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INTERACTIONS BETWEEN HOMOCONJUGATED DIENE AND EPOXIDE FUNCTIONS. EFFECT ON DIELS-ALDER REGIOSELECTIVITY

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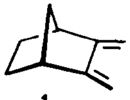
Summary. *Unexpected regioselectivities were observed for the Diels-Alder additions of* 5exo,5endo- *and* 5endo,5exo-*(epoxymethano)-2,3-bis(methylene)bicyclo[2.2.1]heptanes and of* 5exo,5endo- *and* 5endo,5exo-*(epoxymethano)-2,3,6-tris(methylene)-7-oxabicyclo[2.2.1]heptanes.*

Chemical and spectroscopic properties of the diene functionality in 2,3-bis(methylene)-bicyclo[2.2.n]alkanes can be modified by remote substitution of the bicyclic skeleton.[1] For example, the homoconjugated carbonyl and epoxide groups in 2[2] and 3[3], respectively, retard their Diels-Alder cycloadditions relative to those of the parent diene 1, and this is expected for dienes substituted by electron withdrawing substituents.[4] Nevertheless, the "para" regioselectivity observed for the cycloadditions of 2 to strong dienophiles is better explained by invoking an electron donating ability to the homoconjugated carbonyl group.[5] The methylene group at C-5 in triene 4 also induces good "para" regioselectivity in the Diels-Alder additions of this system.[6] This property has been exploited to develop a regioselective and doubly-convergent synthesis of anthracyclinones, including daunomycinone, based on the regioselective cycloadditions of diene 5.[6] The homoconjugative interaction between the methylene and diene functionalities in 4 and 5 does not manifest itself in the shapes[7] of the frontier orbitals (FMO's).[8] The preferred "para" regioselectivity observed in their Diels-Alder additions can be interpreted by invoking an electron-donating effect to the homoconjugated methylene group which acts to stabilize the Diels-Alder transition states. This can be visualized using the diradicaloid ⟷ charge-transfer-limiting structure model[9] depicted below for the cycloadditions of methyl propynoate.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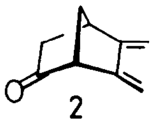
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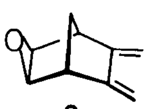
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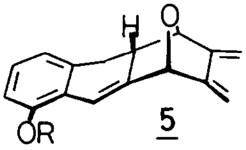

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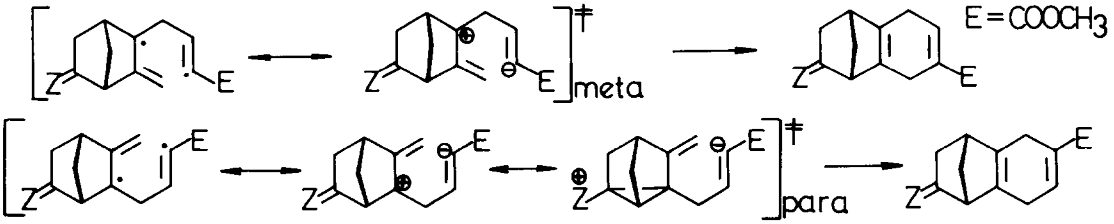
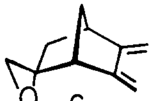


These homoconjugated exocyclic dienes are becoming test systems for the theories of Diels-Alder reactivity and regioselectivity.[4,7,9] We have now prepared the new dienes 6 and 7 in which the exocyclic *s-cis*-butadiene group is remotely perturbed by an epoxide function, and trienes 8 and 9 where the diene moiety is homoconjugated to both epoxide and methylene functions. Examination of the FMO's and subFMO's of these molecules[8] did not support a prediction of significant regioselectivity for their cycloadditions, contrary to the observations we report here. Most stricking was the finding that the regioselectivity (relative to the epoxide function) is "para" for the *endo*-epoxides 6 and 8 and "meta" for the *exo* isomers 7 and 9.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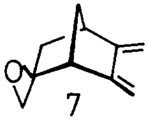
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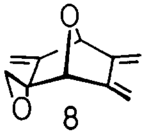
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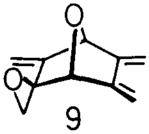
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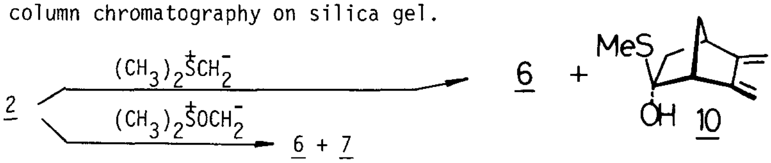
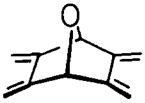
Treatment of dienone 2 with dimethylsulfonium methide[10] in THF (0°) afforded a mixture of *endo*-epoxydiene 6 (25 % isolated) and dienol 10 (12 %). No trace of the *exo* isomeric epoxide 7 could be detected under these conditions. When 2 was treated with dimethylsulfoniumoxide methide, a 1:1 mixture of the two epoxides 6 and 7 was obtained.[11] These compounds were readily separated by column chromatography on silica gel.

