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A Facially Dissymmetric 1,3-Cyclohexadiene as a Dienophile in Diels-Alder Reactions with Polyhalocyclopentadienes†

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Abstract. Diels-Alder cycloaddition of 1,2,3,4,5,5-hexachloro- and of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**2a** and **2b**, respectively) to hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione (**1**) occurs in each case with highly stereoselective attack of the diene upon that face of the dienophile which is *anti* to the carbonyl groups. The corresponding *endo,anti* adduct (i. e., **6** and **8**, respectively) is obtained as the exclusive cycloadduct in each case. The structures of **6** and **8** were established unequivocally via X-ray crystallographic methods. The results of AM1 semi-empirical MO calculations for cycloaddition of **1** to **2a** are in accord with experiment.

Introduction. Hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione (**1**) has received considerable attention as a substrate for investigation of the factors which determine π-facial selectivity in Diels-Alder reactions of a wide variety of dienophiles to a facially dissymmetric 1,3-cyclohexadiene.[1,2] In the present investigation, we have extended these studies to include the corresponding reactions of **1** with two polyhalocyclopentadienes, i. e., 1,2,3,4,5,5-hexachlorocyclopentadiene and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**2a** and **2b**, respectively). In such reactions, inverse electron demand Diels-Alder reactions[3] might be expected to occur in which **1** functions as the dienophile by undergoing [4 + 2] cyclo-addition to each of the electron poor dienes **2a** and **2b**.

The corresponding reaction of **1** with cyclopentadiene (CPD) has been studied previously.[1b,4] This reaction affords a 1:1 and a 2:1 cycloadduct (**4** and **5**, respectively, Scheme 1), whose structures have been elucidated by a combination of 1D and 2D NMR methods. Interestingly, **1** undergoes electrocyclic ring opening prior to its reaction with CPD. Thus, both **4** and **5** result via Diels-Alder reaction of cyclopentadiene (diene) with the intermediate ring-opened triene, **3** (dienophile), which is derived from **1**. It was of interest to determine if this same behavior would be observed for Diels-Alder reactions of **1** with **2a** and **2b**.

Experimental Results. The results of these two thermal cycloaddition reactions are summarized in Scheme 2. The structures of **6** and **8** were established unequivocally by X-ray crystallographic methods.

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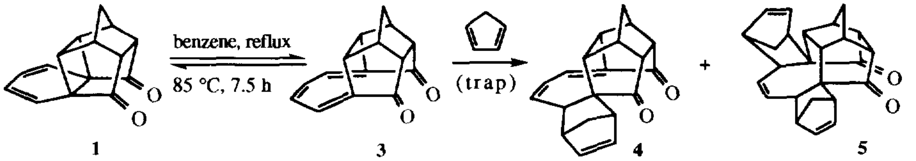
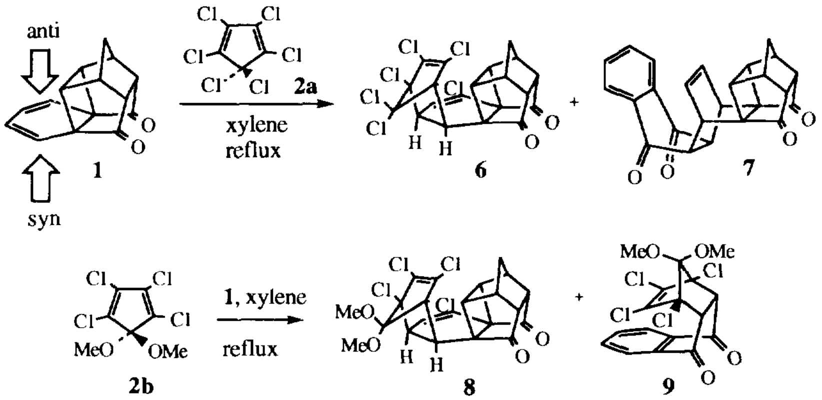
†Dedicated to Dr. A. V. Rama Rao on the occasion of his 60th birthday.

