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THE STEREOCHEMISTRY OF DIELS–ALDER REACTIONS OF CYCLOPROPENES[1]

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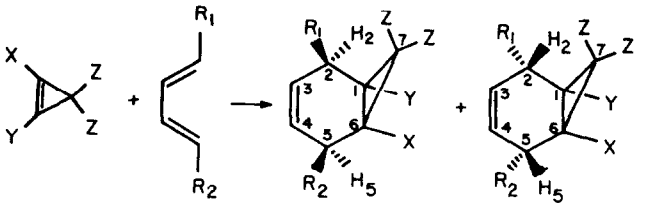
Abstract. The stereochemistry of the Diels-Alder reactions of 3 cyclopropenes was determined unequivocally by X-ray and NOE studies. Tetrachlorocyclopropene yields exo-adducts with (E)-1-R-1,3-butadiene (R=OCH_3, $OCOCH_3$, $OSiMe_3$), with 1,4-diphenylbutadiene and with furan. 1,2-bromochlorocyclopropene yields with (E)-1-R-butadienes (R=OCH_3, $OSiMe_3$) endo:exo-adducts in a ratio of 9:1. Cyclopropene + 1-methoxybutadiene yield only the endo-adduct.

The Diels-Alder (DA) reaction is the most important method for formation of six-membered rings and it has been extensively studied.[2] Recently, special attention has been devoted to the study of the stereochemistry and the mechanism of this reaction.[2b,c] In the course of the synthesis of substituted bicyclo[4.1.0]hept-3-enes we have realized, to our suprise, that the available information on the stereochemistry of DA reactions of substituted cyclopropenes (CPs),[3] e.g., eq. 1, which are useful synthetic synthons,[3,4] is incomplete (e.g., the stereochemistry of the DA reeactions of the parent CP with open-chain dienes is not known[5]) and in some cases the data is internally inconsistent (see below); e.g., compare the reports in ref. 4 with those in ref. 6a and 6b. Furthermore, most of the previous stereochemical assignments were based on NMR data or mechanistic assumptions[3] which, according to our judgement, were in many cases inconclusive (see below). Consequently, reliable predictions of the stereochemistry of DA reactions of CPs could not be made.

We report here **unequivocal determination**, based on X-ray analysis and H-NMR Nuclear Overhauser Effect (NOE) studies, **of the stereochemistry of the DA reactions of three CPs** (the parent CP, 1,2-chlorobromocyclopropene and tetrachlorocyclopropene) **having different steric requirements, with both open-chain and cyclic dienes. These experiments provide guidelines which allow, for the first time, to predict with confidence the stereochemistry of similar DA reactions.** A critical evaluation using these guidelines of part of the literature has revealed two erroneous reports.[6a,b] This calls for a careful examination, and in some cases (particularly data from the older literature) for a reinvestigation, of some of the previous reports.

Tetrachlorocyclopropene (1a) adds to three (E)-1-substituted-1,3-dienes (2a, 2b, and 2c) to give only one adduct in each case. The stereochemistry of one of these adducts[7a] (4b) was determined by X-ray diffraction to be exo.[7b] The other 2 adducts also have exo-stereochemistry (i.e., 4a and 4c), as shown by the conversion of 4c into 4b via hydrolysis to the corresponding alcohol followed by acetylation, and the conversion of 4b to 4a via hydrolysis and O-methylation. Molecular models show that the exo-stereoselectivity may be attributed to steric factors (see also ref. 4). Thus, the steric interactions between one of the flagpole geminal-chlorines of 1a and the butadiene skeleton appear to be much larger in the endo- than in the exo-transition states (TS).



(1)

1 2 3 - endo 4 - exo

1a,	X=Y=Z=Cl	2a,	R_1=OCH_3, R_2=H	3a, X=Y=Z=Cl, R_1=OCH_3,R_2=H	,4a
1b,	X=Cl,Y=Br,Z=H	2b,	R_1=$OCOCH_3$,R_2=H	3b, X=Y=Z=Cl, R_1=$OCOCH_3$,R_2=H	,4b
1c,	X=Y=Z=H	2c,	R_1=$OSiMe_3$,R_2=H	3c, X=Y=Z=Cl, R_1=$OSiMe_3$,R_2=H	,4c
1d,	X=Y=H,	2d,	R_1=R_2=Ph	3d, X=Cl,Y=Br,Z=H,R_1=OCH_3,R_2=H	,4d
	Z= -$O(CH_2)_3O$-			3e, X=Cl,Y=Br,Z=H,R_1=$OSiMe_3$,R_2=H	,4e
				3f, X=Y=Z=H,R_1=OCH_3,R_2=H	,4f
				3g, X=Y=Z=Cl,R_1=R_2=Ph	,4g
				3h, X=Y=H,Z= -$O(CH_2)_3O$-,R_1=OCH_3,R_2=H	,4h