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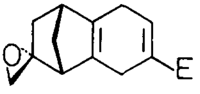
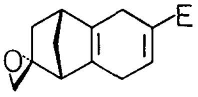
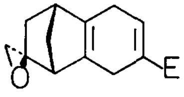
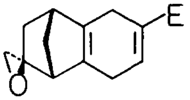
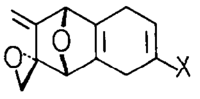
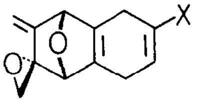
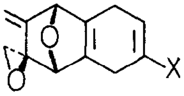
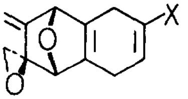
Partial epoxidation of tetraene 11[12] (1 mol. equiv. of metachloroperbenzoic acid, CH_2Cl_2, 0-20°) furnished a 1:5.7 mixture of the epoxy-trienes 8 and 9; 9 was isolated pure by fractional crystallization. Epoxidation of the diene in 8 or 9 proceeded more slowly than epoxidation of 11; this reaction was "para" regioselective with 9.[13] The structures of 6-9 were determined by their elemental analyses and their spectral data.[14] The distinction between *endo* and *exo* epoxides 6,8 vs. 7,9, respectively was based on the proton coupled ^{13}C-NMR and 360 MHz ^{1}H-NMR spectra (NOE & LIS measurements).[13,15]

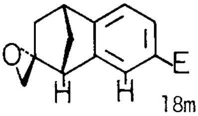
12m / 12p 20:80 (100°)
17:83 (80°)

13m / 13p 55:45

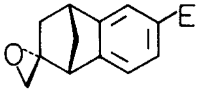





X = $COOCH_3$: 14m / 14p 28:72 15m / 15p 76:24
X = $COCH_3$: 16m / 16p 26:74 17m / 17p 67:33

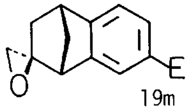
The Diels-Alder additions of 6-9 to methyl propynoate (3-6 mol. equiv. in C_6H_6, 100°, 6-12h) gave mixtures of the corresponding adduct pairs 12-15 (90-98 %). Butynone (3 mol. equiv., toluene, 110°, 14 h) added to 8 and 9 yielding adduct pairs 16 and 17 (89-93 %), respectively. The "meta" vs. "para" product ratios (Diels-Alder regioselectivities, see above) were determined on the crude reaction mixtures by ^{13}C-NMR spectroscopy. As 8 could not be isolated in the pure state, a mixture of 8 and 9 was used for the cycloadditions. The corresponding adducts 14-17, however, could be separated and isolated by column chromatography or by fractional crystallization. They were characterized by a combination of ^{13}C- and ^{1}H-NMR spectroscopic techniques.[13] The structures of adduct pairs 12 and 13 were also given by ^{13}C- and ^{1}H-NMR spectroscopy. They were further confirmed by oxidation with dichlorodicyanobenzoquinone (DDQ, C_6H_6, 80°, 2-15 min) to yield the corresponding benzoates 18 and 19 whose structures could be established unambigously by 360 MHz ^{1}H-NMR spectroscopy and NOE measurements between the bridgehead and aromatic protons.



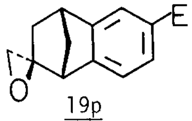
18m



18p



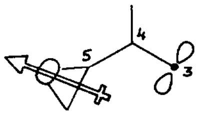
19m

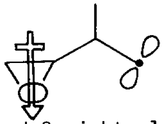


19p

Our results demonstrate that an epoxide ring can affect the Diels-Alder regioselectivity of a homoconjugated diene. They also point out that the direction of the long range substituent effect can be reversed by inverting the stereochemistry of the oxirane. The rigid exocyclic dienes 6-9 are modified by subtle, remote substitution only, thus geometry and steric factors should not play a dominant role in determining the regioselectivity of their cycloadditions. Dipole-dipole (hard) interactions between the reacting molecules could be important and thus affect the regioselectivity of their cycloadditions.[16]