Scheme 1



Scheme 2



Of particular interest is the fact that, in each case, the diene reacts preferentially to one of the two C=C double bonds in the ring-closed 1,3-cyclohexadiene system in **1** directly. Furthermore, in each case the approach of the diene occurs stereoselectively via that π-face of the diene system in **1** which lies *anti* to the carbonyl groups. We find no evidence of formation of a product from either of these reactions which results via cycloaddition of the polyhalocyclopentadiene to a C=C double bond in the tautomeric ring-opened triene (i. e., **3**). This result stands in contrast with that reported for the Diels-Alder reaction of **1** with cyclopentadiene, as noted above and depicted in Scheme 1.[1b,4] Since the reactions of **1** with both **2a** and **2b** were performed at a temperature which is significantly higher than that employed to promote the corresponding reaction of **1** with cyclopentadiene (i. e., 140 °C vs. 85 °C), it seems reasonable to assume that both the 1,3-cyclohexadiene and hexatriene valence tautomers of the dienophile (i. e., **1** and **3**, respectively) were present in solution at the time of reaction with **2a** and **2b**.

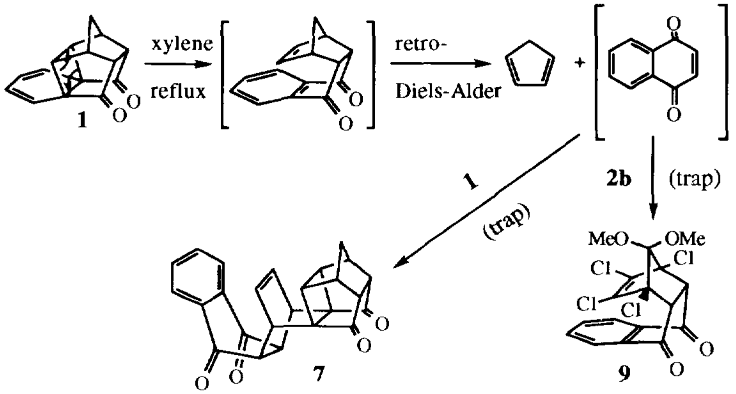
In addition to Diels-Alder adducts **6** and **8**, a second product was isolated in each reaction (i. e., **7** and **9**, respectively; see Scheme 2). It seems likely that these products arose via Diels-Alder trapping of 1,4-naphthoquinone (formed via thermal degradation of **1**) by **1** and **2b**, respectively (see Scheme 3).

Two important features of the two Diels-Alder cycloadditions shown in Scheme 2 merit further scrutiny:

(i) Why does Diels-Alder cycloaddition of cyclopentadiene occur via the hexatriene tautomer of the dienophile (i. e., **3**), whereas the corresponding cycloaddition of dienes **2a** and **2b** to this same dienophile proceeds via the corresponding cyclohexadiene tautomer (i. e., **1**)?

(ii) Diels-Alder cycloadditions of **1** (diene) to electron-poor dieneophiles (e.g., *p*-benzoquinone[1b], maleic anhydride,[1b] methyl acrylate[1b,1d]) have been reported to occur with stereoselective addition to the π-face

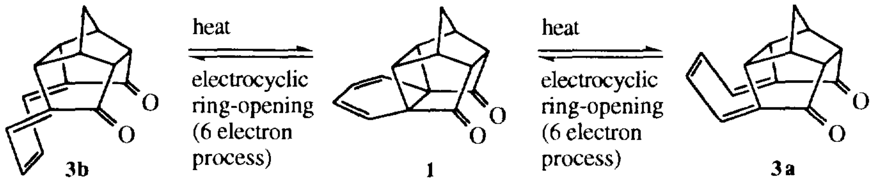
Scheme 3



of the diene system in **1** which lies *syn* to the carbonyl groups. In the present study (in which **1** functions as the dienophile with electron-poor dienes **2a** and **2b**), cycloaddition occurs with the opposite stereoselectivity, i. e., with approach of the diene upon the π-face of the diene system in **1** which lies *anti* to the carbonyl groups. The question arises: Is the origin of the unusal stereoselectivity in these reactions steric or electronic in nature?

Results of Semi-empirical (AM1) Calculations. We recently reported[4b] the results of semi-empirical MO calculations, which were performed to evaluate the relative energies of diene **1** and of the two possible conformational isomers of its "valence isomer", i. e., the corresponding triene (**3a** and **3b**, respectively, Scheme 4). The resulting relative AM1 energies of the product trienes indicated **3a** to be favored thermodynamically relative to **3b** by *ca.* 24 kcal-mol^{-1}.[4b] The relatively large difference in energy requirements of the two pathways for thermal electrocyclic ring opening of **1** is reflected by the relative energies of the corresponding transition states. Thus, the transition structure which leads to **3a** was predicted to be *ca.* 22 kcal mol^{-1} lower in energy than that which leads to **3b**.[4b] It follows that any Diels-Alder reactions which might involve a cage triene valence tautomer of **1** are expected to occur via triene **3a** rather than the higher energy structure, **3b**. Interestingly, the results of these AM1 calculations suggest that **3a** is *less* stable than **1** by *ca.* 4 kcal-mol^{-1}.[4b]

