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ASYMMETRIC INDUCTION IN DIELS-ALDER REACTIONS OF o-QUINODIMETHANES

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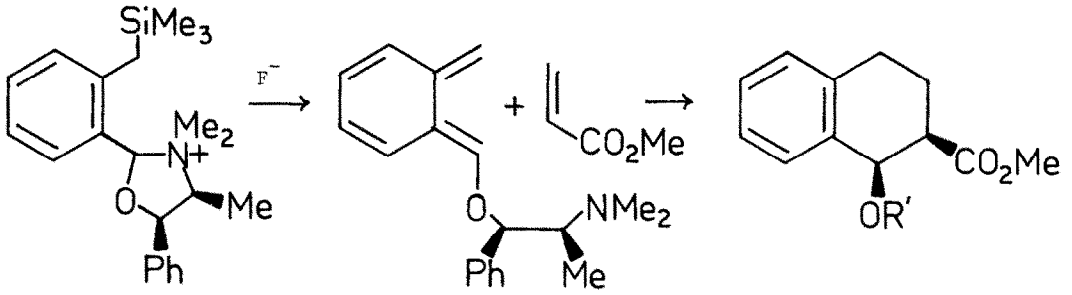
Summary: Asymmetric inductive effects have been measured on the Diels-Alder reaction of dimethyl fumarate with o-quinodimethane bearing a chiral α-alkoxy group. The chiral substituents used were 1-phenylethoxy, 2-(1-phenyl)propoxy, 1-(2-phenyl)propoxy, 2-(4-phenyl)-butoxy and 1-cyclohexylethoxy. The greatest asymmetric induction was found with the first of these chiral substituents (47% ee). A π-stacking effect, previously suggested as the rationale for asymmetric induction in a similar system, is shown to be inconsistent with the results from this study.

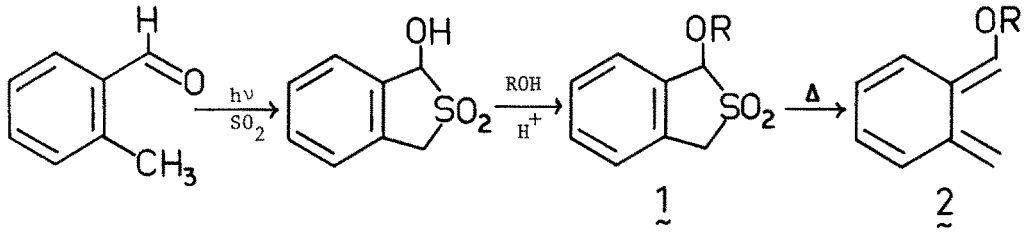
While there have been several studies on asymmetric Diels-Alder reactions of dienes (1,2), there have been more limited studies on o-quinodimethanes (o-QDMs) (3-6). Earlier studies focussed on intramolecular reactions and the asymmetric synthesis of steroids (3). More recently there have been two studies on asymmetric induction in intermolecular additions (5,6). A study by Ito and coworkers is unique in that it uses a chiral substituent in the o-QDM rather than in the dienophile to control the cycloaddition (5).



In the analysis of the mechanism of the asymmetric induction, it was claimed that π-stacking by the phenyl group in the chiral substituent, blocked one face of the o-QDM preventing addition to that face thereby leading to the asymmetric induction. The analysis was based on similar studies of the effects of π-stacking on Diels-Alder reactions of dienes by Trost and Dauben (1,2). However, in Ito's case it appeared that π-stacking was sterically impossible. Also, a careful analysis of the stereochemical results indicated that the reaction would have had to involve the more sterically hindered and less stable of the two π-stacked o-QDM intermediates.

We have now completed a more extensive study of the stereochemical control exerted by phenyl bearing chiral substituents on the Diels-Alder reactions of o-QDMs.

