Organic Reactions at High Pressure. Cycloadditions with Enol and Dienol Derivatives[1]

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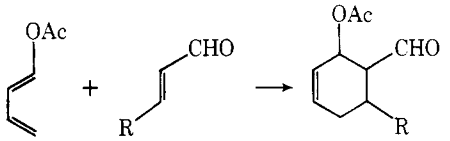
Cycloaddition reactions between 1-acetoxybutadiene and various monofunctionalized (CHO, $COCH_3$, CO_2CH_3, and CN) ethylenes (i.e., acrylic dienophiles) or propylenes (i.e., crotonic dienophiles) under the influence of 15 000 atm pressure and room temperature have been studied. With the acrylic dienophiles only the ortho-cis cycloadducts were obtained in fair to good yields; with the crotonic dienophiles only crotonaldehyde gave the desired cyclized product in 5% yield. The diminished reactivity of the crotonic dienophiles compared to their acrylic counterparts is ascribed to the combination of unfavorable steric and electronic effects brought about by the introduction of the β-methyl group. Similar results were found when 1-methoxybutadiene was employed as the diene component. No cycloaddition products were generated from ethyl vinyl ether and 1-carboalkoxybutadienes (Diels–Alder reactions with inverse electron demand) under the high pressure conditions. The utilization of high pressures (15 000–20 000 atm) and moderate temperatures (24–110 °C) provides a valuable synthetic technique in preparation of 2-alkoxy-3,4-dihydro-2*H*-pyrans from α,β-unsaturated aldehydes or ketones and vinyl ethers (heterodiene synthesis) since the high-pressure reactions can be conducted at temperatures substantially lower than those required when the reactions are carried out at atmospheric pressure. The steric and electronic effects of methyl substitution on the diene and/or dienophile are described.

The formation of a six-membered carbocyclic ring by the [4 + 2] cycloaddition process is a reaction sequence which has found extensive synthetic utilization.[3] Of the many variable parameters which could be changed to affect the success of the cycloaddition process, most attention has been directed to the study of electronic, steric, and thermal effects, and Lewis acidity catalysis. The [4 + 2] cycloaddition reaction generally possesses the interesting property of having the volume occupied by the transition state smaller than the volume occupied by the reactants, i.e., the reaction possesses a negative $\Delta V^{\ddagger}$. Indeed, this property of the cycloaddition process has led to many studies focused on the kinetic and the thermodynamic aspects of the reaction sequence as a means of gaining insight into the mechanism of the reaction sequence.[4-8] Such studies have clearly indicated that the cycloaddition reaction should proceed more readily under very high pressure since a reaction with a negative $\Delta V^{\ddagger}$ should experience an enhanced reaction rate under such conditions. Although the utility of very high pressure (8000–20 000 atm) in organic synthesis is conceptually obvious, such a parameter has not, in fact, been adequately explored.[9-11]

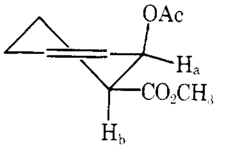
When reactions are performed at these very high pressures, the system does not follow the ideal rate equation since the $\Delta V^{\ddagger}$, itself, is pressure dependent. However, for cycloaddition reactions with a $-\Delta V^{\ddagger}$ of ~25 ml/mol, the rule of thumb, based upon experimental findings, is that above 1000 atm pressure (1 kbar), every kbar increase doubles the rate of the reaction.[7] Thus, the rate enhancement closely follows the general temperature dependency and indicates that a cycloaddition which occurs at 100 °C at atmospheric pressure could be achieved at 20 °C with a pressure of 9–10 kbar. The initial studies in this laboratory of the cycloaddition of heat-sensitive enamines and dienamines to electrophilic olefins at room temperature clearly demonstrated the synthetic utility of synthesis at very high pressure.[12] This study has now been extended to the cycloaddition of derivatives of enols and dienols to electron-poor unsaturated systems.

Results and Discussion

A. Cycloadditions with 1-Acetoxybutadiene. In 1947 Wichterle and Hudlicky reported that 1-acetoxybutadiene could serve as the diene component in a Diels–Alder reaction with acrolein (**1a**) to produce the cycloadduct **2a** in 50% yield after 4 h at 100 °C.[13] Similarly, the use of crotonaldehyde (**1b**) as the dienophile gave the cycloadduct **2b** in 20% yield after 4 h at 130 °C. These transformations (eq 1) as well as some related reactions have been examined at very high pressure and the results are summarized in Table I; in no case have the reaction conditions been optimized. In each case the cycloadduct consisted of only one diastereomer based upon NMR and GC analyses. Decoupling experiments showed that the acetoxy group and the Y substituent (see Table I) were situated ortho-cis to one another, a result in complete accord with the documented[2] regioselectivity and stereospecificity of the Diels–alder reaction and consistent with the dipolar natures of the reactants. For example, it was demonstrated that upon irradiation of the olefinic protons of the cycloadduct obtained from 1-acetoxybutadiene and methyl acrylate (entry 5) proton H_a is resolved into a doublet with a coupling constant of 4 Hz; such a *J* value is consonant with protons H_a and H_b being in a pseudoequatorial/axial arrangement as depicted in formula **3**.[14]



1 2
a, R = H
b, R = CH_3
(1)



