REGIOSELECTIVITIES OF DIELS-ALDER CYCLOADDITIONS TO METHOXY-SUBSTITUTED QUINONES

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Summary: Diels-Alder cycloadducts of unsymmetrical electron-rich dienes and methoxy-benzoquinones or naphthoquinones produce adducts in which the more nucleophilic diene terminus becomes bonded to the non-methoxylated carbon. These results support the "secondary orbital", but not the "schizophrenic", model for donor substituent effects on regioselectivity.

We recently noted that the cycloadditions of electron-rich cycloaddends to electron-deficient alkenes which are unsymmetrically substituted by alkyl substituents give anomalous regioselectivities;[2] the preferred products are not those predicted by frontier molecular orbital theory.[3] That is, the LUMO coefficient of the alkyl-substituted carbon is larger than that of the unsubstituted carbon.[3] This leads to the prediction that the substituted carbon should be attacked by the more nucleophilic terminus of an electron-rich diene; the opposite is observed experimentally. We suggested that one of two electronic effects -- (1) secondary orbital interactions or (2) alkyl group "substituent schizophrenia"[4] -- could be responsible for these anomalies, and we proposed experimental tests to determine which of these effects is chemically significant. We report here the results of these experimental tests, which indicate that "substituent schizophrenia" is not important in producing selectivity in these cases. In the accompanying Communication,[5] we describe a general refinement of frontier molecular orbital theory to predict the influence of donor substituents on the regio-selectivity of electron-deficient alkene addition and cycloaddition reactions with nucleophilic species.

Many examples of preferred _ortho_ or _para_ regioselectivity in cycloadditions of unsymmetrical dienes to methylbenzoquinones are known.[2] Additional examples that we have studied include the cycloadditions of piperylene, isoprene and 1-methoxy-3-trimethylsiloxybutadiene (MTSB)[6] to 2,5-dimethylbenzoquinone (Scheme I).[7,8]

Piperylene gives a 5:1 mixture of _ortho_ and _meta_ adducts, 1a and 2a, in 75% yield, isoprene gives a 70% yield of adducts with no regioselectivity, and MTSB gives only the _ortho_, _para_ regioisomer, 1c (90% yield), which was hydrolyzed to give pure 3 in 50% yield. Although the difference between regiochemical results obtained with isoprene and piperylene is rather extreme in these cases,

isoprene has often been observed to be less regioselective than piperylene.[9] Only the cis-endo adducts are obtained in each case, although isomerization to the trans compound is easily achieved by treatment with dilute base or upon silica gel chromatography.
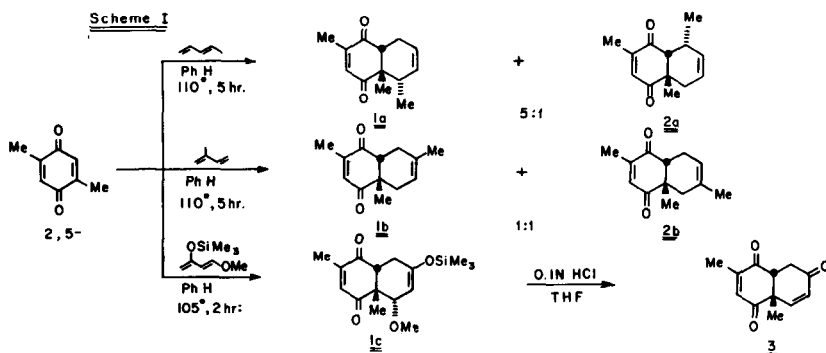

The reactions of these three dienes with 2,6-dimethoxybenzoquinone are slower, but yield similar regiochemical results (Scheme II). From isoprene, nearly equal amounts of the meta- and para- cis,endo adducts (4b and 5b) are obtained, while piperylene and MTSB give only the ortho, 4a (70% yield), and ortho,para adducts, 4c (60% yield), respectively. Upon silica gel chromatography, methanol was eliminated from 4a, 4b, and 5b, and the resulting dihydronaphthoquinones were easily air oxidized to the naphthoquinones. Adduct 4c can be hydrolyzed without loss of methanol to give 6,
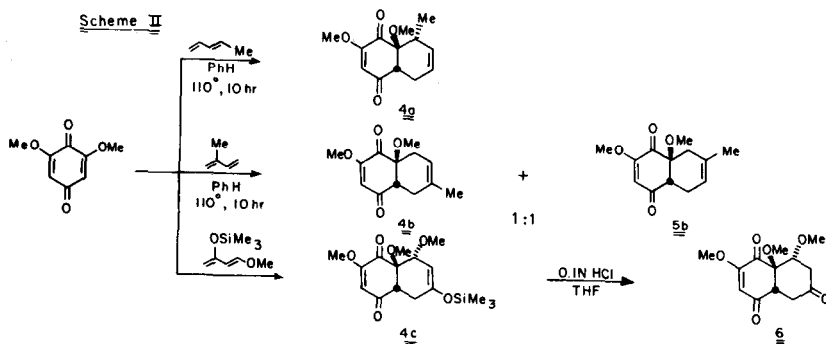

