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STEREOSELECTIVITIES OF BENZONITRILE OXIDE CYCLOADDITIONS TO CIS DISUBSTITUTED CYCLOPENTENES AND DIHYDROFURANS

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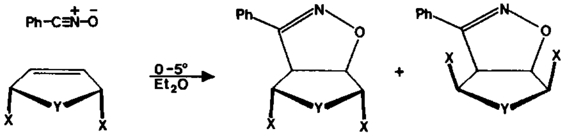
Abstract: Benzonitrile oxide cycloadds preferentially anti to the substituents of cis-3,5-di-X-cyclopentenes, where X = OMe, OAc, OCOPh, Br, Cl, and OH. Higher stereoselectivities are found for cis-2,5-di-X-2,5-dihydrofurans. The origins of these selectivities, and contrasts with acyclic and cyclobutene analogs, are described.

We wish to report several highly stereoselective 1,3-dipolar cycloadditions to cis-3,5-disubstituted cyclopentenes and the increased stereoselectivity of cycloadditions to analogous dihydrofurans. These results are complementary to studies reported for acyclic alkenes,[2] monosubstituted cycloalkenes,[3] and disubstituted cyclobutenes[4] and are rationalized on the basis of a model recently developed for the conformations of cycloaddition transition structures.[5]

Cycloadditions of benzonitrile oxide to cis-3,5-disubstituted cyclopentenes and cis-2,5-disubstituted-2,5-dihydrofurans[6] were carried out at 0-5°C in diethyl ether solutions. The results are given below,[7] along with the stereoselectivities observed earlier for cycloadditions to related cyclobutenes.[4]



1
a: $Y=CH_2$
b: Y=O
c: Y=nil

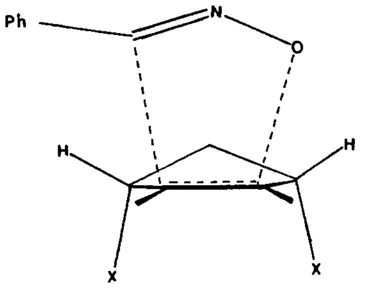
2
(anti)

3
(syn)

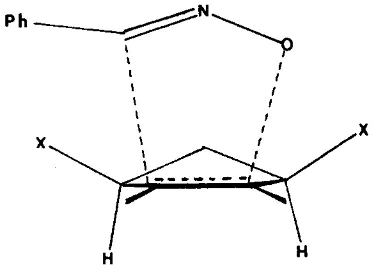
X	2 : 3		
	Y=CH$_2$	Y=O	Y=nil
Br	>99 : 1		
OCOPh	96 : 4		
OCH$_3$	93 : 7	>99 : 1	
OCOCH$_3$	91 : 9	>99 : 1	10 : 90
OH	82 : 18		5 : 95
Cl	–[7]		52 : 48

In each case, the anti stereoisomers, 2, were isolated. In cycloadditions to dialkoxycyclopentenes, the minor syn adducts, 3, could also be isolated and characterized, whereas in cycloadditions to dibromocyclopentene and to the dihydrofurans only the anti adducts could be isolated in over 90% yield. Careful examination of the mother liquors by tlc and nmr indicates that syn adducts are no more than 1% of the product mixture. Syn cycloaddition is more significant in the reactions of cyclopentenediols (18%). However, the anti/syn ratio is solvent dependent, and in polar and hydroxylic solvents, this ratio increases to roughly the same value observed for the alkoxy derivatives.[8] This observation is compatible with hydrogen-bonding between the nitrile oxide oxygen and the hydroxyl group of the dipolarophile, which directs attack to the *syn* face, as has been observed with other cyclic systems.[3a] Structural assignments of the adducts are based upon nmr data. The coupling constants between the isoxazoline hydrogens and the vicinal hydrogens are 0-3 Hz in the *anti* adducts, 2, and 5-8 Hz in the *syn* adducts, 3. In *cis*-disubstituted cyclopentenes, *anti* attack is favored by 1.4-2.7 kcal/mol. *Anti* addition is more highly preferred (>2.7 kcal/mol) in the related dihydrofurans, whereas a shift toward *syn* addition is observed in the related cyclobutenes carrying electronegative substituents.