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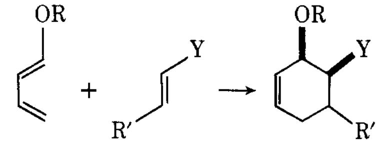
As can be seen from the data in Table I, the employment of very high pressure in the reaction of acrolein with 1-acetoxybutadiene offers a significant improvement in the yield of the cycloadduct **1a** as compared to the thermally promoted reaction. In the case of crotonaldehyde, however, the high-pressure procedure gave cycloadduct **2a** in a significantly lower yield than did the thermal reaction; considerable polymerization of the reactants attended the high-pressure experiment (entry 2). Likewise, substantial amounts of polymer were produced when methyl acrylate or acrylonitrile (entries 5 and 7, respectively) served as dienophiles. With the exception of crotonaldehyde (entry 2), none of the crotonic dieno-

Table I. Products from Cycloadditions with 1-Acetoxybutadiene[a]



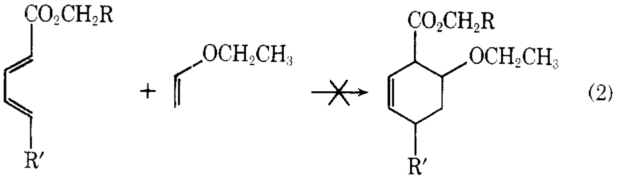
Registry no.	Entry	R	R′	Y	Time, h	Yield,[b,c] %
	1	CH_3CO	H	CHO	4	81[d]
	2	CH_3CO	CH_3	CHO	11	5[e]
	3	CH_3CO	H	$COCH_3$	4	45[d]
	4	CH_3CO	CH_3	$COCH_3$	11	0[e]
60581-96-6	5	CH_3CO	H	CO_2CH_3	4	19[e]
	6	CH_3CO	CH_3	CO_2CH_3	4	0[e]
60581-97-7	7	CH_3CO	H	CN	4	5[d]
	8	CH_3CO	CH_3	CN	12	0[e]
	9	CH_3	H	CHO	4	47[d]
60581-98-8	10	CH_3	CH_3	CHO	4	30[e]
	11	CH_3	CH_3	CO_2CH_3	12	0[d]

[a] All reactions were conducted at 15 000 atm pressure and room temperature for the times indicated. [b] Yields refer to isolated, purified materials. [c] All products displayed NMR, IR, and MS data consistent with the assigned structures. All new compounds gave satisfactory combustion analyses. [d] Unreacted starting material. [e] Unreacted starting material and polymer.

philes (entries 4, 6, and 8) gave any monomeric products. The diminished reactivity of the crotonic dienophiles compared to their acrylic counterparts very likely reflects a retardation of the rate of cycloaddition as a consequence of the combination of unfavorable steric and electronic effects imparted by the β-methyl group.

In addition to the cycloadditions of 1-acetoxybutadiene (entries 1–8), a few cycloaddition reactions with 1-methoxybutadiene (entries 9–11) were investigated. Again, a single diastereomeric cycloadduct was produced from each reaction (entries 9 and 10), and homonuclear decoupling experiments showed that the methoxy and formyl groups were disposed in an ortho-cis arrangement. The thermally induced reactions have been reported to take place in yields of 62% (100 °C, 3 h) with acrolein and 55% (150 °C, 6 h) with crotonaldehyde,[15] which are somewhat better than the high pressure promoted reactions.

B. Cycloadditions with 1-Carboalkoxybutadienes. The cycloadditions assembled in Table I are examples of Diels–Alder reactions with normal electron demand. Diene syntheses with *inverse electron demand*[3] have also been studied in which the diene component has an electron-withdrawing carbonyl group attached to a terminus and the dienophile is an enol ether (eq 2). In no case was the desired cycloadduct produced in detectable amount. Thus, at 15 kbar and 25 °C, 1-carbomethoxybutadiene (**4a**) and ethyl vinyl ether gave only polymeric material. Only starting materials were recovered when ethyl sorbate (**4b**) and ethyl vinyl ether were allowed to react at 15 kbar and room temperature, while when the reactions were carried out under more forcing conditions (15 kbar and 87 °C or 40 kbar[16] and room temperature) only polymeric material was produced. Subjecting the doubly activated diene dimethyl muconate (**4c**) and ethyl vinyl ether to 15 kbar pressure and 25 °C resulted in no reaction. The results of the present study may be contrasted with those reported previously for enamines in which generally high yields (greater than 80%) of cycloadducts are obtained from the very high pressure induced inverse Diels–Alder reactions.[12]

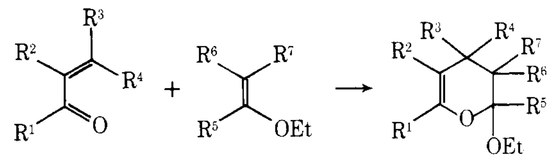


4

(2)

a, R = R′ = H
b, R = R′ = CH_3
c, R = H; R′ = CO_2CH_3

C. Heterodiene Synthesis with Vinyl Ethers. In 1950 Longley and Emerson described the thermally promoted cycloadditions of enol ethers and α,β-unsaturated aldehydes and ketones (eq 3).[17] The dihydropyran adducts have proved to be useful synthetic intermediates[18] and research on this cycloaddition process remains active.[19] A systematic investigation on the utilization of high pressure for the heterodiene synthesis has been undertaken and the results are collected in Table II. Inspection of the data in Table II reveals several interesting features. For the reactions involving acrolein and enol ethers (entries 12–14) respectable yields of cycloadducts were obtained from the high-pressure experiments compared to the purely thermal reactions. As anticipated, increasing the number of β-methyl groups on the dienophile from zero (entry 12) to two (entry 14) brought about successive, moderate reductions in the yields of dihydropyran formation, probably reflecting the retardation of the rate of reaction as a consequence of steric hindrance in the transition state. The fact that more drastic reductions in yields were not observed is ascribable to the enhancement of the dienophilicity by the electron-donating inductive effects of the methyl groups which tend to counteract the unfavorable steric effects.



