

Table IV. NMR Spectral Data for Cyclic Peroxides

compd	$^1\text{H}$ , $\delta$	$^{13}\text{C}$ , ppm
20	0.95 (t, 3 H), 1.3–1.5 (m, 4 H), 2.0–2.3 (m, 1 H), 2.5–2.8 (m, 1 H), 4.0–4.2 (m, 3 H)	14.04, 19.70, 35.73, 40.77, 69.66, 80.36
21 <sup>a</sup>	1.3 (s, 6 H), 2.3 (t, 2 H), 4.0 (5, 2 H)	25.83, 47.02, 70.09, 82.11
22	0.95 (t, 3 H), 1.4–2.0 (m, 4 H), 3.9–4.2 (m, 2 H)	
23 <sup>a</sup>	1.1 (d, 3 H), 1.5–1.9 (m, 6 H), 3.8– 4.2 (m, 3 H)	19.41, 22.50, 30.62, 37.52, 75.29, 80.57

<sup>a</sup> See Table II, footnote a.

period followed by stirring for an additional 4 min. Methylene chloride (75 mL) was then added, and the resulting mixture was immediately filtered into a separatory funnel. The organic layer was collected, washed once with H<sub>2</sub>O (15 mL), and dried over anhydrous sodium sulfate. The dried solution was then filtered and the solvent removed on a rotary evaporator with a bath temperature of 0 °C. The recovered liquid, clear and colorless, was chromatographed in a jacketed column at –20 °C on 15 g of silica gel (pentane/methylene chloride), yield 0.111 g (55%).<sup>18</sup>

The spectral data for the cyclic peroxides are presented in Table IV.

**Registry No.**—2, 60653-71-6; 8, 55175-91-2; 9, 67393-81-1; 10, 60653-70-5; 11, 67393-65-1; 12, 67393-66-2; 13, 67393-82-2; 14,

67393-67-3; 15, 67393-68-4; 16a, 67393-75-3; 16b, 67393-74-2; 17, 67393-76-4; 18a, 67393-77-5; 18b, 67393-78-6; 19a, 67393-79-7; 19b, 67393-80-0; 20, 67393-69-5; 21, 67393-70-8; 22, 67393-71-9; 23, 67393-72-0; cis-24, 67393-83-3; trans-24, 67393-84-4; 25, 59954-67-5; 26, 67393-73-1; trans-hexa-3,5-dien-1-ol mesylate, 67393-85-5.

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- (19) NIH Career Development Awardee, 1977–1982

## Secondary Orbital Interactions Determining Regioselectivity in the Diels–Alder Reaction. 4. Experimental and Theoretical Examination of the Reaction of Acrylonitrile with 1-(Phenylthio)-2-methoxy-1,3-butadiene. Determination of the Conformations of the Four Cyclohexene Adducts by $^1\text{H}$ NMR Spectroscopy

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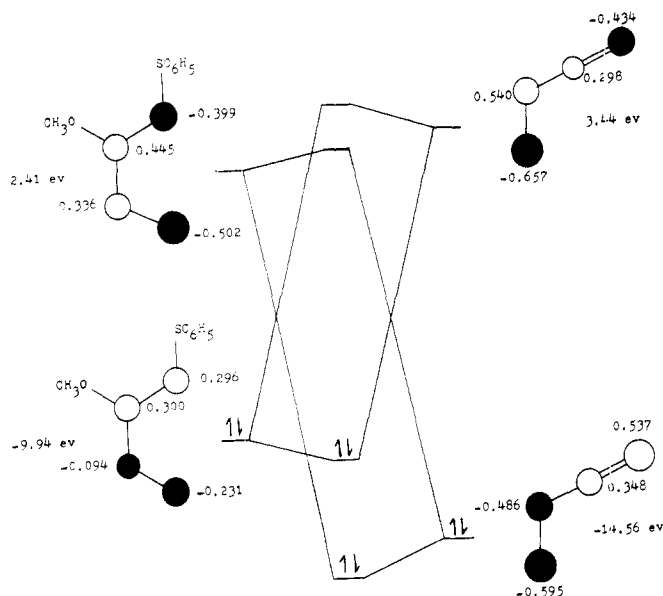
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The importance of secondary orbital interactions in controlling regiochemistry in the Diels–Alder reaction has been assessed by determining the composition of the adduct mixture formed by the reaction of (*Z*)-1-(phenylthio)-2-methoxy-1,3-butadiene with acrylonitrile. All four possible regio- and stereoisomers were separated by high-pressure liquid chromatography and their structures and approximate conformational preferences were determined by 250-MHz proton magnetic resonance spectroscopy. It was also determined that the product composition remains invariant with time under the reaction conditions. As predicted by frontier molecular orbital theory, the ratio of ortho (phenylthio and cyano groups) to meta regioisomers is greater (three to four times) in the (*cis*) products of endo addition than in the (*trans*) products of exo addition, thus indicating that secondary orbital interactions, which can only occur in the transition states for endo addition, play a substantial role in controlling regiochemistry.