Substitution of the geminal CP chlorines by hydrogens is expected to reduce the difference in the steric congestion between the isomeric TS, but models suggest that the endo-TS is still the more encumbered. Suprisingly, 1,2-bromochlorocyclopropene (1b)[8] adds to both 2a and 2c with opposite stereoselectivity than 1a, yielding predominantly the endo- adducts, 3d and 3e, respectively. (3d and 3e are each 1:1 mixtures of 2 regioisomers, e.g., 3d and its isomer where X=Br , Y=Cl). In both cases the endo:exo product ratio (i.e., 3d:4d or 3e:4e) is 9:1. The stereochemistry of 3 and 4 was determined on the basis of NOE experiments. Thus in 4d or 4e (but not in 3d or 3e) there is a strong H2-H7 NOE. This assignment was secured by an X-ray structure[7b] of 3, X=Cl, Y=Br, Z=H, R_2=H, R_1=$OCOC_6H_4$-NO_2-p, which was obtained by hydrolysis of 3e followed by esterification.

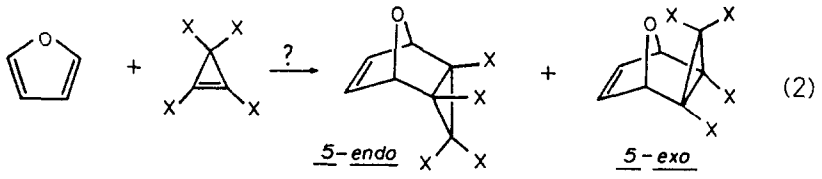
Endo stereoselectivity is higher with the parent cyclopropene (CP). 1c + 2a give only the endo- product 3f (i.e., 4f < 1%). The stereochemical assignments are based on the absence of H2-H7 NOE, although the distant H2-H5 NOE is observed.

The above results reveal a strong **"Intrinsic" endo-preference in the DA reactions of CP with simple open-chain butadienes.** As steric effects favor the exo-TS, the observed endo-addition may reasonably be attributed to overriding electronic factors. The nature of these electronic factors, are currently being studied theoretically.[7b] The "intrinsic" endo-stereoselectivity can be reversed by steric effects, as exemplified by 1a.

The following empirical guidelines, for predicting and analysing the stereochemistry of the kinetic products in DA reactions of CPs, can be derived from a combination of our experiments, calculations[7b] and the literature.[9] The parent CP and 1,2-disubstituted CPs are expected to yield endo-adducts, exclusively or predominantly. 3,3-gem-disubstituted CPs are predicted to yield exo-adducts with open-chain dienes, or with cyclic dienes where the bridging unit introduces in the exo-TS relatively small additional steric interactions (e.g., furan). With cyclic dienes where the bridging unit is more sterically demanding (e.g., cyclopentadiene), endo-products are expected.[9]

On the basis of the above results we have analysed some of the previous reports regarding the DA reactions of tetrahalocyclopropenes. The exo-stereoselectivity that we have observed for 1a and that Boger reported for 1d (e.g., with 2a)[4,10] is consistent with steric control of the stereoselectivity, as the ketal substituent in 1d is of comparable (or larger) size to the chlorines in 1a. However, if this is the case then these experiments appear to conflict with the report that 1a + 2d give an endo-adduct.[6b] We have therefore repeated this experiment and determined by X-ray diffraction [7b] that the DA product is indeed the exo-isomer 4g.[11,12] The reversal of the earlier stereochemistry assignment has a bearing on the analysis of dehydrohalogenation reactions of 4g and analogous bicyclic adducts, which provide access to cyclopropabenzenes.[6b,13]

The report that tetrahalocyclopropenes and furan (eq. 2) give the endo-DA adducts 5-endo[6a] is also in apparent conflict with our analysis. Assuming that the oxygen in furan exerts a relatively modest steric effect we expected, in analogy to the reaction of 1a + 2a, that the reactions in eq. 2 should proceed by exo-addition. Repeating this reaction at 20°C, we find that for X=Cl this is indeed the case. X-ray[7b] and GC analysis established that the product is 5-exo, contrasting with the previous assignment.[6a] We believe that the other DA reactions reported in ref. 6a also proceed with exo (not endo[6a]) stereoselectivity. The wrong stereochemistry assigned to 5 was unfortunately carried over to other studies (vide supra).[6b]



(2)

Furan and CP yield a 1:1 mixture of exo- and endo-DA adducts.[14] This appears to be in conflict with our model that predicts an endo-addition. However, Lee and Herndon have demonstrated that the DA reaction of furan and maleic anhydride is reversible,[15] so that the above reaction[14] might be also thermodynamically controlled.[15] The same considerations may apply to other cycloadditions of furan or isobenzofuran which yield exo-adducts or mixtures of exo- and endo-products.[16] On the other hand, our prediction is consistent (assuming that C=O is sterically similar to O) with the report that CP + tetraphenylcyclopentadienone yield an endo-adduct.[17]

We continue our mechanistic (kinetic and stereochemical) and theoretical studies of the above mentioned (e.g., ref. 16) and related systems, and will report our results subsequently.

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References and Notes.