(3)

For the reactions of crotonaldehyde with various enol ethers (entries 17–19) external heating was required to render the yields of cycloadduct production satisfactory. Thus, when crotonaldehyde and ethyl vinyl ether were subjected to 15 kbar pressure for 19 h at room temperature only about a 30% yield of the desired dihydropyran was produced; unreacted starting materials made up the remainder of the material balance. When the reaction was conducted at 15 kbar pressure and 75 °C, the cycloadduct was obtained in 89% yield. Crotonaldehyde and ethyl propenyl ether failed to react when subjected to 15 kbar pressure at room temperature, but did provide a 35% yield of cycloadduct when the reaction was carried out at 15 kbar pressure and 100 °C (entry 18). For the

Table II. Products from the Heterodiene Synthesis

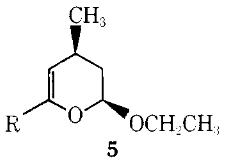
								High pressure reaction data				Thermal reaction data			
Entry	R^1	R^2	R^3	R^4	R^5	R^6	R^7	P, kbar	t, h	T,[a] °C	%[b]	t, h	T, °C	%[b]	Ref
12	H	H	H	H	H	H	H	15	20	RT	69	12	140	84	17a
13[d]	H	H	H	H	H	H	CH_3	15	23	RT	53[e]			28	*f*
14	H	H	H	H	H	CH_3	CH_3	15	20	RT	44	3	180	54	*g*
15	H	H	H	H	CH_3	H	H	15	19	RT	23	16	130	50	17a
16	H	CH_3	H	H	H	H	H	15	20	RT	0	21	150	40	17a
17	H	H	CH_3	H	H	H	H	15	24	75	89	15	175	87	17a
18[d,k]	H	H	CH_3	H	H	H	CH_3	15	20	100	35[h]				
19	H	H	CH_3	H	H	CH_3	CH_3	15	20	100	0				
20	H	H	C_6H_5	H	H	H	H	15	24	75	95	12	180	60	17a
21	CH_3	H	H	H	H	H	H	15	20	RT	62	16	140	50	17a
22[l]	CH_3	H	CH_3	H	H	H	H	15	20	110	68				
23	CH_3	H	CH_3	CH_3	H	H	H	20	18	110	50	18	200	0	*h*
24	H	H	H	H	OC_2H_5	H	H	15	2	RT	39	14	125	70	*i*
25	H	H	CH_3	H	OC_2H_5	H	H	15	2	RT	9				
26	CH_3	H	H	H	OC_2H_5	H	H	15	2	RT	0	16	125	24	*i*

[a] RT stands for room temperature, nominally about 24 °C. [b] Yields refer to isolated, purified materials. All products displayed NMR, IR, and MS data consistent with assigned structures; all new products gave satisfactory combustion analyses. [d] The ethyl propenyl ether used consisted of a 68:32 mixture of the cis ($R^7 = CH_3$) and trans ($R^6 = CH_3$) isomers. [e] Product consisted of a 61:39 mixture of cis and trans cycloadducts; see Experimental Section. [f] G. Descotes, J.-C. Martin, and N. Mathicolonis, *Bull. Soc. Chim. Fr.*, 1077 (1972). [g] K. C. Brannock, *J. Org. Chem.*, **25**, 258 (1960). [h] Product consisted of an inseparable mixture of diastereomers. [i] This work. [j] V. M. Thuy, *Bull. Soc. Chim. Fr.*, 4429 (1970). [k] Registry no., 322-32-7. [l] Registry no., 60581-99-9.

reaction of crotonaldede and ethyl isobutenyl ether (entry 19) no cycloadduct was produced even after 20 h at 15 kbar pressure and 100 °C. The diminished reactivity of crotonaldehyde compared to the corresponding reactions with acrolein is attributable to the β-methyl group which introduces steric hindrance in the transition state and also renders the diene less electron poor as a consequence of induction.

Additional insight on the effects of alkyl substitution on the diene component was gained by studying the reactions of a series of α,β-unsaturated ketones with ethyl vinyl ether (entries 21–23). With methyl vinyl ketone the dihydropyran cycloadduct was obtained in 62% yield after 20 h at 15 kbar pressure and room temperature. With pent-3-en-2-one and ethyl vinyl ether no reaction took place at 15 kbar pressure and room temperature, but at 15 kbar pressure and 110 °C, a 68% yield of the cycloadduct was obtained. With mesityl oxide (which bears two β-methyl groups) and ethyl vinyl ether only a trace of the desired product was generated (according to NMR analysis) after 20 h at 15 kbar pressure and 110 °C, but by increasing the pressure to 20 kbar and maintaining the temperature at 110 °C a 50% yield of the dihydropyran was achieved. When this latter reaction was conducted in a normal sealed tube at 200 °C only unreacted starting materials and a small amount of polymer were recovered. Thus, the combination of very high pressure and moderate temperatures is extremely effective in overcoming the combined adverse steric and electronic effects which can occur in the heterodiene cycloaddition process.