The origin of the regioselectivity, which is so crucial to the magnificent synthetic utility of the Diels–Alder reaction, has intrigued organic chemists since the discovery of the reaction by Diels and Alder.<sup>2</sup> Of the many theories which have been proposed to explain this regioselectivity, the frontier molecular orbital (FMO) approach has been the most successful. In the application of FMO theory, several investiga-

tors<sup>3–6</sup> have used just the primary orbital interactions to predict the preferred regioisomer; however, we have observed numerous cases in which this approach failed to predict the regioselectivity that was observed.<sup>7</sup> In these cases the preferred regioisomer can be predicted by including secondary orbital interactions<sup>8</sup> in the theory.

An obvious test of the influence of secondary orbital in-



**Figure 1.** CNDO/2 frontier molecular orbital interaction diagram for the Diels-Alder reaction between 1-(phenylthio)-2-methoxy-1,3-butadiene and acrylonitrile.

teractions would involve determining the relationship of stereoselectivity to regioselectivity in a Diels-Alder reaction which produces all four possible isomers and in which a different regioselectivity is predicted for the exo and endo transition states. Before the advent of high-performance chromatographic techniques and nuclear magnetic resonance instruments utilizing superconducting magnets, this would have been a formidable if not an impossible task. Indeed, even reported yields for one or two major products frequently have been of questionable validity due to the extensive purification procedures that have been required or to the undetermined purities of these products.<sup>9</sup> In the words of Inukai and Kojima,<sup>10</sup> "many of the reported isomer ratios are suspect or at best only semiquantitative." Furthermore, experiments designed to determine whether the products decompose to unknown materials or revert to reactants (therefore resulting in products of thermodynamic rather than kinetic control) have only rarely been performed.

Because none of the published data of which we are aware are appropriate for such a test of secondary orbital interactions,<sup>13</sup> we initiated a study of the reaction of the readily obtainable (*Z*)-1-(phenylthio)-2-methoxy-1,3-butadiene (**1**)<sup>11,12</sup> with acrylonitrile. We have previously shown<sup>7c</sup> that secondary orbital interactions are expected to have a significant effect on the regiochemistry of addition of this diene to methyl vinyl ketone, and as predicted the product is exclusively that of endo addition (*cis*) with the phenylthio group vicinally oriented with respect to the acetyl group.<sup>11</sup> In order to provide for weaker secondary orbital interactions in the transition state and thus to promote the formation of the other possible isomeric products, the weaker dienophile acrylonitrile was chosen.

## Results and Discussion

**Theoretical Expectations.** CNDO/2 calculations<sup>14</sup> predict that the energy separation between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile is considerably smaller than the energy separation between the LUMO of the diene and the HOMO of the dienophile. Thus, the principal stabilization of the transition state will result from the former MO interaction, and the latter is usually neglected in such cases.<sup>3-7,15</sup> However, because of the large difference in the magnitudes of the primary orbital coefficients

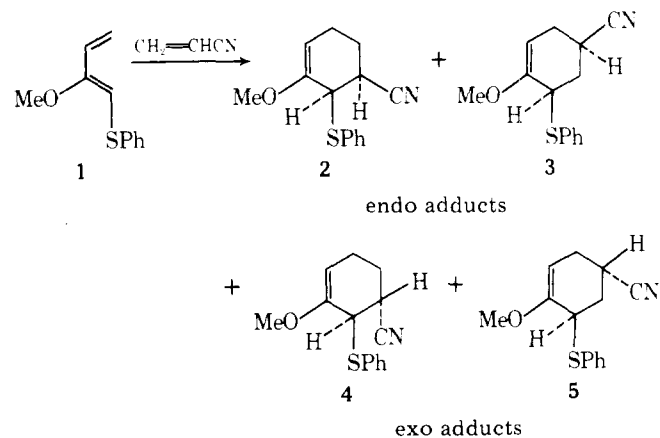
of the diene LUMO, the latter MO interaction does significantly affect the regioselectivity and can not be neglected in this case (Figure 1).

Using CNDO/2 frontier molecular orbital energies and coefficients, the stabilization energies for the two regioisomeric transition states have been calculated from eq 1 in both the endo and the exo modes of addition of the dienophile to the diene.<sup>16,17</sup> In this equation the  $\gamma$ 's are the atomic orbital

$$\Delta E = \frac{2 \left( \sum_{rs} c_r c_s \gamma_{rs} \right)^2}{E_r^{\text{HOMO}} - E_s^{\text{LUMO}}} + \frac{2 \left( \sum_{rs} c_r c_s \gamma_{rs} \right)^2}{E_s^{\text{HOMO}} - E_r^{\text{LUMO}}} \quad (1)$$

orbital transition state resonance integrals for the  $p_z$  carbon atomic orbitals. The  $c_r$ 's and  $c_s$ 's are the coefficients of the atomic orbitals which have a bonding interaction in the transition state. The  $E_r$ 's and  $E_s$ 's are the energies of the interacting molecular orbitals. The resonance integrals for the primary orbital interactions and the secondary orbital interactions were assigned values of 7 and 2.8 eV, respectively. The value of 7 eV for the resonance integral of the primary orbital interactions was derived from the concerted transition state that ab initio calculations<sup>17</sup> predicted for the cycloaddition of ethylene to butadiene along with consideration for the narrowing of the FMO energy separation in the transition state and a larger than experimental CNDO/2 energy separation between the interacting MO's. The resonance integral for the secondary orbital interactions was assigned a smaller value because the geometry of the transition state favors the overlap between the primary orbitals at the expense of the secondary orbital overlap. These values have been used with CNDO/2 FMO energies and coefficients to predict the preferred regioisomer in approximately 100 examples of the Diels-Alder reaction.<sup>7c</sup>