Scheme 4



Next, the energetics of Diels-Alder cycloadditions of hexachlorocyclopentadiene (**2a**) with cage diene **1** and triene **3a** were compared (Figures 1 and 3). Four modes of cycloaddition of **2a** to **1** were considered specifically: (i) *endo,anti* addition via TS **10**; (ii) *exo,anti* addition via TS **11**; (iii) *syn,endo* addition via TS **12**; (iv) *syn,exo* addition via TS **13** (Figure 1). The results of AM1 calculations[5] indicate that TS **10**, which leads to the formation of **6**, is lower in energy by at least 3 kcal mol^{-1} than are the alternative transition struc-tures, TS **11** - TS **13**, which correspond to the remaining three possible modes of cycloaddition of **2a** to **1**.

The calculations also predict **6** to be the most thermodynamically stable product that can result via Diels-Alder reaction of **1** to **2a**. Thus, **6** has a lower ΔH_f than the other possible products formed via addi-tion of **2a** to **1** (**14-16**, Figure 1) and those from addition of **2a** to **3a** (**17** and **18**, Figure 2). The activation energies to the formation of transition structures **17** and **18** for the addition of **2a** to triene **3a** are *ca.* 49 and 51 kcal mol^{-1}, respectively (Figure 2). The lower value is similar to that found for the energetically most favorable pathway for the addition of **1** to **2a** via TS **10** (activation barrier *ca.* 49 kcal-mol^{-1}, Figure 1).

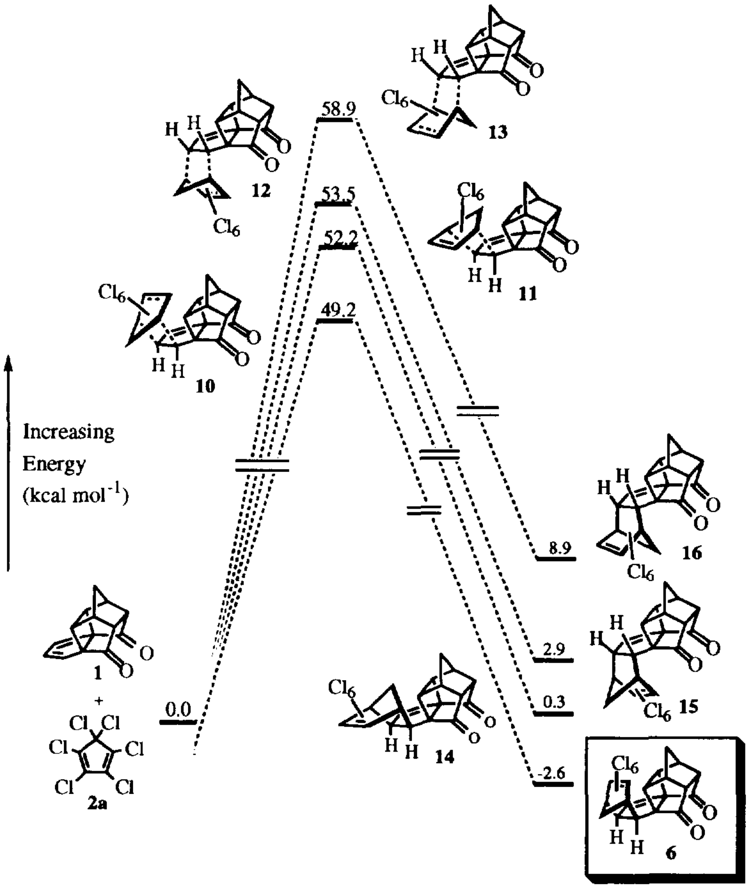


Figure 1. Relative energy diagram which compares the four possible modes of Diels-Alder cycloaddition of **1** and **2a**

It should be noted the net energy required to form **19** [i. e. ΔE ($\mathbf{1} \rightarrow \mathbf{3a}$) + $\Delta E^{\neq}$($\mathbf{3a} + \mathbf{2a} \rightarrow \mathbf{19}$) = 53 kcal-mol^{-1}] is predicted to be *ca.* 4 kcal-mol^{-1} higher than that required for the formation of **10** [i. e., $\Delta E^{\neq}$($\mathbf{1} + \mathbf{2a} \rightarrow \mathbf{10}$) = 49 kcal-mol^{-1}, Figure 1]. This result is consistent with the experimental observation that **1** is the most reactive tautomer of the dienophile toward Diels-Alder cycloaddition with **2a**.