The isomeric 2,5-dimethoxybenzoquinone reacts very sluggishly, and an 18% yield of the piperylene adduct, 7, was obtained only after 7 days at 150° (Scheme III). Partial loss of methanol occurred upon silica gel chromatographic purification; therefore, the reaction mixture was all converted to the dihydronaphthoquinone, 8, for analysis. The nmr spectrum of 8 proved to be superimposable on that of the product formed by loss of methanol from 4a, even at 200 MHz. However, by addition of Eu(fod)$_3$, it was possible to differentiate these isomers by nmr. Eu(fod)$_3$ complexes more readily at the less sterically crowded and more electron-rich carbonyl group, a, so that the

methyl and methine protons experience greater lanthanide-induced shifts in $\underset{\sim}{8}$ than in the adduct formed from $\underset{\sim}{4a}$.
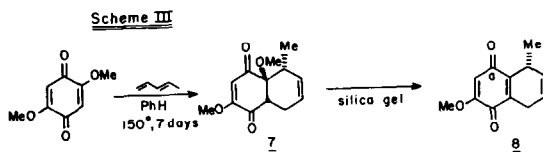
Scheme III

With both 2-methyl- and 2-methoxynaphthoquinones, similar results were obtained (Scheme IV). The methoxylated quinone adducts could be isolated with the methoxy group intact, although ready elimination of methanol was observed upon silica gel chromatography. The MTSB adduct was most conveniently analyzed after hydrolysis to the α,β-unsaturated ketone.

Scheme IV
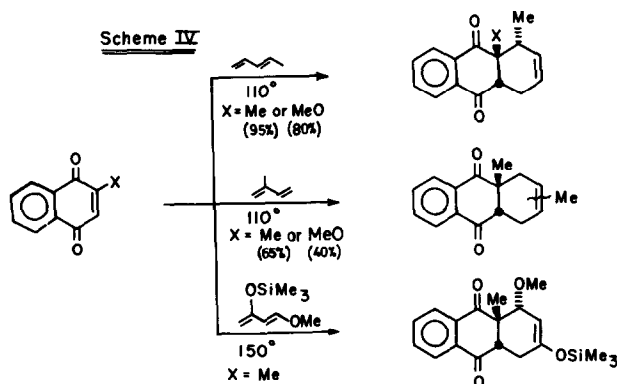
In all of these cases, the more nucleophilic terminus of the diene becomes attached to the less substituted terminus of the quinone double bond; thus, the same oreintations are observed for Diels-Alder cycloadditions of electron-rich dienes to electron-deficient dienophiles made unsymmetrical by either methyl or methoxy substituents. Since the methoxy group cannot exhibit the "schizophrenic" substituent effect described earlier,[2] but nevertheless directs regioselectivity in the same manner as the methyl group, there is no further reason to invoke "substituent schizophrenia" as a source of anomalous regioselectivity in methyl substituted cases. Although polarization of π bonds induced by an approaching reagent is undoubtedly important in magnifying certain frontier orbital coefficient differences and in causing electron-withdrawing groups to act, in part, as electron donors,[2,5,10] this effect must not be dominant in the anomalous cases described earlier.[2]

Instead, the attack of the most nucleophilic terminus of the electron-rich dienes on the less substituted terminus of the dienophile is attributed to repulsive effects. These may be specific secondary orbital repulsive effects between the diene nucleophilic terminus and substituent orbitals, as generalized in the following Communication.[5] Classical steric effects may also play a role, but these steric effects do not merely lead to the less crowded final adduct. The bond to the more nucleophilic diene terminus should be more completely formed in the transition state. Repulsive

steric effects in the vicinity of this partially formed bond will be greater than those at the less fully-formed bond, and the preferred transition state will be that which minimizes steric repulsions at the more completely formed bond.

References and Notes

1. Address correspondence to the University of Pittsburgh.

2. K. N. Houk, L. N. Domelsmith, R. W. Strozier, R. T. Patterson, J. Am. Chem. Soc., 100, 6531 (1978).

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4. "Substituent schizophrenia" refers to the ability of an alkyl aubstituent simultaneously to behave as a donor (rate influence) and as an acceptor (regioselectivity influence).[2]

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6. S. Danishefsky and T. Kitahara, J. Am. Chem. Soc., 96, 7807 (1974).

7. Bohlmann and coworkers also studied the reaction of piperylene with 2,5-dimethylbenzoquinone, but reported formation of only the ortho adduct: F. Bohlmann, J. Forster, and C. H. Fischer, Justus Liebigs Ann. Chem., 1487 (1976).

8. Reactions were carried out in benzene or ethanol with excess diene solution at 110-130°. Products were purified by column chromatography or HPLC and product structures were determined by 200 MHz NMR.

9. T. Kojima, T. Inukai, J. Org. Chem., 35, 1342 (1970); I. N. Nozarov, Yu. A. Titov, and A. K. Kuznetsova, Dolk Akad. Nauk. S.S.S.R., 124, 1959 (1959).

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