In the endo addition, which includes both the primary and secondary orbital interactions, the energy difference between the regioisomeric transition states was 5.4 kcal/mol in favor of the ortho regioisomer (**2**) (in which the phenylthio and nitrile groups are on adjacent carbon atoms). In the exo addition, which has no secondary orbital interactions, the ortho regioisomer (**4**) was favored again, but only by 0.6 kcal/mol. Consequently, our theory predicts less regioselectivity in the exo addition than in the endo addition.<sup>18</sup> If only the primary orbital interactions are considered, the same regioselectivity is predicted for both stereochemical modes of addition.



**Experimental Findings.** Early attempts to perform the reaction of 1-(phenylthio)-2-methoxy-1,3-butadiene (**1**) with acrylonitrile, either neat or in methanol at 125 °C, in the presence of 5 mol % of the free radical inhibitor, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (to prevent polymerization of the reactants), resulted in yields in the vicinity of 25%. One reason for the low yields is that the *Z* diene

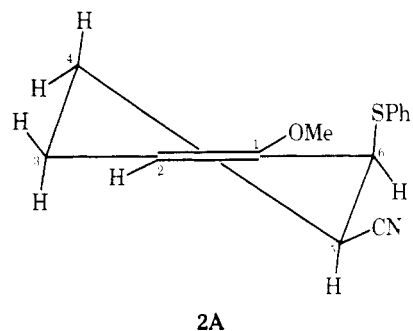
isomerizes fairly readily to the more stable *E* diene.<sup>12</sup> A sample of the latter was prepared by heating the *Z* isomer in methylene chloride and removing the small quantity of unisomerized *Z* diene as its Diels–Alder adduct with methyl vinyl ketone; as expected, the reaction of the *E* isomer with acrylonitrile was far slower than that of the *Z* isomer and the reaction yields a mixture which includes only a small proportion of Diels–Alder adducts. The rate of this isomerization was reduced and the yield of purified (see below) adducts thus increased to 39–45% by the inclusion of diisopropylethylamine in the reaction medium; the reaction was performed at 110 °C for 44 h. The rate of isomerization was further reduced and the yield of adducts increased to 69% when, in addition, a silanized reaction vessel was used.

The adducts could be separated from unreacted diene by gravity chromatography on silica gel using benzene as eluent. Gas chromatography of the adduct mixture was not capable of separating all four isomers, but it appeared to reveal two isomers in a ratio of ca. 2:1; lesser components were apparently present, but the areas of the minor peaks (and to some extent of the major ones as well) were found to depend on the GLC conditions due to a minor degree of decomposition in the injection port. It thus became evident that GLC could not be used to completely analyze the reaction mixture. The two major products (but not the minor ones) could be isolated in pure form by gravity chromatography on silica using 1:5 ethyl acetate–hexane as eluent. The spectroscopic analyses of these two isomers were performed on samples obtained by this procedure.

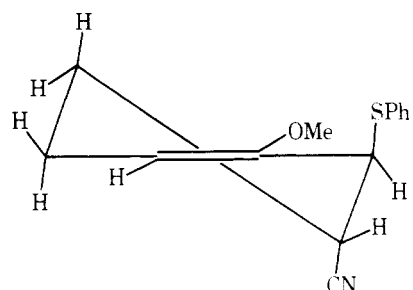
The quantitative determination of all four adducts and isolation of the two minor isomers required the use of high-pressure liquid chromatography. All four adducts exhibited correct elemental composition data,<sup>19</sup> and all had 15-eV mass spectra which exhibited a parent peak of *m/e* 245, a base peak in which the elements of thiophenol had been lost, and other expected fragments (see Experimental Section). Unequivocal structural assignments were made on the basis of the 250-mHz <sup>1</sup>H NMR spectra in deuteriochloroform.