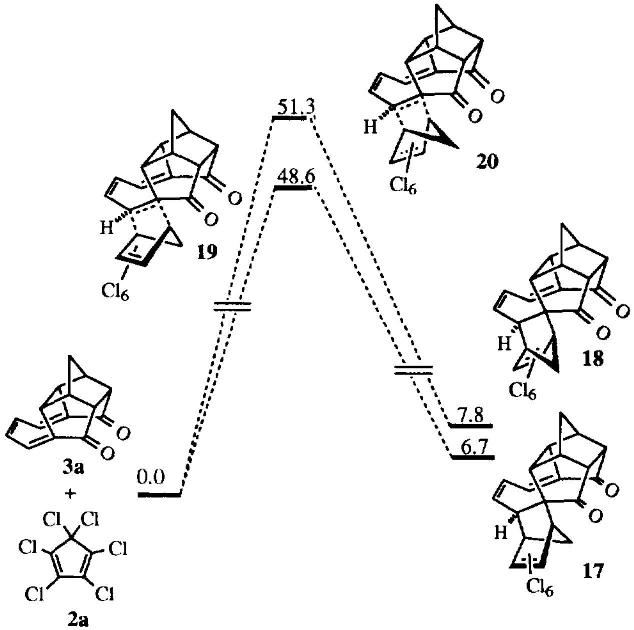


Figure 2. Results of AM1 calculations[5] for Diels-Alder cycloaddition of **2a** to **3a**

Results of Ab Initio Calculations. The HOMO and LUMO energies of **1**, **2a** and **3a**, calculated at the HF/3-21G(*) level of theory, are shown in Table 1. The energy differences between the LUMO and HOMO orbital energies of **1**/**2a** and **3a**/**2a** ($\Delta E = E_{LUMO} - E_{HOMO}$) are shown in Table 2.

Table 1. Energies (eV) of the HOMO and LUMO orbitals of **1**, **2a** and **3a** calculated at the HF/3-21G(*) level of theory.

Compound	**HOMO (eV)**	**LUMO (eV)**
1	-8.39	3.07
2a	-9.70	0.95
3a	-9.60	2.39

Table 2. Energy differences ($\Delta E = E_{LUMO} - E_{HOMO}$), in eV, of the HOMO and LUMO orbitals of **1** and **3a** with respect to **2a** calculated at the HF/3-21G(*) level of theory.

Compound	**2a (LUMO)**	**2a (HOMO)**
1 (HOMO)	9.34	
3a (HOMO)	10.55	
1 (LUMO)		12.77
3a (LUMO)		12.09

From FMO theory, the smaller the difference in HOMO-LUMO energies the greater the stability of the forming filled molecular orbital. The data in Table 2 suggest that the smallest difference in orbital energies occurs upon mixing of the LUMO of **2a** with the HOMO of **1**. This orbital mixing is expected to afford the most favorable orbital interaction, a result which is in accord with the general tendency of electron deficient dienes to undergo inverse electron demand Diels-Alder reactions.[6] The greater orbital stabilization that results from this orbital mixing is expected to be reflected in the transition state energies and may be a significant factor in determining the relative reactivity of "valence isomers" **1** and **3a** toward electron-deficient dienes.

Results of Molecular Mechanics Calculations. Molecular mechanics calculations could not be performed on transition states **10-13**, **19**, and **20**, due to the lack of available parameters. MMX molecular mechanic calculations[7,8] performed on products **6** and **14-18** (Table 3) indicate that Diels-Alder cyclo-addition to triene **3a** results in the formation of a sterically more favorable product. The results of these cal-culations show little difference in energy between structures **6**, **14** and **15** which result from addition to **1**, thereby indicating that, on a steric basis, there is little selectivity for a particular product. Presumably, the steric effects incurred in the corresponding transition structures show similar trends to those observed in the reaction products. Thus, it appears that electronic effects, such as secondary orbital interactions and HOMO/LUMO energy differences, control not only the stereoselectivity of the cycloaddition but also the regioselectivity of the reaction, and hence the relative reactivity of valence isomers **1** and **3a**. In this case, the molecular mechanics results indicate that steric effects have little effect on the course of the reaction.

