹⁶ which results from the raising of the alkene HOMO energy. Experimentally, with substituted benzoquinones, electron-rich dienes add to the most "electron-deficient" double bond,¹⁷ but, when cycloaddition occurs to a methylated double bond, the orientation is that expected if methyl were acting as an acceptor.

The effect is a transition state analogue of the recent gas phase equilibrium and isotope effects found for methyl-substituted anions.¹⁸ Thus, anions are stabilized by alkyl groups in the gas phase as a result of the admixture of the high-lying anion lone-pair orbital with the relatively low-lying $\pi^*_{\text{CH}_3}$ of the methyl group, or the analogous acceptor orbitals of larger alkyls. In such cases, these two-electron stabilizing interactions surpass the four-electron destabilizing interactions between the anion lone-pair and the alkyl π_{CH_3} orbitals.^{18b,19}

The ability of an electron acceptor to polarize the HOMO in the direction expected for a donor is even larger, as demonstrated by the proton and hydride "polarization complexes" of acrylonitrile shown in Figure 2. Upon approach of a nucleophile, modeled by a hydride, the polarization of the LUMO is accentuated, while that of the HOMO is reversed compared with the direction of polarization in the isolated molecule. This clearly results from a greater influence of the π^*_{CN} than the π_{CN} upon both the π^* LUMO and π HOMO of the alkene. In the isolated molecule, the π^*_{CN} orbital dominates the LUMO polarization, but the π_{CN} influence on the HOMO slightly surpasses that of the π^*_{CN} , leading to the polarization shown. Upon approach of an electrophile, modeled here by a proton,

the HOMO polarization is accentuated, while that of the LUMO is decreased. Here the π_{CN} influence on both orbitals increases. Once again, the contributions of the cyano group to the HOMO and LUMO in various models prove the validity of this explanation.

The results not only indicate that the cyano group can act as a donor in cases of extreme electron demand (at least where HOMO polarization is concerned), but removes the uncertainty as to the "true" HOMO polarization in unsymmetrical electron-deficient alkenes.²⁰ As an electrophile approaches such a species, the less substituted terminus gains electron density and is, therefore, the predicted site of attack by electrophiles.²¹

Secondary orbital interactions²² are also expected to influence regioselectivities of cycloadditions when primary interactions provide little preference for one regioisomer. For example, a nucleophile attacking the substituted carbon of propene will experience repulsive secondary orbital interactions with the hydrogen orbital part of the LUMO. This further reduces the "effective" LUMO coefficient at the substituted carbon. Similarly, an electrophile attacking the substituted carbon of acrylonitrile will experience a destabilizing secondary orbital interaction with the carbon of the cyano group. In the cases under consideration, these effects reinforce the "reversal" of polarization discussed earlier.

By contrast, alkenes substituted by donors such as alkoxy or amino groups, which lack π acceptor orbitals, cannot experience the reversal of polarization demonstrated here for methyl substituted alkenes. If polarization reversal is most important, then reactions such as 1-3 with RO or R₂N substituents instead of Me will give meta orientation, since the LUMO will have the larger coefficient at the substituted carbon. If secondary orbital interactions dominate, these substituents will direct attack of nucleophiles to the more remote carbon, and ortho or para orientation will still be observed. Such an experimental test is in progress.

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References and Notes

- (1) K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975); (b) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley-Interscience, New York, 1976, and references therein.
- (2) F. Bohlmann, W. Mathar, and H. Schwarz, *Chem. Ber.*, **110**, 2028 (1977). See also F. Bohlmann, J. Förster, and C. H. Fischer, *Justus Liebig's Ann. Chem.*, 1487 (1976); M. F. Ansell and G. T. Brooks, *J. Chem. Soc.*, 4518 (1961), and 201 (1961); M. F. Ansell and G. C. Culling, *ibid.*, 2908 (1961).
- (3) C. Schmidt and S. Sabnis, unpublished results referred to in T. T. H. Liu and C. Schmidt, *Tetrahedron*, **27**, 5289 (1977); R. A. Dickinson, R. Kubela, G. A. MacAlpine, Z. Stojanac, and Z. Valenta, *Can. J. Chem.*, **50**, 2377 (1972); K. Alder, J. Haydn, and B. Krüger, *Chem. Ber.*, **86**, 1372 (1953); W. E. Bachmann and L. B. Scott, *J. Am. Chem. Soc.*, **70**, 1462 (1948). See also C. Schmidt, *J. Org. Chem.*, **35**, 1324 (1970); C. Schmidt, S. D. Sabnis, E. Schmidt, and D. K. Taylor, *Can. J. Chem.*, **49**, 372 (1971); W. E. Bachmann and J. M. Chermardon, *J. Am. Chem. Soc.*, **70**, 1468 (1948); V. Georgina and J. Lepe, *J. Org. Chem.*, **29**, 45 (1964); J.-L. Gras, *Tetrahedron Lett.*, 4117 (1977). Nucleophilic alkyl radicals also add to the less substituted carbon of citraconic anhydride: B. Giese and J. Meixner, *Tetrahedron Lett.*, 2779 (1977).
- (4) F. M. Dean, L. E. Houghton, and R. B. Morton, *J. Chem. Soc. C*, 1980 (1967); T. V. van Auken and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **84**, 3737 (1971); A. G. Brook and P. F. Jones, *Can. J. Chem.*, **49**, 1841 (1971). See also N. El-Ghandour, O. Henri-Rousseau, and J. Soulier, *Bull. Soc. Chim. Fr.*, 2817 (1972); K. Kondo and I. Ojima, *Chem. Lett.*, 771 (1972); F. M. Dean, P. G. Jones, R. B. Morton, and P. Sidisunthorn, *J. Chem. Soc.*, 5336 (1963); B. Eistert, H. Fink, J. Riedinger, H. G. Hahn, and H. Buere, *Chem. Ber.*, **102**, 3111 (1969).
- (5) I. Fleming, F. L. Gianni, and T. Mah, *Tetrahedron Lett.*, 881 (1976), reported several Diels-Alder reactions of two electron-rich species which give a slight preference for formation of the products (meta) predicted by these generalizations.
- (6) K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973); K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozler, and J. K. George, *ibid.*, **95**, 7287 (1973); K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, **95**, 7301 (1973).
- (7) K. N. Houk in A. P. Marchand and R. E. Lehr, Ed., "Pericyclic Reactions", Vol. 2, Academic Press, New York, 1977.
- (8) Fleming assumed that the ground-state LUMO polarization of citraconic anhydride was opposite to that predicted by our earlier generalizations.^{1b}