For the reactions involving crotonaldehyde or pent-3-en-2-one with ethyl vinyl ether (entries 17 and 22, respectively) two stereoisomeric cycloadducts are possible, depending upon whether the 4-methyl group and the ethoxy group are cis (**5**)



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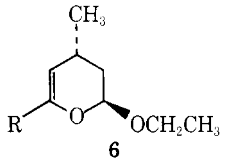

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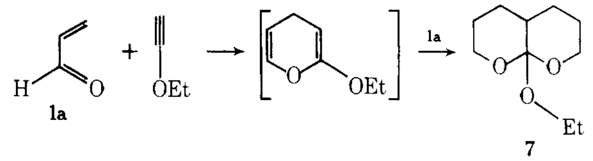
a, R = H
b, R = CH_3

or trans (**6**) to one another. In the high-pressure experiment with *trans*-crotonaldehyde, a single dihydropyran cycloadduct was produced whose NMR spectrum is identical with that of authentic *cis*-2-ethoxy-4-methyl-3,4-dihydro-2*H*-pyran (**5a**).[20] Likewise, *trans*-pent-3-en-2-one reacted in a highly stereoselective manner to afford a 10:1 mixture of diastereomers (as determined by GC analysis). Previous results have demonstrated that the cis isomer (i.e., **5a** or **5b**) predominates in heterodiene syntheses involving β-substituted α,β-unsaturated aldehydes or ketones and β-unsubstituted vinyl ethers.[21]

Several other miscellaneous heterodiene synthesis reactions have been investigated at high pressure. Substitution of vinyl acetate for ethyl vinyl ether and isopropenyl acetate for ethyl isopropenyl ether in reactions with acrolein led only to polymeric materials after subjection to 15 kbar pressure. Similarly, 1-ethoxycyclopentene or dihydropyran and acrolein gave mostly polymeric material in addition to some unconsumed reactants.[22] Employment of 1,1-diethoxyethylene was expected to produce substantial improvements in the yields of dihydropyran adducts compared to those attained with ethyl vinyl ether. However, polymerization of the reactants was the predominant reaction course, and relative to the thermally promoted reactions[23] the yields of cycloadducts from the high-pressure reactions (entries 24–26) are low. Likewise, utilizing 1-ethoxyacetylene as the dienophile in the heterodiene synthesis was not very successful owing to extensive polymer formation; only with acrolein was any cycloadduct obtained, which consisted entirely of the bis adduct **7** (eq 4).



(4)

Conclusion

The utilization of very high pressures (15 000–20 000 atm) as a technique in organic synthesis has been a valuable parameter. While the results presented here for the [4 + 2] cycloadditions involving enol and dienol derivatives have not been as highly successful as those reported by us previously for the Diels–Alder reactions of enamines and dienamines[12]

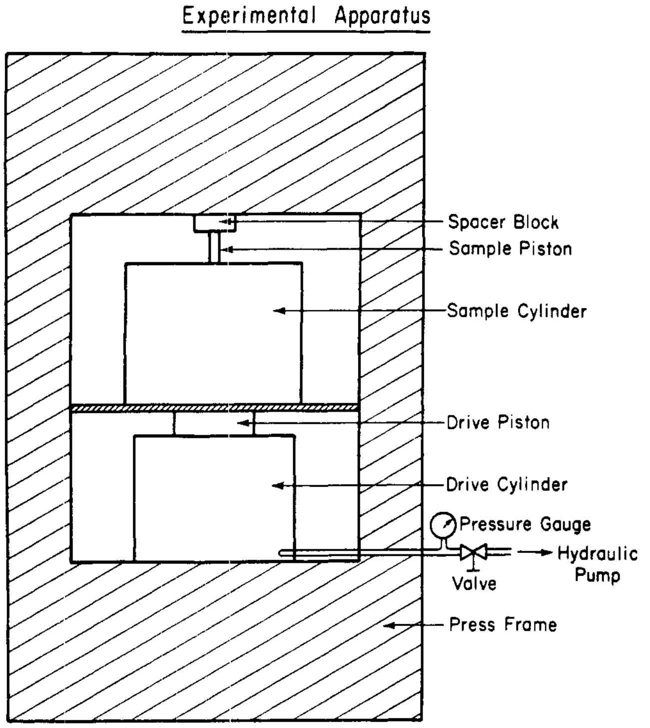


Figure 1. Schematic representation of apparatus for high-pressure experiments.

or furans,[24] the high-pressure procedure does provide the important advantage of being able to carry out reactions at temperatures substantially lower than those required at atmospheric pressure.

Experimental Section

Apparatus.[25] Figure 1 presents a schematic version of the equipment used in our high-pressure studies. The apparatus consists essentially of a press frame, a drive cylinder, and a sample cylinder. The press frame was made from 8-in. thick hot rolled plate steel; its exterior dimensions are 5 ft long by 3 ft wide, and the cavity for the drive and sample cylinders measures 3 ft long by 2 ft wide. The drive cylinder (fabricated from hardened S-5 tool steel) is shown diagrammatically in Figure 2. The cylinder body is 13 in. long by 12 in. diameter, and the piston assembly has a diameter of 6 in. The two-stage arrangement of the piston and piston head provides for a Bridgeman unsupported-area seal. The sample cylinder system (also made from S-5 tool steel) consists of a cylinder body which measures 8 in. o.d. by 2 in. i.d. by 8 in. long, and a hardened 2 in. o.d. by 0.75 in. i.d. liner which is press-fitted into the bore of the cylinder body; a 0.5 in. thick wall aluminum tube is employed as a safety shield around the cylinder body (Figure 3). The bottom of the liner bore is stoppered by means of a stationary plug, which like the moveable piston at the top is equipped with a combination O-ring and delta ring sealing assembly to prevent leakage of the pressure transmitting fluid (kerosene) during pressurization. The reaction vessel is merely an annularly bellowed copper tube with a nut and bolt assembly at the top to contain the sample.