Table 3. Calculated MMX[7,8] product energies (kcal-mol^{-1})

Structure	**MMX product energies (kcal-mol^{-1})**
6	107.6
14	108.0
15	107.6
16	112.5
17	91.5
18	90.5

Summary and Conclusions. Diels-Alder cycloaddition of **2a** and of **2b** to **1** each proceed to afford the corrsponding *anti,endo* [4 + 2] cycloadduct (i. e., **6** and **8**, respectively). Based upon the foregoing analysis, we conclude that the results of the AM1 calculations performed for Diels-Alder cycloaddition of **2a** to **1** correctly predict that (i) **1** is the most reactive tautomer of the dienophile towards **2a** and (ii) this cycloaddition proceeds to afford exclusively the corresponding *endo,anti* cycloadduct (**6**). Consideration of the four possible transition states for [4 + 2] cycloaddition of **2a** to **1** (Figure 2) suggests that the origin of the observed preference for *anti* π-facial stereoselectivity in this reaction may be due to electronic effects, rather than unfavorable nonbonded interactions between the diene and the dienophile, in TS **10** relative to the other three possible transition structures (TS **11-13**, Figure 2).

Experimental Section

Melting points are uncorrected. Elemental microanalyses were obtained by Schwartzkopf Microanalytical Laboratory, Woodside, NY. Calculations were performed by using MOPAC (version 6.0)[9] or SPARTAN (version 3.1)[10] with the AM1 Hamiltonian.[5] MOPAC calculations were carried out by using the keyword

PRECISE in all cases, and transition structures were located by using the keyword TS. SPARTAN calculations were performed by using the default convergence and optimization criteria for the selected type of stationary point to be located. Transition structures were located by using RHF theory and by assuming that the Diels-Alder reaction proceeds via a concerted mechanism.[11] Molecular mechanics calculations (MMX force-field)[7] were performed by using PCMODEL (version 4.0).[8]

Diels-Alder reaction of 1 with Hexachlorocyclopentadiene. A solution of **1** (536 mg, 2.48 mmol) and hexachlorocyclopentadiene (**2a**, 1.70 g, 6.23 mmol) in dry xylene (15 mL) was refluxed under argon for 90 h. The progress of the reaction was monitored periodically via ^{1}H NMR spectroscopy. The reaction mixture was allowed to cool, and solvent was removed *in vacuo*. The residue was purified via column chromatography on silica gel by using 4:1 hexane-EtOAc as eluent. The first chromatography fraction afforded **6** (653 mg, 53%). Recrystallization of the product thereby obtained from acetone-EtOAc-hexane mixed solvent afforded pure **6** as a colorless microcrystalline solid: mp 209 °C; IR (KBr) 1750 (s), 1738 (s), 1591 (m), 1204 (m), 1161 (w), 1084 (m), 1056 (m), 901 (w), 858 (w), 703 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.95 (*A*B, J_{AB} = 11.4 Hz, 1 H), 2.11 (A*B*, J_{AB} = 11.4 Hz, 1 H), 2.73-2.97 (m, 5 H), 3.25 (dt, J_1 = 9,3 Hz, J_2 = 2.4 Hz, 1 H), 3.44-3.55 (complex m, 1 H), 4.01 (d, J = 9.4 Hz, 1 H), 5.66 (dd, J_1 = 10.7 Hz, J_2 = 2.4 Hz, 1 H), 6.00 (dd, J_1 = 10.7 Hz, J_2 = 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 39.94 (d), 41.21 (t), 42.59 (d), 43.23 (d), 43.42 (d), 43.89 (d), 45.42 (d), 47.28 (s), 49.21 (s), 53.53 (d), 55.33 (d), 81.94 (s), 82.26 (s), 104.2 (s), 124.7 (d), 125.4 (d), 129.8 (d), 134.9 (s), 209.5 (s), 210.6 (s). Anal. Calcd for $C_{20}H_{12}Cl_6O_2$: C, 48.33; H, 2.43. Found: C, 48.59; H, 2.41. Continued elution of the chromatography column afforded **7** (127 mg, 12%). Recrystallization of this material from CH_2Cl_2 afforded pure **7** as a colorless microcrystalline solid, mp 292 °C lit.[1a] mp 291-292 °C). The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained agreed with the corresponding values reported in the literature for **7**.[1a]