However, CNDO/2 and STO-3G calculations indicate that the LUMO of citraconic anhydride has the larger coefficient at the site of methyl substitution.

- (9) L. Libit and R. Hoffmann, *J. Am. Chem. Soc.*, **96**, 1370 (1974).
- (10) In most of these cases, however, these schizophrenic tendencies show up even in the frontier molecular orbitals of the isolated molecules.⁷ See, for example, the regioselectivities of cycloadditions to 2-methylthiomaleic anhydride: B. M. Trost and G. Lunn, *J. Am. Chem. Soc.*, **99**, 7079 (1977).
- (11) K. N. Houk, E. J. McAlduff, P. D. Mollère, R. W. Strozler, and Y.-M. Chang, *J. Chem. Soc., Chem. Commun.*, 141 (1977).
- (12) Ethylene: -1.6 eV (P. D. Burrow and K. D. Jordan, *Chem. Phys., Lett.*, **36**, 594 (1975)). Propene: -2.0 eV (K. D. Jordan, J. A. Michejda, and P. D. Burrow, *Chem. Phys. Lett.*, **42**, 227 (1976)).
- (13) W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton, and J. A. Pople, Gaussian 70, QCPE No. 236.
- (14) 4-31G calculations show a somewhat larger effect, due both to greater basis set flexibility and to lower energy and closer spacing of the vacant orbitals.
- (15) The subroutine of Morokuma (W. A. Lathan, G. R. Pack, and K. Morokuma, *J. Am. Chem. Soc.*, **97**, 6624 (1975)), in which matrix elements involving overlap between the H 1s orbital and all orbitals of the propene were set equal to zero were used.
- (16) P. Caramella, K. N. Houk, and L. N. Domelsmith, *J. Am. Chem. Soc.*, **99**, 4511 (1977), and references therein.
- (17) M. F. Ansell, B. W. Nash, and D. A. Wilson, *J. Chem. Soc.*, 3006, 3012 (1963).
- (18) (a) J. I. Brauman and L. K. Blair, *J. Am. Chem. Soc.*, **92**, 5986 (1970); (b) D. J. Defrees, J. E. Bartmess, J. K. Kim, R. T. McIver, Jr., and W. J. Hehre, *ibid.*, **99**, 6451 (1977), and references therein.
- (19) R. F. Hudson, O. Eisenstein, and N. T. Anh, *Tetrahedron*, **31**, 751 (1975).
- (20) The relative sizes of the HOMO coefficients of electron-deficient alkenes are different in various types of calculations: see ref 7 and references therein.
- (21) STO-3G calculations indicate that the 1-cyanoethyl cation is 15 kcal/mol more stable than the 2-cyanoethyl cation, while both are considerably less stable than the ethyl cation or N-protonated acrylonitrile.
- (22) R. Hoffmann, C. C. Levin, and R. A. Moss, *J. Am. Chem. Soc.*, **95**, 629 (1973).

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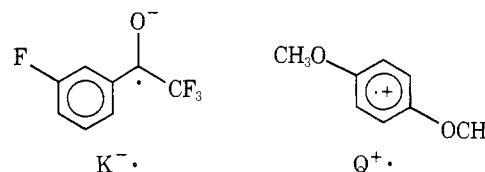
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Simultaneous Observation of Nuclear Spin Polarization and Line Broadening. Evidence for an Alternative Polarization Mechanism

Sir:

We report the simultaneous observation of chemically induced nuclear spin polarization and of line broadening during the ultraviolet irradiation of *m*-fluoro- α,α,α -trifluoroacetophenone (K) in the presence of 1,4-dimethoxybenzene (Q). Both effects are ascribed to the intermediacy of radical ions, K^{-•} and Q^{+•}, generated by electron transfer from Q to photoexcited K. The quencher concentration dependence of the



two effects is substantially different: the spin polarization shows a maximum near [Q] = 10⁻¹ M, whereas the broadening is optimized near [Q] = 6 × 10⁻³ M. We interpret these findings as evidence for two nonidentical precursors for the radical ions: the triplet state of the ketone, ³K, and an electron spin polarized state, ³K[±], respectively. This assignment implies an alternative spin polarization mechanism, the photo-triplet-Overhauser mechanism.^{1,2}

The observation of CIDNP effects in photoinitiated electron-transfer reactions is well established.^{3,4} In several donor-acceptor systems, illumination results in line broadening.^{3c-e,4} Occasionally, both effects are observed simulta-