Carrying out a high-pressure reaction is simple. The sample tube is filled completely with the reactants and an appropriate solvent, sealed with a lead washer, and immersed in the kerosene-filled bore of the cylinder. The sample piston is seated at the top of the bore, and then forced into the bore by raising the sample cylinder by means of a hydraulic pump until the desired applied pressure is attained. To conduct a reaction at elevated temperature the sample cylinder system is first heated to the desired temperature with a tubular heating mantel. At the conclusion of the high-pressure experiment the pressure is relieved and the reaction processed in the usual fashion.

Materials. 1-Acetoxybutadiene,[26] 1-methoxybutadiene,[27] 1-carbomethoxybutadiene,[28] dimethyl muconate,[29] ethyl propenyl ether,[30] ethyl isobutenyl ether,[31] ethyl isopropenyl ether,[32] and 1,1-diethoxyethylene[33] were prepared and purified according to literature procedures; other reagents were available from commercial sources.

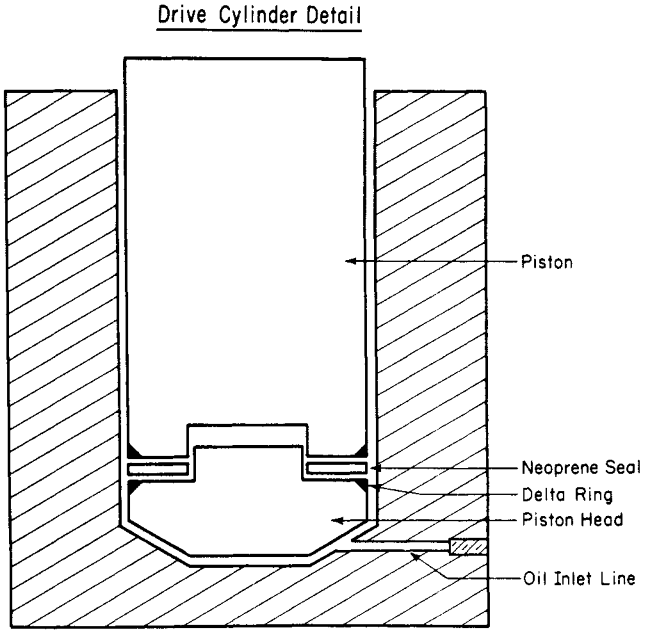


Figure 2. Detailed schematic version of the drive cylinder component of the high-pressure apparatus.

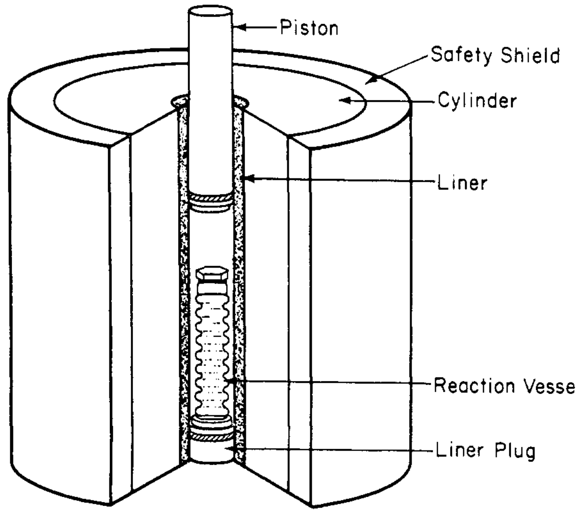


Figure 3. Detailed sketch of the sample cylinder system for high-pressure experiments.

General. Boiling points are uncorrected. Infrared spectra were obtained as neat films with a Perkin-Elmer 137 or 710A spectrometer. Nuclear magnetic resonance spectra were recorded as solutions in carbon tetrachloride with internal Me_4Si on a Varian Associates T-60 or Hitachi Perkin-Elmer R24B spectrometer. Gas chromatographic analyses and collections were performed on a Hewlett-Packard 5700A instrument utilizing a 10 ft by 0.25 in. diameter stainless steel column packed with 10% SE-30 on Chromosorb W. Mass spectra were measured at 70 eV on a MS-12 instrument. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley. Representative high-pressure experiments are detailed below. Complete spectral data for all new monomeric products obtained in the present investigation appear in the microfilm edition; see paragraph at end of paper regarding supplementary material.

***cis*-1-Acetoxy-2-acetylcyclohex-5-ene.** A solution of 1-acetoxybutadiene (1.30 g, 11.6 mmol) and methyl vinyl ketone (0.86 g, 12.3 mmol) in diethyl ether (approximately 10 ml) was subjected to 15 000 atm hydrostatic pressure for 4 h at 24 °C, after which the reaction mixture was filtered to remove a small amount of white, sticky material plus starting material. The filtrate was concentrated on a rotary evaporator to give 1.62 g of a clear, slightly yellow liquid which was distilled (bp 76–79 °C, 0.30 Torr) to provide 0.94 g (45%) of the pure cycloadduct as a clear, colorless liquid: NMR δ 5.5–6.3 (m, 3, olefinic and $\mathrm{C\mathbf{H}OCOCH_3}$), 2.4–2.8 (m, 1, $\mathrm{C\mathbf{H}COCH_3}$), 1.7–2.4 (m, 4, $\mathrm{C\mathbf{H}_2C\mathbf{H}_2}$), 2.10 (s, 3, $\mathrm{CHOCOC\mathbf{H}_3}$), 1.93 (s, 3, $\mathrm{CHCOC\mathbf{H}_3}$); IR 3040, 1730, 1710, 1240 cm^{-1}; MS *m/e* (rel intensity) 122 (52, M − $\mathrm{CH_3CO_2H}$), 107 (44, M − $\mathrm{CH_3CO_2H}$ − $\mathrm{CH_3}$), 78 (100).