Cyclopentenes exist in envelope conformations with a low barrier to inversion.[9] In the transition structures for cycloadditions, additional folding of the cyclopentene moiety occurs, and bond formation will occur inside the flap, as shown below:[10]



X-ANTI



X-OUTSIDE

This conformation occurs to permit staggering along the bonds to the alkene carbons in the transition structure. The resulting structure resembles that for *exo* attack on norbornene.[5b] For *cis*-3,5-disubstituted cyclopentenes, the allylic groups may either be "*outside*", with dihedral angles of 30-45° with respect to the partially formed bonds, or "*anti*", with dihedral angles of 150-165°. We have shown earlier that electronegative substituents prefer the "*inside*" conformation,[2c] but this is, of course, not accessible to the substituent in cyclic systems. For allylic oxygen substituents, the *anti* conformation is lower in energy than the *outside*,[2c] and the energy of the conformation with oxygen *outside* increases rapidly as the dihedral angle is made smaller.[11] Although the cyclopentene moiety is altered in the transition structure, the factors which control substituent conformations in cyclopentenes will operate to some extent in transition structures, as well, without violating the Curtin-Hammett principle. For *cis*-2,5-dihydroxy- and *cis*-2,5-dibenzoyloxy-cyclopentenes, there is a very small energetic preference for the diequatorial conformation: nmr studies indicate diequatorial:diaxial ratios of 1.8:1 and 1.1:1, respectively.[12] For *cis*-3,5-dibromocyclopentene, nmr evidence supports a preferential (4:1) diaxial conformer for this dipolarophile.[12] Thus, the repulsive Br-O interaction which favors the *anti*-Br conformation is reinforced by a preference for the Br's to assume axial conformations in species related to cyclopentene. The exclusive *anti* stereoselectivities observed with the dihydrofurans are also a manifestation of inherent conformational features present in reactants, and, to at least some extent, in transition structures. Dihydrofuran itself is planar,[13] but STO-3G optimizations of the *cis*-2,4-difluoro derivative show that it distorts toward a diaxial conformation. Electronegative substituents tend to be diaxial because of the anomeric effect.[14] This diaxial preference should also be present in the dialkoxy derivatives. The more nearly planar conformation of the dihydrofuran, and the flattening of this ring in the transition state, forces a *syn* substituent oxygen nearer the nitrile oxide oxygen, creating more repulsion in the *syn* transition state. Thus, the *anti* cycloadditions are strongly preferred.

Why does *cis*-3,4-diacetoxycyclobutene show a preference for *syn* addition,[4] in spite of the considerable repulsions between the allylic oxygens and the nitrile oxide? STO-3G optimizations of *cis*-3,4-difluorocyclobutene show pyramidalization of the alkene carbons, so that the hydrogens move away from the fluorines.[15] This deformation arises to minimize σ_{CH}/π and maximize σ^{*}_{CF}/π interactions.[5] The energetic effects of these interactions are accentuated as the dipolarophile pyramidalizes to attain the TS geometry. An *anti* 10° bending of the hydrogens away from planarity is favored by 1 kcal/mol over the corresponding *syn* bending. This sizable difference is almost entirely maintained in STO-3G model calculations on the *anti* and *syn* transition states of fulminic acid cycloadditions. This effect can compensate for the repulsion between the substituents and the reactants. The *syn* preference is further enhanced for more nucleophilic cycloaddends, such as diazoalkanes,[16] but can be overcome by steric effects. The origin of this unique effect in cyclobutenes is being investigated further.