We have recently developed a simple photochemical synthesis of 1-hydroxy-1,3-dihydrobenzo-[b]thiophene-2,2-dioxide which can be easily converted to α-alkoxy-o-QDMs 2 via the alkoxybenzosulfones 1 as shown (7).

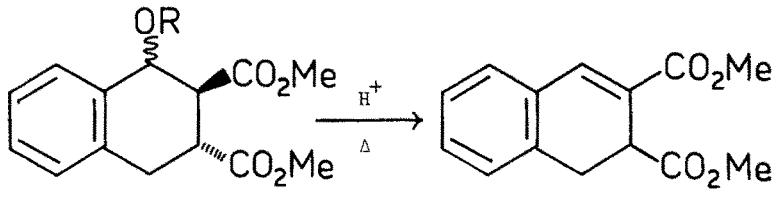


1 2

In the presence study benzosulfones with chiral alkoxy groups (structures 1a-e)(see Table) have been synthesized for a systematic study of the asymmetric induction in cycloaddition reactions of chiral o-QDMs. The first four substituents were chosen in order to assess the effect of the position of the phenyl group and the position of the chiral center on the degree of asymmetric induction in the cycloaddition reactions. The last substituent, (e), exchanges the phenyl group for the more flexible cyclohexyl substituent.

Since the benzylic carbon in the alkoxybenzosulfones 1a-e is chiral, these compounds exist as a mixture of diasteriomers and there is asymmeric induction in their formation as well as in the formation of the dimethyl fumarate cycloadducts 3a-e. The extent of the asymmetric induction in both the sulfones and the cycloadducts was measured by determining the diasteriomer ratio in the crude products by 300 MHz ^{1}H nmr. The endo products 3 were the major cycloaddition products as expected (5,7,8) although smaller amounts (20-30%) of the exo products 4 could be detected by nmr.

The cycloaddition products were further characterized by elimination to the dihydro naphthalene 5 (7).



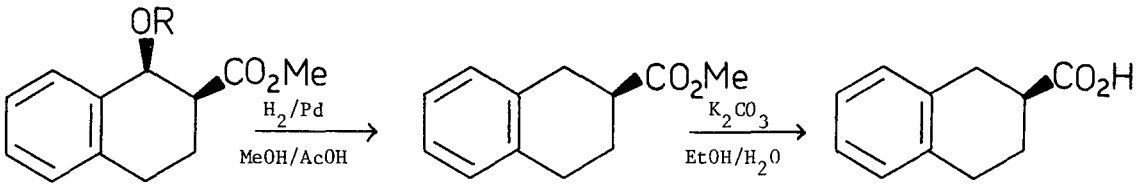
3,4 5

The yield of the alkoxybenzosulfones 1a-e, the total yield of the cycloadducts with dimethyl fumarate 3+4a-e, the yield of the elimination product 5 and the diasteriomer ratios in 1a-e and 3a-e are given in the table.

From the diasteriomer ratios it can be seen that the greatest asymmetric induction occurs with the substituent (a), both for 1 and 3. One might be tempted to ascribe the induction in 3

to the result of a chiral memory from the corresponding sulfone 1 but this cannot be the case since the chirality at the benzylic carbon of the sulfone is lost when it is converted to the o-QDM.

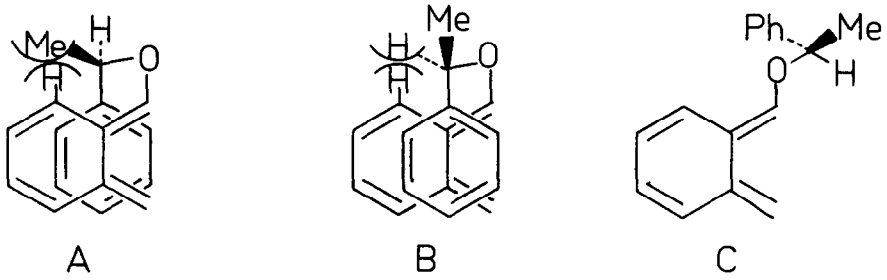
In order to determine the absolute configuration induced in the cycloadducts, the orthoquinodimethane 2(R=R-(+)-sec-phenylethoxy) was added to dimethyl acrylate and the major cis-adduct 6, isolated by chromatography and recrystallization (40% by nmr, 24% isolated), (9) was converted to 1,2,3,4- tetrahydronaphthalene-2-carboxylic acid 7 whose absolute configuration and rotation is known (10).