If one considers the diradicaloïd ↔ zwitterion model[9] of the Diels-Alder transition states (see above), it appears that the epoxide function acts, as expected, as a weak electron-withdrawing group (field effect) in the cycloadditions of 7 and 9. The larger "meta" regioselectivity observed with 9, relative to that of 7, can be attributed to the "para" orienting effect of the methylene group at C-6 in 9. This latter effect is definitively overwhelmed by the competing "para" orienting effect of the *endo* epoxide ring in 8. This substituent effect corresponds thus to an electron-donating effect of the *endo* oxirane. This hypothesis awaits further experimental confirmations. In any events the field effect of the epoxide dipole is expected to be stronger at the homoconjugated diene moiety for *exo* than for *endo* relative configurations, as shown below.





The oxygen electron pairs of the *endo* derivatives 6 and 8 might also assist somehow (coordination to the dienophile, anchimeric effect ?) the "para" cycloadditions.[16,17]

The effects discussed here are very small in energy terms, nevertheless it is desirable to understand them. We plan to use them in the development of new synthetic strategies.

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References and Notes.

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8. EHT, MINDO/3, MNDO and *ab initio* STO 3G calculations performed by Dr. P.-A. Carrupt and Mr. J.-L. Birbaum. They will be reported in a full paper.
9. W. E. McEwen, I. C. W. Huang, C. P. C. Marin, F. McCarty, E. M. Segnini, C. M. Zeppe, III & J. J. Lubinkowski, J. Org. Chem. 47, 3098 (1982) and lit. cited therein; R. B. Woodward & T. J. Katz, Tetrahedron 5, 70 (1959); N. D. Epiotis, in "Theory of Organic Reactions", Springer-Verlag, Berlin, 1978.
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11. R. Bly, C. DuBose & J. Konizer, J. Org. Chem. 33, 2188 (1968).
12. C. Mahaim, P.-A. Carrupt, J.-P. Hagenbuch, A. Florey & P. Vogel, Helv. Chim. Acta 63, 1149 (1980).
13. Details will be given in a full paper.
14. Characteristics of 6: δ_H 5.38 & 5.25(2s,2H), 4.95(br.s,2H), 3.0-2.7(m,3H), 2.4(m,1H), 2.1 (dxd,1H), 1.88-1.33(m,3H); UV(isooctane): 237(sh,8670), 247(9440), 255(sh,6070); 7: δ_H 5.29 (s,1H), 5.23(s,1H), 4.94(br.s,2H), 3.0(m,1H), 2.83(br.s,2H), 2.38(m,1H), 2.06-1.5(m,4H). UV(isooctane): 237(sh,8390), 244(8940), 253(sh,5940); 8: δ_C 146.4, 145.1, 143.4, 105.5, 104, 102.9, 84.4, 81.6, 64.4, 49.7; MS(70eV): 162(2), 133(45), 105(50), 91(100); 9: m.p. 105°; δ_H 5.35, 5.30, 5.20, 5.10, 5.05, 4.85, 5.1, 4.4(8s), 3.02(d,1H,J=4 Hz), 2.98(d,1H,J=4 Hz); δ_C 146.4, 145.1, 143.4, 105.5, 104.0, 102.9, 84.9, 84.8, 64.4, 49.7; UV(EtOH 95%): 245(3500), 220(sh,3200); MS(70eV): 162(5), 113(38), 105(50), 91(100).
15. The *exo* epoxides were solvolyzed at 20° in a few min. in $CF_3CHOHCF_3$ containing a trace of acid, whereas the *endo* isomers were stable under these conditions; see: J.-M. Sonney, P. Vogel & U. Burger, Helv. Chim. Acta 63, 1016 (1980).
16. The additions of strong dienophiles to 5,6-bis(methylene)-2exo-norbornyl alcohol and acetate were not regioselective. Depending upon the nature of the dienophile, the cycloadditions of the corresponding endo derivatives were slightly "para" or "meta" regioselective[5a] thus confirming the unique behavior of the epoxide function in 6-9; see also the accompanying paper on the CD spectra of optically active epoxy-dienes 6 and 7.
17. The study of the regioselectivity of the Diels-Alder additions of 6-9 should also consider the face selectivity of these reactions, see e.g.: C. Mahaim & P. Vogel, Helv. Chim. Acta 65, 866 (1982) and references cited therein.
18. We are grateful to Prof. J. Lauterwein and to Mr. J. Wernly for their help in the measurements of high field NMR spectra.

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