The major isomer exhibited peaks at  $\delta$  1.934–2.259 (m, H<sub>3a'</sub>, H<sub>3e'</sub>, H<sub>4a</sub>, and H<sub>4e</sub>, 4 H), 2.971 (m, H<sub>5</sub>, 1 H), 3.517 (d,  $J_{5,6} = 4.6$  Hz, H<sub>6</sub>, 1 H), 3.551 (s, CH<sub>3</sub>, 3 H), 4.621 (m, four peaks with shoulders, H<sub>2</sub>, 1 H), and 7.23–7.77 (m, aromatic H, 5 H). Upon irradiation at the frequency of H<sub>6</sub>, the peak for H<sub>5</sub> at  $\delta$  2.971 narrowed slightly and changed its splitting pattern to a doublet of doublets ( $J_{4,5 \text{ trans}} = 9.6$  Hz and  $J_{4,5 \text{ cis}} = 3.9$  Hz) and the peak for H<sub>2</sub> at  $\delta$  4.621 very slightly narrowed and changed shape, indicating slight allylic coupling between H<sub>2</sub> and H<sub>6</sub>. The chemical shift and especially the coupling pattern of H<sub>6</sub> clearly establish that it is on a carbon atom adjacent to that bearing the methoxyl group, while the decoupling experiment establishes that the nitrile and phenylthio functions are on adjacent carbon atoms. The stereochemistry is defined as *cis* (structure 2) by the coupling constants  $J_{5,6}$  and  $J_{4,5 \text{ trans}}$ .<sup>20,21</sup> The spectrum is consistent with that<sup>11</sup> of the sole adduct (ortho, *cis*) of the same diene with methyl vinyl ketone; as expected, the acetyl group, being considerably bulkier than the nitrile function, assumes a more nearly completely, probably totally, equatorial conformation as indicated by the value of 13 Hz for  $J_{4,5 \text{ trans}}$  and 2.5 Hz for  $J_{4,5 \text{ cis}}$ .<sup>24,25</sup> Assuming a value of 13.0<sup>24</sup> and 4.9 Hz,<sup>21</sup> respectively, for  $J_{4a,5a}$  and  $J_{4e,5e}$ , the value of  $J_{4,5 \text{ trans}}$  (9.6 Hz) for 2 indicates that this adduct exists to the extent of ca. 58% in conformation 2A.

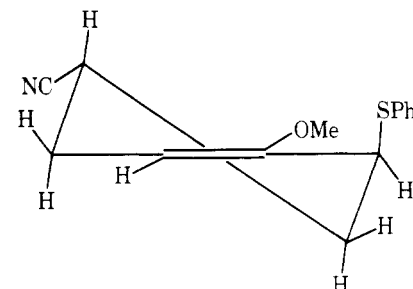
The second most prevalent adduct showed  $\delta$  1.828 (broad m, H<sub>4a</sub>, 1 H), 2.120–2.235 (m, H<sub>3e'</sub> or H<sub>3a'</sub> and H<sub>4e</sub>, 2 H), 2.373 (m,  $\sum J = 33.5$  Hz, H<sub>3e'</sub> or H<sub>3a'</sub>, 1 H), 2.935 (m, H<sub>5</sub>, 1 H), 3.565 (s, CH<sub>3</sub>, 3 H), 3.750 (m, width at half-height = 5 Hz, H<sub>6</sub>, 1 H), 4.792 (t, width at half-height = 10 Hz, H<sub>2</sub>, 1 H), and 7.15–7.43 (m, aromatic H, 5 H). Upon irradiation of the sample at the frequency of H<sub>6</sub>, the H<sub>5</sub> peak at  $\delta$  2.935 perceptibly narrowed



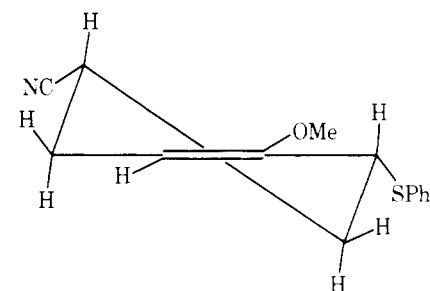
2A



4A



5A



3A

and appeared as a triplet ( $J_{4,5 \text{ cis}} \approx J_{4,5} \approx 3.5$  Hz). None of the other peaks changed shape noticeably during this decoupling experiment. Upon irradiation at the frequency of H<sub>5</sub>, the peak at  $\delta$  3.750 narrowed somewhat and changed shape. The chemical shift of H<sub>6</sub> and the fact that irradiation at its frequency did not noticeably perturb the peak of the vinyl hydrogen place the phenylthio group on the allylic carbon atom (C<sub>6</sub>) adjacent to that bearing the methoxy group. The decoupling experiments place the nitrile group on the other adjacent carbon atom (C<sub>5</sub>). The narrow peak width due to H<sub>6</sub> and the small value of  $J_{4,5}$  (3.5 Hz) clearly establish the conformation very predominantly as 4A in which the substituents are axial and quasiallial.