Anal. Calcd for $\mathrm{C_{10}H_{14}O_3}$: C, 65.92; H, 7.74. Found: C, 66.19; H, 7.81.

***cis*-1-Methoxy-2-formylcyclohex-5-ene.** A solution of 1-methoxybutadiene (0.42 g, 5 mmol) and acrolein (0.5 ml, 7.5 mmol) in diethyl ether (10 ml) was held at 15 000 atm pressure for 4 h at room temperature, after which the reaction mixture was concentrated to afford 0.73 g of a clear, colorless liquid which was distilled (bp 45–46 °C, 0.40 Torr) to provide 0.33 g (47%) of the pure cycloadduct as a colorless oil: NMR δ 9.65 (s, 1, CHO), 5.8–6.2 (m, 2, olefinic), 4.1 (m, 1, $\mathrm{C\mathbf{H}OCH_3}$), 3.36 (s, 3, $\mathrm{OCH_3}$), 1.6–2.6 (m, 5, $\mathrm{C\mathbf{H}C\mathbf{H}_2C\mathbf{H}_2}$); IR 3030, 2820, 2720, 1720, 1085 cm^{-1}; MS *m/e* (rel intensity) 108 (36, M − $\mathrm{CH_3OH}$), 84 (45), 79 (100).

Anal. Calcd for $\mathrm{C_8H_{12}O_2}$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.53.

***cis*- and *trans*-2-Ethoxy-3-methyl-3,4-dihydro-2*H*-pyrans.** Ethyl propenyl ether (2.90 g, 33.7 mmol) as a 68:32 mixture of cis and trans isomers and acrolein (1.86 g, 33.2 mmol) in diethyl ether (40 ml) were allowed to react under the influence of 15 000 atm hydrostatic pressure for 23 h at room temperature, after which the solution was concentrated to a clear, colorless liquid (2.50 g, 53%) which contained a trace amount of starting material. Pure material consisting of a 61:39 mixture of **7** and **8** according to GC analysis was obtained by distillation (bp 44–45 °C, 13.5 Torr).

Anal. Calcd for $\mathrm{C_8H_{14}O_2}$: C, 67.57; H, 9.92. Found: C, 67.28; H, 9.68.

Pure samples of the cis and trans isomers were obtained by preparative GC. Cis adduct: NMR δ 6.07 (d of t, *J* = 6, 1 Hz, 1, =CHO), 4.89 (d, *J* = 1 Hz, 1, O–CH–O), 4.6 (m, 1, $\mathrm{C\mathbf{H}{=}CH{-}O}$), 3.62 (m, 2, $\mathrm{OCH_3}$), 1.83 (m, 3, $\mathrm{C\mathbf{H}_2C\mathbf{H}}$), 1.35 (t, *J* = 7 Hz, 3, $\mathrm{CH_2C\mathbf{H}_3}$), 0.95 (d, *J* = 6 Hz, 3, $\mathrm{CHC\mathbf{H}_3}$); IR 3020, 1645, 730 cm^{-1}; MS *m/e* (rel intensity) 142 ($\mathrm{M^+}$, 18), 97 (15), 86 (82), 58 (100), 57 (35). Trans adduct: NMR δ 6.08 (d of t, *J* = 6, 1 Hz, 1, C=CHO), 4.6 (m, 1, $\mathrm{C\mathbf{H}{=}CH{-}O}$), 4.50 (d, *J* = 4 Hz, 1, $\mathrm{OC\mathbf{H}OCH_2}$), 3.64 (m, 2, $\mathrm{OCH_2}$), 1.3–2.6 (m, 3, $\mathrm{C\mathbf{H}_2C\mathbf{H}}$), 1.20 (t, *J* = 6 Hz, 3, $\mathrm{CH_2C\mathbf{H}_3}$), 0.96 (d, *J* = 7 Hz, 3, $\mathrm{CHC\mathbf{H}_3}$); IR 3025, 1650, 732 cm^{-1}; MS *m/e* (rel intensity) 142 ($\mathrm{M^+}$, 15), 97 (12), 86 (75), 58 (100), 57 (36).

***cis*-2-Ethoxy-4-methyl-3,4-dihydro-2*H*-pyran (5a).** Crotonaldehyde (3.50 g, 50 mmol) and ethyl vinyl ether (10 ml, 100 mmol) dissolved in diethyl ether (total volume approximately 50 ml) were subjected to 15 kbar pressure at 75 °C for 20 h, after which the solvent and unreacted starting materials were removed on a rotary evaporator providing 6.30 g (89%) of **5a** as a clear, colorless liquid whose NMR and IR spectra and gas chromatogram revealed the product to be pure: NMR δ 6.10 (d of d, *J* = 6, 2 Hz, 1, =CHO), 4.79 (d of d, *J* = 8, 2 Hz, 1, O–CH–O), 4.5 (m, 1, $\mathrm{C\mathbf{H}{=}CH{-}O}$), 3.60 (m, 2, $\mathrm{OCH_2}$), 1.4–2.6 (m, 3, $\mathrm{C\mathbf{H}C\mathbf{H}_2}$), 1.17 (t, *J* = 7 Hz, 3, $\mathrm{CH_2C\mathbf{H}_3}$), 1.01 (d, *J* = 7 Hz, 3, $\mathrm{CHC\mathbf{H}_3}$); IR 3025, 1639, 740 cm^{-1}; MS *m/e* (rel intensity) 142 ($\mathrm{M^+}$, 12), 99 (13), 97 (19), 96 (24), 72 (82), 44 (100).