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References and Notes

1. (a) Catania, (b) Pavia, (c) Pittsburgh.
2. (a) A.P. Kozikowski and A.K. Ghosh, *J. Am. Chem. Soc.*, *104*, 5788 (1982); (b) V. Jäger, R. Schohe, and E.F. Paulus, *Tetrahedron Lett.*, *24*, 5501 (1983); (c) K.N. Houk, S.R. Moses, Y.-D. Wu, N.G. Rondan, V. Jäger, R. Schohe, and F.R. Fronczek, submitted for publication, and references therein.
3. (a) P. Caramella and G. Cellerino, *Tetrahedron Lett.*, 229 (1974); P. Beltrame, P.L. Beltrame, P. Caramella, G. Cellerino, and R. Fantechi, *Tetrahedron Lett.*, 3543 (1975); E.J. McAlduff, P. Caramella, and K.N. Houk, *J. Am. Chem. Soc.*, *100*, 105 (1978).
4. G. Bianchi, C. DeMicheli, A. Gamba, and R. Gandolfi, *J. Chem. Soc. Perkin I*, 137 (1974); C. DeMicheli, A. Gamba-Invernizzi, and R. Gandolfi, *Tetrahedron Lett.*, 2493

(1975); C. DeMicheli, A. Gamba Invernizzi, R. Gandolfi, and L. Scevola, J. Chem. Soc., Chem. Comm., 246 (1976); R. Gandolfi, unpublished results.

5. (a) N.G. Rondan, M.N. Paddon-Row, P. Caramella, and K.N. Houk, J. Am. Chem. Soc., 103, 2436 (1981); (b) P. Caramella, N.G. Rondan, M.N. Paddon-Row, and K.N. Houk, J. Am. Chem. Soc., 103, 2438 (1981); (c) M.N. Paddon-Row, N.G. Rondan, and K.N. Houk, J. Am. Chem. Soc., 104, 7162(1982); (d) N.G. Rondan, M.N. Paddon-Row, P. Caramella, J. Mareda, P.H. Mueller, and K.N. Houk, J. Am. Chem. Soc., 104, 4974 (1982).
6. Y=CH_2, X=Br: W.G. Young, H.K. Hall, and S. Winstein, J. Am. Chem. Soc., 78, 4338 (1956); X=OMe: F. Tailly, Bull. Chem. Soc. Belg., 38 (1962); X=OH, OAc, OBz: H.Z. Sable and T. Pasternak, Helv. Chim. Acta, 45, 370 (1962); X=Cl: V.L. Heasley, P.D. Davis, D.M. Ingle, K.D. Rold, and G.E. Heasley, J. Org. Chem., 39, 736 (1974); Y=O, X=OMe: D. Gagnaire and P. Vottero, Bull. Soc. Chim. France, 2779 (1963); X=OAc: J.P. Jacobsen, J.T. Nielsen, and K. Schaumburg, Acta Chem. Scand., 25, 2785 (1971).
7. The cycloaddition to cis-3,5-dichlorocyclopentene was complicated by difficulties with separation of cis-3,5-dichlorocyclopentenes from cis-3,4-dichlorocyclopentenes. However, the anti product is clearly favored in this reaction.
8. The anti/syn ratios are 5:95 in ethyl acetate and 4:96 in ethanol. However, the ratios are highly dependent on the sample of diols used. Since diols are hygroscopic, presumably the water content influences the stereoselectivity.
9. (a) J. Laane and R.C. Lord, J. Chem. Phys., 47, 4941 (1967); (b) N.L. Allinger, H. Dodziuk, D.W. Rogers, and S.N. Naik, Tetrahedron, 38, 1593 (1982).
10. The drawings are tracings of computer plots of the fulminic acid - cyclopentene transition states obtained from the MM2 model described earlier.[2c]
11. Related conformational preferences are found in ethanediol and 1,2-dialkoxyalkanes. L. Radom, W.A. Lathan, W.J. Hehre, and J.A. Pople, J. Am. Chem. Soc., 95, 693 (1973); U. Burkert, Tetrahedron, 35, 1945 (1979).
12. R. Steyn and H.Z. Sable, Tetrahedron, 27, 4429 (1971).
13. K. Tamagawa and R.L. Hilderbrandt, J. Am. Chem. Soc., 106, 20 (1984).
14. W.A. Szarek and D. Horton, Eds., "The Anomeric Effect", American Chemical Society, ACS Symposium No. 87, Washington, D.C., 1979.
15. The vinyl hydrogens are bent out-of-plane by 1.5°. This slight out-of-plane bending is comparable to the π-distortions of other cyclic molecules.[5a]
16. M. Franck-Neumann, Angew. Chem. Int. Ed. Engl., 8, 210 (1969); Tetrahedron Lett., 2979 (1968).

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