One of the two very minor products exhibited  $\delta$  2.074 (ddd,  $J_{5,5} = 13.4$  Hz,  $J_{4,5 \text{ trans}} = 11.7$  Hz,  $J_{5,6 \text{ cis}} = 4.2$  Hz, H<sub>5a</sub>, 1 H), 2.185 (m, H<sub>5e</sub>, 1 H), 2.350 (ddd,  $J_{3,3} = 16.7$  Hz,  $J_{3,4 \text{ trans}} = 10.7$  Hz,  $J_{2,3a'} = 2.9$  Hz, H<sub>3a'</sub>, 1 H), 2.534 (d of t,  $J_{3,3} = 16.7$  Hz,  $J_{3,4 \text{ cis}} = 5.4$  Hz,  $J_{2,3e'} = 5.4$  Hz, H<sub>3e'</sub>, 1 H), 3.112 (12 line m,  $J_{4,5 \text{ trans}} = 11.7$  Hz,  $J_{3,4 \text{ trans}} = 10.7$  Hz,  $J_{3,4 \text{ cis}} = 5.4$  Hz,  $J_{4,5 \text{ cis}} = 3.4$  Hz, H<sub>4</sub>, 1 H), 3.533 (s, CH<sub>3</sub>, 3 H), 3.655 (dd,  $J_{5,6 \text{ cis}} \approx J_{5,6 \text{ trans}} \approx 4$  Hz, H<sub>6</sub>, 1 H), 4.630 (dd,  $J_{2,3e} = 5.4$  Hz,  $J_{2,3a'} = 2.9$

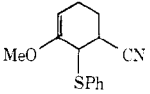
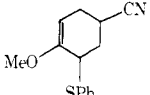
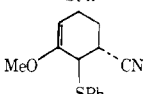
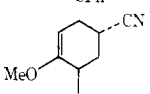
H<sub>z</sub>, H<sub>2</sub>, 1 H), 7.260 (m, meta and para aromatic H, 3 H), and 7.420 (dd, ortho aromatic, 2 H). The similarity of the chemical shift of H<sub>6</sub> to those of the corresponding protons of **2** and **4** makes it appear very likely that this proton is on an allylic carbon atom which is attached to both the phenylthio group and the vinyl carbon atom bearing the methoxy group. The chemical shifts of the protons on C<sub>3</sub> and, particularly, the nature of their coupling to H<sub>2</sub>, to H<sub>4</sub>, and to each other clearly indicate that C<sub>3</sub> is the other, and unsubstituted, allylic carbon atom and that it is adjacent to the carbon atom bearing the nitrile function. The large magnitude of the two vicinal couplings of H<sub>4</sub> requires that the latter be predominantly axial. Finally, the coupling pattern of the protons on C<sub>5</sub> indicates that it is unsubstituted and flanked by one predominantly axial and one predominantly equatorial vicinal proton. Thus, the structure is clearly **5** and, using the assumptions discussed for **2** above, approximately 84% of this material is in conformation **5A**.

The second very minor product showed  $\delta$  1.963 (ddd,  $J_{5,5} = 13.2$  Hz,  $J_{4,5 \text{ trans}} = 12.1$  Hz,  $J_{5,6 \text{ trans}} = 10.4$  Hz, H<sub>5a</sub>, 1 H), 2.233–2.459 (m, H<sub>3a'</sub>, H<sub>3e'</sub>, and H<sub>5e</sub>, 3 H), 2.559 (15 line multiplet,  $J_{4,5 \text{ trans}} = 12.1$  Hz,  $J_{3,4 \text{ trans}} = 10.5$  Hz,  $J_{3,4 \text{ cis}} = 4.8$  Hz,  $J_{4,5 \text{ cis}} = 3.1$  Hz, H<sub>4</sub>, 1 H), 3.550 (s, CH<sub>3</sub>, 3 H), 3.664 (broad m, H<sub>6</sub>, 1 H), 4.643 (dd,  $J_{2,3e'} = 5.1$  Hz,  $J_{2,3a'} = 2.1$  Hz, H<sub>2</sub>, 1 H), 7.244 (m, meta and para aromatic H, 3 H), 7.400 (dd, ortho aromatic H, 2 H). Upon irradiation at the frequency of H<sub>5a</sub>, the multiplet at  $\delta$  2.233–2.459 narrowed and exhibited less peaks, the 15 line multiplet at  $\delta$  2.559 for the proton  $\alpha$  to the nitrile function narrowed and simplified to an 8 line multiplet, and the broad peak for the proton on the sulfur-bearing carbon atom at  $\delta$  3.664 narrowed considerably. The structure is thus clearly **3** and, according to the value (12.1 Hz) of  $J_{4,5 \text{ trans}}$ , it is approximately 89% in conformation **3A**.