Diels-Alder reaction of 1 with 5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene. A solution of **1** (620 mg, 2.76 mmol) and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**2b**, 1.50 g, 5.69 mmol) in dry xylene (10 mL) was refluxed under argon for 64 h. The progress of the reaction was monitored periodically via ^{1}H NMR spectroscopy. The reaction mixture was allowed to cool, and solvent was removed *in vacuo*. The residue was purified via column chromatography on silica gel by using 4:1 hexane-EtOAc as eluent. The first chromatography fraction afforded **8** (756 mg, 56%). Recrystallization of this material from EtOAc-hexane afforded pure **8** as a colorless microcrystalline solid: mp 191 °C; IR (KBr) 2979 (w), 2937 (w), 1756 (s), 1734 (s), 1598 (w), 1450 (w), 1267 (w), 1203 (m), 1190 (s), 1133 (m), 1091 (m), 781 (m), 717 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.94 (*A*B, J_{AB} = 11.3 Hz, 1 H), 2.09 (A*B*, J_{AB} = 11.3 Hz, 1 H), 2.68-1.95 (m, 6 H), 3.14 (dt, J = 9.4, 2.4 Hz, 1 H), 3.53 (s, 3 H), 3.61 (s, 3 H), 3.74 (d, J = 9.5 Hz, 1 H), 5.61 (dd, J = 10.7, 2.5 Hz, 1 H), 5.98 (dd, J = 10.7, 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 39.47 (d), 41.15 (t), 42.40 (d), 43.15 (d), 43.34 (d), 43.55 (d), 46.39 (d), 47.39 (s), 49.27 (s), 51.56 (q), 52.90 (q), 53.73 (d), 55.39 (d), 77.88 (s), 78.64 (s), 113.7 (s), 124.6 (d), 125.2 (d), 128.1 (s), 131.4 (s), 210.5 (s), 211.4 (s). Anal Calcd for $C_{22}H_{18}Cl_4O_4$: C, 54.13; H, 3.62. Found: C, 54.26; H, 3.79. Continued elution of the chromatography column afforded **9** (194 mg, 17%). Recrystallization of this material from EtOAc-hexane afforded pure **9** as a colorless microcrytalline solid, mp 235-236 °C lit.[12] mp 232-233 °C). The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained agreed with the corres-ponding values reported in the literature for **9**.[12]

X-ray Structures of 6 and 8. All data were collected on an Enraf-Nonius CAD-4 diffractometer by using the ω (**6**) or ω–2θ (**8**) scan technique, Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator. Standard procedures used in our laboratory for this purpose have been described previously.[13] Pertinent X-ray data are given in Table 4. Data were corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods (MULTAN[14]) and the model was refined by using full-matrix least-squares techniques. The treatment of thermal parameters was based on the number of observed data. In **6**, the Cl, O, and methylene carbon atoms were treated anisotropically, whereas in **8**, sufficient data were available to enable all non-hydrogen atoms to be treated anisotropically. Hydrogen atoms were located on difference maps and then were included in the model in idealized positions {U(H) = 1.3 B_{eq}(C)]. All computations other than those specified were performed by using MolEN.[15] Scattering factors were taken from the usual sources.[16]

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Table 4. X-ray structure data for **6** and **8**.

Compound	**6**	**8**		**6**	**8**
Formula	$C_{20}H_{12}Cl_6O_2$	$C_{22}H_{18}Cl_4O_4$	D_c (g-cm^{-3})	1.695	1.554
Size (mm)	.24 x .35 x .42	.08 x .35 x .65	μ (cm^{-1})	9.02	5.96
Space Group	$P2_1/c$	P1-bar	ω–2θ (2θ_{max})	44	44
a (Å)	9.6393 (6)	8.4579 (7)	Total refl.	5245	2551
b (Å)	23.957 (2)	11.7373 (6)	Unique refl.	4915	2551
c (Å)	17.344 (1)	12.4735 (8)	R_{int}	0.027	- -
α (°)	90	65.614 (5)	$I \geq 3\sigma(I)$	2122	2239
β (°)	103.394 (5)	87.174 (6)	Parameters	305	271
γ (°)	90	68.715 (5)	R, wR	.042, .045	.034, .035
V (Å^3)	3896.3 (5)	1043.4 (1)	$(\Delta/\sigma)_{max}$	<0.01	<0.01
Z	8	2	ρ_{min}; ρ_{max}	0.28; -0.16	0.26; -0.23

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