$[\alpha]_D^{20} = -50°$ 6 $[\alpha]_D^{20} = -45°$ 100% $[\alpha]_D^{20} = -53°$ 7, 95%

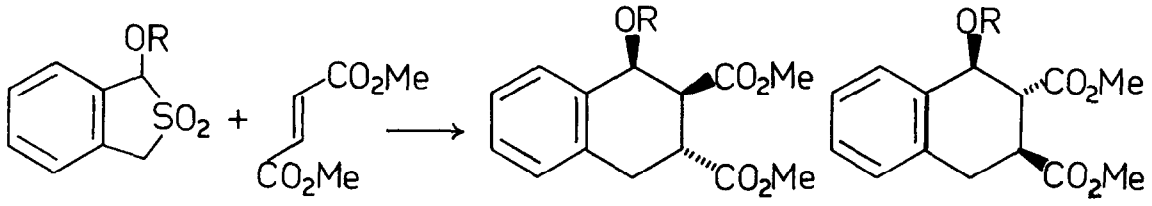
The (-) rotation identified the acid 7 as having the S-configuration and therefore the adduct 6 has the (1'R, 1S, 2S)configuration as shown.

Our result parallels that of Ito (5) who proposed that the induction was due to π-stacking in 2 as shown by conformations A and B below.



Besides being sterically impossible, the explanation is inconsistent with the results since addition of acrylate to the favoured conformation B would have given 7 in the R configuration. Approach to the sterically less hindered face of 2 in conformation C is a more likely explanation for the induction. The steric effect must be rather subtle however, since the substituent (e) shows no induction at all. With substituents b), c) and d) where π-stacking would be more sterically possible no asymmetric induction was found.

Table 1. Asymmetric Diels-Alder Reactions of Orthoquinodimethanes



1 3 4

R	Yields [a] 1	Yields [a] 3+4	Yields [a] 5	Diasteriomer Ratio 1	Diasteriomer Ratio 3
a) 	85	85(100)	81	4.3:1	2.8:1
b) 	83	77(87)	90	1.7:1	1.9:1
c) 	93	79(91)	87	1.1:1	1:1
d) 	84	-(63)	76	1.1:1	1:1
e) 	65	-(56)	-	1:1	1:1

[a] Yields are after chromatography. Crude yields of 3+4 are in brackets.

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9. 6: ^{1}H NMR ($CDCl_3$) 1.42 ($H_{2'}$, d, J=6.42), 2.06 (H_{3e}, m, $J_{3e,2}$=3.36, $J_{3,3}$=-13.66, $J_{3e,4e}$=2.99, $J_{3e,4a}$=6.68), 2.42 (H_{3a}, m, $J_{3a,2}$=12.01, $J_{3a,4e}$=6.40, $J_{3a,4a}$=11.12), 2.72 (H_{4a}, m, $J_{4,4}$=-17.32), 2.79 (H_2, m, $J_{2,1}$=3.26), 2.99 (H_{4e}, m), 3.82 (OCH_3, s), 4.59 ($H_{1'}$, q, J=6.42), 4.85 (H_1, d, J = 3.26), 6.71 (brd, H_8, J=8.1), 6.9-7.45 (aromatics, m); IR (CH_2Cl_2) 1738 cm^{-1}; $[\alpha]_D^{20}$ = -28° (c=1.72, $CHCl_3$).
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