In order to ascertain the yields of the four adducts and to provide evidence concerning the stability of the products to the reaction conditions, a mixture of diene, excess acrylonitrile, diisopropylethylamine, and a small quantity of the radical inhibitor was divided into several silanized ampules which were sealed in an argon atmosphere and heated at 110 °C for lengths of time from 1 to 40 h. The percent conversion of diene to adducts in an ampule could be determined either by weighing the unreacted diene and the adducts after separation of the two fractions on preparative thin-layer chromatography (TLC) or by estimating the composition of the diene–adduct mixture by analytical LC using calibrated response factors. In this way, it was determined that at the end of 1 and 40 h, respectively, 36 and 68% of the diene had been converted to adducts. The incomplete conversion to adducts in the 40-h run was undoubtedly due to isomerization of the *Z* diene to the far less reactive *E* isomer, a process which is competitive with the addition. The recovered diene (32% of that charged) from the 40-h ampule was almost certainly (see above) of the *E* configuration. Since the 1-h reaction had already proceeded to a moderate extent, only the 1-h and 40-h samples were analyzed in the most rigorous fashion on the high-pressure analytical liquid chromatographic assembly in order to determine the relative yields of the four adducts both early and at the end of the reaction. In addition, the contents of each ampule were submitted to preparative thin-layer chromatography to separate the adducts, diene, and radical scavenger; the dienes and adduct mixtures were weighed, and the latter from each of the 2-, 4-, 8-, and 40-h ampules was separated into its four components in the preparative LC assembly. The percent compositions in the 1-h and 40-h runs, as determined by integration of the liquid chromatograms, and the compositions determined by isolation (upon separation by preparative LC) of the combined samples from the 2-, 4-, 8-, and 40-h experiments are compared in Table I.

The differences between the compositions at the end of 1

Table I. Adduct Composition

no.	adduct	% composition		
		1 h	40 h	isolated
2		61	64	62
3		5.6	5.7	5.4
4		27	22	25
5		6.8	8.1	6.8

and 40 h are considered to be within experimental error, and the adducts therefore appear to be stable to the reaction conditions and almost certainly are the kinetic products. This conclusion is also consistent with the finding, made before the LC technique was developed, that the major product (**2**), when treated under the reaction conditions for 46 h, undergoes no isomerization to the next most prevalent adduct, **4**, its exo counterpart. Confidence in the reliability of the data is enhanced by the gratifying correspondence between the product compositions as determined by integration of the detector responses and those obtained upon isolation.

The predictions made assuming a role for secondary orbital interactions in the control of regiochemistry are seen to be qualitatively valid. The ratio of ortho to meta product (**2/3**) generated in the endo transition state is three to four times greater than the same regioisomeric ratio (**4/5**) generated in the exo transition state. As indicated above, these ratios should be approximately equal in the absence of secondary orbital interactions: yield ratio of endo adducts **2/3** = 11; yield ratio of exo adducts **4/5** = 3.4.

With regard to the preferred conformations of these adducts, it should be recognized that the percentages given are only fairly crude approximations of the true values because coupling constants vary with changes in dihedral angles, which may be substituent sensitive. Nevertheless, there can be little doubt that the equilibria lie far in favor of **3A**, **4A**, and **5A** and that in the case of **2**, there is no great preference for **2A** or its ring inverted conformational isomer. Conformation **3A** is, of course, simple to rationalize since the substituents are oriented in an equatorial and quasiequatorial fashion. Although the  $A^{29}$  value of phenylthio is presumably far larger than that of cyano<sup>27</sup> and the corresponding value ( $E_4$ )<sup>29</sup> for the latter group in the 4 position of a cyclohexene is about 0,<sup>25c,26c,30</sup> the phenylthio group assumes the quasial axial orientation partially in **2** and substantially in **5**; however, it is clear that the preference of substituents for the quasiequatorial position on a cyclohexene ring is far less than that for the equatorial position on a cyclohexane ring,<sup>20</sup> and the interactions between the phenylthio group and the other substituents on the rings in all of the half-chair conformations are difficult to evaluate. Many of the same factors are probably responsible for the very predominant axial–quasial conformation of **4A** with the added and probably decisive factor of a strong vicinal repulsion that must occur between the cyano and phenylthio groups when they are equatorial–quasiequatorial.

#### Experimental Section

**Analytical Procedure.** The analytical high-pressure liquid chromatography was performed on a Dupont Model 830 instrument

utilizing ultraviolet (254 nm) detection. Two 25 cm × 4 mm columns, in series, packed with Partisil 10 were used; the theoretical plate count was about 9000. All four adducts could be estimated quantitatively on a very small drop of the crude concentrated reaction mixture when a solution of 15% ethyl acetate–85% hexane was used as eluent at a flow rate of 1.5 mL/min at 600 psi.

The preparative LC was performed on a Waters apparatus using refractive index detection and four 30 cm × 8 mm columns, in series, packed with Lichrosorb 10; the theoretical plate count was ca. 15 000. Preparative TLC using benzene for development was used to separate the adducts from other components (as above). Individual injections were 60–70 mg of adduct, and the eluent was the same as above; the flow rate was 6 mL/min at 1850 psi.

<sup>1</sup>H NMR spectra were measured on a custom built 250-MHz instrument maintained by NIH Grant R.R.00292-6 to the Mellon-Pitt-Carnegie (M.P.C.) Corp. The spectrometer utilizes a supercooled solenoid and is interfaced with a Sigma 5 computer, which allows printouts of the peak positions accurate to at least ±0.16 Hz. A number (usually between 10 and 50) of fast scans (0.6–0.8 s sweep time) were accumulated for each spectrum, and the signal to noise ratio was enhanced by the correlation technique.<sup>31</sup> On this high-field instrument, most of the coupling constants of interest (all of those reported) could be obtained by first-order analyses.