1. Reported in part in meetings: (a) "Computational Methods in Chemical Design", Schloss Elmau, Garmisch-Partenkirchen, Federal Republic of Germany, 20-24 October, 1986;

(b) International Symposium on "Organic Reactivity", Paris, France, 6-10 July, 1987.

2. (a) Oppolzer, W., Angew. Chem. Int. Ed. Engl., **1984**, 23, 876; (b) Sauer, J.; Sustmann, R., Angew. Chem. Int. Ed. Engl., **1980**, 19, 779; (c) Fox, M.A.; Cardona, R.; Kiwiet, N.J., J. Org. Chem., **1987**, 52, 1469.
3. (a) Deem, M.L., Synthesis, **1972**, 675; (b) Halton, B.; Banwell, M. in "The Chemistry of the Cyclopropyl Group", Rappoport, Z, Ed., Wiley, Chichester, **1987**, Ch. 32; (c) Reissig, H.-V., ibid, Ch. 8.; (d) An extensive set of references can be found in reference 4.
4. (a) Boger, D.L.; Brotherton, C.F., J. Am. Chem. Soc., **1986**, 108, 6695; (b) Tetrahedron, **1986**, 42, 2777.
5. CP + cyclopentadiene give the endo-adduct; See: Wiberg, K.B.; Bartley, W.J., J. Am. Chem. Soc., **1980**, 82, 6375.
6. (a) Law, D.C.F.; Tobey, S.W.,J. Am. Chem. Soc., **1968**, 90, 2376; (b) Halton, B.; Milsom, P.J.; Woolhouse, A.D., J. Chem. Soc. Perkin I, **1977**, 732.
7. (a) All compounds showed the expected elementary analysis, N.M.R., I.R. and M.S. spectra; (b) Full details will be reported in the full paper.
8. Billups, W.E.; Arney, Jr., B.E.; Lim, L.-J., J. Org. Chem., **1984**, 49, 3436.
9. Such simple guidelines are certainly not general or definitive, but they provide a consistent tool for analysing the literature and pointing out reports which may be erroneous (see below) or cases where effects, not considered in the model, are important.
10. Boger and Brotherton provided, in an extensive set of experiments, strong spectroscopic evidence in support of their exo-assignment.[4] However, this assignment was not secured by X-ray crystallography, and the authors note that: "unambiguous proof of the stereochemistry is not available" (ref. 4b, p. 2780). Evaluation of previous stereochemical assignments was not attempted by these authors.
11. 4g has identical physical and spectral properties to those assigned erroneously to 3g.[6b]
12. Similar conclcusions were reached recently for the DA reaction of 1-phenylbutadiene + 1a. See: Müller, P.; Bernardinelli, G.; Rodriguez, D.; Pfyffer, J.; Schaller, J.-P., Chimia, in press, (1987).
13. For reviews see: Halton, B., Ind. Eng. Chem. Prod. Res. Rev., **1980**, 19, 349; Billups, W.E., Acc. Chem. Res., **1978**, 11, 245.
14. Larochelle, R.W.; Trost, B.M., J. Chem. Soc., Chem. Commun., **1970**, 1353.
15. Lee, M.W.; Herndon, W.C., J. Org. Chem., **1978**, 43, 518.
16. (a) Cava, M.P.; Narasimhan, K., J. Org. Chem., **1971**, 36, 1419; (b) Battiste, M.A.; Sprouse, Jr., C.T., Tetrahedron Lett., **1970**, 4661; ibid, **1969**, 3165; (c) Breslow, R.; Ryan, G.; Groves, J.J., J. Am. Chem. Soc., **1970**, 92, 998; (d) Dent, B.R.; Halton, B.; Smith, A.M.F., Aust. J. Chem., **1986**, 39, 1621; (e) Chan, T.H; Massuda, D., Tetrahedron Lett., **1975**, 3383; (f) Dietrich-Buchecker, C.; Franck-Neumann, M., Tetrahedron, **1977**, 33, 751; Dietrich-Buchecker, C.; Martina, D.; Franck-Neumann, M., J. Chem. Res., S, **1978**, 78; (g) Bolesov, I.G., Zaitseva, L.G.; Plemenkov, V.V.; Avezov, I.B.; Surmina, L.S., Zh. Org. Khim., **1978**, 14, 71; (h) Plemenkov, V.V.; Bolesov, I.G., Dokl. Akad. Nauk SSSR, **1979**, 248, 887; (i) Latypova, M.M.; Plemenkov, V.V.; Tuzova, V.B.;Giniyakov, Kh.Z.; Bolesov, I.G., Zh. Org. Khim., **1982**, 18, 1650; (j) Müller, P.; Schaller, J.-P., Chimia, **1986**, 40, 430; (k) Wiberg, K.B.; Bonneville, G., Tetrahedron Lett., **1982**, 5385.
17. Plemenkov, V.V.; Breus, V.A.; Grechkin, A.N.; Novikova,L.K.,Zh. Org. Khim., **1976**,12, 787.

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