2-Ethoxy-4,4,6-trimethyl-3,4-dihydro-2*H*-pyran. A solution of mesityl oxide (2.50 g, 25.5 mmol) and ethyl vinyl ether (5.0 ml, 50 mmol) in approximately 20 ml of ethyl ether was subjected to 20 000 atm pressure for 18 h at 110 °C. The solution was concentrated to a clear, colorless liquid whose NMR spectrum indicated that the material consisted of the dihydropyran cycloadduct and mesityl oxide in a ratio of about 1:1. By distillation 2.12 g (50%) of pure product was obtained as a clear, water-white liquid: bp 69–70 °C (14 Torr); NMR δ 4.78 (t, *J* = 5 Hz, 1, $\mathrm{OC\mathbf{H}OCH_2CH_3}$), 4.20 (s, 1, =CH), 3.60 (m, 2, $\mathrm{OC\mathbf{H}_2CH_3}$), 1.67 (s, 3, $\mathrm{{=}CCH_3}$), 1.54 (d, *J* = 5 Hz, 2, $\mathrm{CHC\mathbf{H}_2}$), 1.16 (t, *J* = 7 Hz, 3, $\mathrm{OCH_2C\mathbf{H}_3}$), 1.03 (s, 3, $\mathrm{CCH_3}$), 0.98 (s, 3, $\mathrm{CCH_3}$); IR 3020, 1660, 787 cm^{-1}; MS *m/e* (rel intensity) 170 ($\mathrm{M^+}$, 17), 155 (21), 125 (12), 109 (17), 85 (16), 83 (28), 81 (11), 73 (11), 72 (100), 44 (58), 43 (97).

Anal. Calcd for $\mathrm{C_{10}H_{18}O_2}$: C, 70.55; H, 10.66. Found: C, 70.28; H, 10.46.

2,2-Diethoxy-4-methyl-3,4-dihydro-2*H*-pyran. An ethereal solution of crotonaldehyde (0.86 g, 12.3 mmol) and 1,1-diethoxyethylene (1.42 g, 13.6 mmol) and a few milligrams of hydroquinone was held at 15 kbar pressure for 4 h at room temperature, after which the reaction mixture was filtered to remove a substantial amount of intractible material and the filtrate concentrated and distilled (bp 40 °C, 0.2 Torr) to provide 0.216 g (9%) of pure product as a clear, colorless liquid: NMR δ 6.09 (d of d, *J* = 7, 2.5 Hz, 1, =CHO), 4.52 (d of t, *J* = 7, 2.5 Hz, 1, $\mathrm{CHC\mathbf{H}{=}CH}$), 3.54 (q, *J* = 7 Hz, 4, $\mathrm{OCH_2}$ and $\mathrm{OCH_2}$), 1.3–2.8 (m, 3, $\mathrm{C\mathbf{H}C\mathbf{H}_2}$), 1.19 (t, *J* = 6 Hz, 3 H, $\mathrm{OCH_2CH_3}$), 1.14 (t, *J* = 6 Hz, 3, $\mathrm{OCH_2C\mathbf{H}_3}$), 1.00 (d, *J* = 8 Hz, 3, $\mathrm{CHC\mathbf{H}_3}$); IR 3050, 1645, 735 cm^{-1}; MS *m/e* (rel intensity) 186 ($\mathrm{M^+}$, 12), 141 (57), 116 (51), 113 (89), 97 (29), 89 (44), 87 (22), 71 (47), 69 (40), 61 (31), 55 (27), 45 (35), 43 (100).

Anal. Calcd for $\mathrm{C_{10}H_{18}O_3}$: C, 64.49; H, 9.74. Found: C, 63.90; H, 9.53.

1-Ethoxy-2,10-dioxabicyclo[4.4.0]deca-3,8-diene (7). Acrolein (1.68 g, 28.4 mmol) and ethoxyacetylene (0.8 g, 11.4 mmol) in ethyl ether (total volume 8 ml) was subjected to 15 kbar for 8 h at room temperature, after which the reaction mixture was filtered to remove quite a bit of white polymeric material and the filtrate concentrated to 0.558 g of viscous, yellow liquid whose NMR spectrum indicated it to be mostly polymer. Preparative GC provided samples of **7** as the only volatile product for spectra: NMR δ 6.02 (d of t, *J* = 6, 1.5 Hz, 2, C=CH–O), 4.6 (m, 2, $\mathrm{C\mathbf{H}{=}CH{-}O}$), 3.74 (q, *J* = 7 Hz, 2, $\mathrm{OC\mathbf{H}_2CH_3}$), 2.3–1.6 (m, 5, $\mathrm{C\mathbf{H}_2C\mathbf{H}C\mathbf{H}_2}$), 1.14 (t, *J* = 7 Hz, 3, $\mathrm{OCH_2C\mathbf{H}_3}$); IR 3020, 1650, 733 cm^{-1}; MS *m/e* (rel intensity) 182 ($\mathrm{M^+}$, 5), 154 (30), 137 (27), 126 (54), 125 (48), 108 (16), 98 (93), 97 (100), 81 (19), 80 (14), 79 (16) 70 (32), 69 (21), 68 (12), 57 (12), 55 (30), 53 (18), 43 (13), 42 (28), 41 (47).