**Diels–Alder Reactions.** The inside surfaces of glass reaction vessels were soaked overnight with aqueous ammonia and rinsed consecutively with water, acetone, and hexane, and the containers were allowed to remain filled with chlorotrimethylsilane containing a little Silyl-8 (a GLC column conditioner sold by Pierce Chemical Co.) for 3 days. The vessel was then rinsed with aqueous ammonia, triethylamine, and hexane and dried in an oven.

(A) A solution containing 0.466 g (2.43 mmol) of (*Z*)-1-(phenylthio)-2-methoxy-1,3-butadiene,<sup>11,12</sup> 0.8 g (15 mmol) of acrylonitrile, 44 mg (0.12 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (Aldrich Chemical Co.), and 940 mg (7.3 mmol) of diisopropylethylamine was heated in a glass pressure reactor (Fisher–Porter tube) immersed in a bath maintained at 110 °C for 44 h. The product mixture was concentrated and chromatographed on silica gel using benzene as eluent, whereby a 69% yield of an adduct mixture was isolated. This mixture, according to its NMR spectrum (see Results and Discussion), consisted approximately of a 2:1 mixture of isomers. The mixture was separated into two components by chromatography on silica gel using 1:5 ethyl acetate–hexane as eluent. Major adduct (2): *R*<sub>f</sub> 0.3; IR (CHCl<sub>3</sub>) 2245 (w), 1665 (m), 1360 (m) cm<sup>-1</sup>; MS (15 eV) *m/e* (relative intensity, assignment) 247 (8.6), 246 (45), 245 (64, P), 192 (24, P – CH<sub>2</sub>CHCN), 136 (71, P – PhS), 135 (100, P – PhSH). Anal. Calcd for C<sub>14</sub>H<sub>15</sub>NOS: C, 68.53; H, 6.16; N, 5.70. Found: C, 68.41; H, 6.06; N, 5.77.

Minor adduct (4): *R*<sub>f</sub> 0.4; IR (CHCl<sub>3</sub>) 2240 (w), 1663 (m), 1365 (m) cm<sup>-1</sup>; MS (15 eV) *m/e* 247 (18), 246 (47), 245 (53, P), 192 (19, P – CH<sub>2</sub>CHCN), 137 (45), 136 (61, P – PhS), 135 (100, P – PhSH). Anal. Found: C, 68.38; H, 6.16.

The <sup>1</sup>H NMR spectra are reported in the Results and Discussion. When the major isomer was heated under the reaction conditions for 46 h, none of the minor isomer was produced as judged by GLC analysis.

(B) A solution of 454 mg (2.36 mmol) of the diene, 0.8 g (15 mmol) of acrylonitrile, 0.8 g (6 mmol) of diisopropylethylamine, and 45 mg (0.12 mmol) of the radical trap was divided into four portions of approximately 100 mg each and a fifth portion containing the remainder (ca. 1.6 g). Each portion was sealed in an ampule under argon and heated at a bath temperature of 110 °C. The small ampules were heated respectively for 1, 2, 4, and 8 h, and the large one was heated for 40 h. Each ampule was broken, and the pale yellow contents were concentrated. All of the adduct samples were analyzed by analytical LC, and all but the 1-h sample were separated into the four components using preparative LC. Compound 5: MS (15 eV) *m/e* 247 (2.9), 246 (10), 245 (48, P), 194 (21), 136 (30, P – PhS), 135 (100, P – PhSH), 110 (22, PhSH<sup>+</sup>). High-resolution mol wt, 245.0863; calcd for C<sub>14</sub>H<sub>15</sub>NOS, 245.0874.

Compound 3: MS (15 eV) *m/e* 247 (2.4), 246 (7.4), 245 (39, P), 136 (30, P – PhS), 135 (100, P – PhSH), 110 (15, PhSH<sup>+</sup>); high-resolution mol wt, 245.0846.

As an example of the determination of the approximate extent of reaction, evaporation of the contents of the 1-h ampule yielded 24.2 mg, which was separated by preparative TLC into 10 mg (0.041 mmol) of adduct and 13.9 mg (0.072 mmol) of diene; since only a trace of polymer (which may or may not have incorporated diene) and no other diene-containing products were in the sample, the extent of conversion was estimated as 0.041/(0.041 + 0.072) = 0.36. In the case of the 40-h sample, the detector response for recovered diene in one injection was

2629, and the combined responses of the four adducts was 2957; when these numbers were corrected for the molar response factors of the two types of compound, it was evident that 68% conversion of diene to adducts had occurred and diene was still present.

**Isomerization of *Z* Diene to *E* Diene and Reaction of the Latter with Acrylonitrile.** A solution of *Z* diene in methylene chloride was heated at reflux for 4 h. Upon TLC analysis (silica, 3:2 benzene–hexane), it was evident that most, but not all, of the *Z* diene had been converted to a slightly faster moving material. The mixture was stirred for 1 day at ambient temperature with an excess of methyl vinyl ketone containing a trace of radical inhibitor, and the extremely slow reacting *E* diene was isolated as a colorless oil by chromatography on silica gel using 3:2 benzene–hexane as eluent: IR (CCl<sub>4</sub>) 1635 (w), 1585 (m), 1555 (s), 1480 (s), 1440 (m), 1215 (s), 1095 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz) δ 3.72 (s, CH<sub>3</sub>, 3 H), 5.13–5.84 (m, CH<sub>2</sub> and CHSPH, 3 H), 6.80 (higher field half of dd; the other half is apparently in the aromatic region; *J*<sub>cis</sub> = 10 Hz, =CHC(OMe)=, 0.5 H), 7.13 (broad s, aromatic plus one-half of vinyl absorption, 5.5 H).

The latter spectrum resembles that<sup>13</sup> of the *Z* isomer. A Diels–Alder reaction between this diene and acrylonitrile was extremely slow, and according to a crude GLC analysis the product was a complex mixture which probably contained small amounts of 2 and 4.

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**Registry No.**—(*Z*)-1, 60466-66-2; (*E*)-1, 67315-81-5; 2, 67315-82-6; 3, 67315-83-7; 4, 67315-84-8; 5, 67315-85-9; acrylonitrile, 107-13-1.

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## Scope of the Homo-Diels–Alder Reaction

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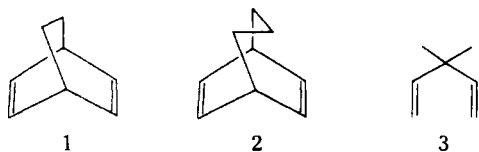
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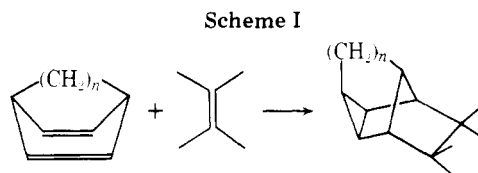
The reactivity of bicyclo[2.2.2]octa-2,5-diene, bicyclo[3.2.2]nona-6,8-diene, and 3,3-dimethyl-1,4-pentadiene in the homo-Diels–Alder reaction has been investigated to aid in an assessment of the scope of this reaction. The scope is seen to be rather limited, with the efficiency of the diene in the reaction generally being related to the distance between the double bonds.

The 1,5-addition of dienophiles to 1,4-dienes (the homo-Diels–Alder reaction) is a useful synthetic reaction for the preparation of certain tetracyclic compounds (Scheme I). Most studies of this reaction have involved norbornadiene with a variety of dienophiles.<sup>1</sup> Recent studies with norbornadiene have been concerned with the stereochemistry of the reaction,<sup>2</sup> a competing ionic reaction,<sup>3</sup> and the effects of Ni(0) catalyst on the reaction.<sup>4</sup> Other diene systems studied include the Dewar benzene,<sup>5</sup> barrelene,<sup>6</sup> and 1,4-cyclohexadiene systems.<sup>7</sup>

We were interested in the scope of the homo-Diels–Alder reaction with regard to the diene to see what the limitations are on the ring systems that can be synthesized by this reaction. Since the ease of the reaction must depend critically on the alignment and distance between the double bonds, we have investigated the behavior in this reaction of several dienes in which the double bonds are at increasingly greater distances than in norbornadiene. The dienes studied were bicyclo[2.2.2]octa-2,5-diene (1), bicyclo[3.2.2]nona-6,8-diene (2), and 3,3-dimethyl-1,4-pentadiene (3). The results of these



studies along with previous information in the literature can be used to assess the scope of the homo-Diels–Alder reaction.



Bicyclo[2.2.2]octa-2,5-diene (1) was prepared by the method of Grob et al.,<sup>8,9</sup> which ultimately involves a Cope elimination from the *N*-oxide of 5-(dimethylamino)bicyclo[2.2.2]oct-2-ene. In order to avoid contamination of the diene with tricyclo[3.2.1.0<sup>2,7</sup>]oct-3-ene, which apparently results from elimination from the exo amine oxide,<sup>10</sup> an attempt was made to prepare the starting material for the synthesis, *endo*-5-carbomethoxybicyclo[2.2.2]oct-2-ene, with a high degree of configurational purity. It was found that the procedure of Inukai et al. for the aluminum chloride catalyzed Diels–Alder reaction<sup>11</sup> gave this ester in yields comparable to the uncatalyzed reaction<sup>12</sup> but the bicyclic ester was 98% endo isomer compared to 76% for the uncatalyzed reaction.

The same procedure was used to prepare bicyclo[3.2.2]nona-6,8-diene (2).<sup>13</sup> In this case, the aluminum chloride catalyzed reaction of ethyl acrylate with 1,3-cycloheptadiene gave the bicyclic ester in 54% yield. Analysis showed that it was 98.5% exo isomer (this relates to the endo isomer in the bicyclooctyl case). 3,3-Dimethyl-1,4-pentadiene (3) was prepared by a modification of the procedure of Ciola and Burwell.<sup>14</sup>