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Registry No.—5a, 17322-76-8; **7,** 60581-95-5; *cis*-1-acetoxy-2-acetylcyclohex-5-ene, 60582-00-5; 1-acetoxybutadiene, 1515-76-0; methyl vinyl ketone, 78-94-4; *cis*-1-methoxy-2-formylcyclohex-5-ene, 60582-01-6; 1-methoxybutadiene, 3036-66-6; acrolein, 107-02-8; *cis*-2-ethoxy-3-methyl-3,4-dihydro-2*H*-pyran, 60582-02-7; *trans*-2-ethoxy-3-methyl-3,4-dihydro-2*H*-pyran, 60582-03-8; *cis*-ethyl propenyl ether, 4696-25-7; *trans*-ethyl propenyl ether, 4696-26-8; ethyl vinyl ether, 109-92-2; 2-ethoxy-4,4,6-trimethyl-3,4-dihydro-2*H*-pyran, 60582-04-9; mesityl oxide, 141-79-7; 2,2-diethoxy-4-methyl-3,4-dihydro-2*H*-pyran, 60582-05-0; 1,1-diethoxyethylene 2678-54-8; ethoxyacetylene, 927-80-0.

Supplementary Material Available. NMR and IR spectral data for all new compounds reported here but not described in the Experimental Section (entries 5, 7, 10, 18, and 22), and complete details for the fabrication of the high-pressure apparatus (13 pages). Ordering information is given on any current masthead page.

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Syntheses of the Optically Active Multilayered [2.2]Paracyclophanes with Known Absolute Configurations[1]

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Starting from (*R*)-(−)-4-methyl[2.2]paracyclophane, a series of optically active, multilayered [2.2]paracyclophanes (**10**, **11**, **14**, and **15**) with known absolute configurations were synthesized; the "chiral recognition" principle was applied for the preparation of (*R*,*R*,*R*)-(−)-five-layered [2.2]paracyclophane (**14**). The chiroptical properties of these compounds are described.

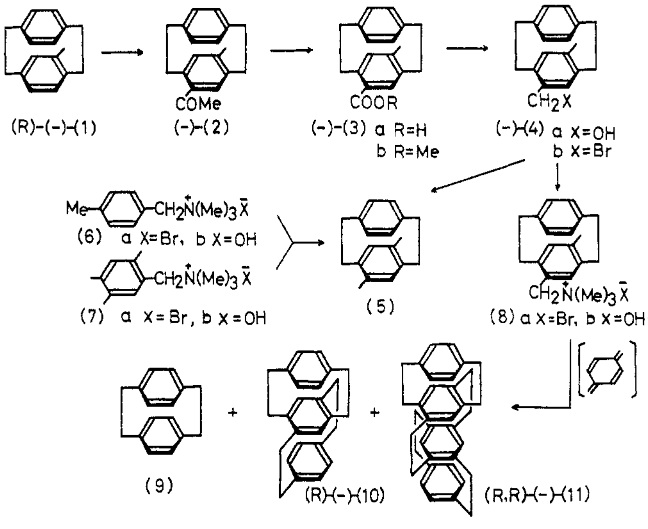
Interesting features about the multilayered [2.2]paracyclophanes with benzene rings closely packed together by means of a *p*-ethano bridge are the distortion of the benzene rings and the transannular interaction caused by the closely spaced face-to-face arrangement of the aromatic rings. Recently, racemic modifications of such multilayered compounds were synthesized and their unusual physical and chemical properties were reported.[2]

In an earlier paper,[3] we reported the preparation of [8][8]- and [8][10]paracyclophanes which have two para bridges spanning the benzene ring giving rise to D_2 and C_2 symmetry, respectively. Upon building up multilayered [2.2]paracyclophanes by Longone's method[2a,b] we also encounter molecules with C_2 or D_2 symmetry, because steric hindrance should cause the formation of molecules with these symmetries to be more favorable. We have been interested in the preparation of these "gyrochiral"[4] compounds with C_2 or D_2 symmetry as well as the chiroptical properties inherent to their helical structures. This contribution is concerned with the synthesis of a series of optically active, multilayered [2.2]paracyclophanes with known absolute configurations.

Results and Discussion

(*R*)-(−)-[3]Chochin (10) and (*R*,*R*)-(−)-[4]Chochin (11).[5] Our general scheme for the preparation of optically active multilayered [2.2]paracyclophanes can be seen in Scheme I, which illustrates the synthetic route to the two- and three-layered [2.2]paracyclophanes, **10** and **11**.

Scheme I



(*R*)-(−)-4-Methyl[2.2]paracyclophane (**1**),[6] whose absolute configuration had been determined, served as our starting material as well as a liaison compound relating the stereochemistry of the [2.2]paracyclophane series to that of our multilayered compounds. Acetylation of **1** with acetyl chloride and anhydrous aluminum chloride afforded the acetyl derivative **2**, which was further converted by a haloform reaction into (*R*)-(−)-carboxylic acid (**3a**), mp 205–206 °C, $[\alpha]^{21}D$ −224°. The methyl ester **3b** of this acid was reduced with lithium aluminum hydride to the alcohol **4a** which was converted into the quaternary ammonium bromide **8a**, mp 213–215 °C, $[\alpha]^{20}D$ −94°, via the bromide **4b**. Since the bromide **4b** is a crucial compound for the following transformations, we established its structure before continuation of our synthesis. Upon lithium aluminum hydride reduction, the bromide **4b** gave a (−)-4,7-dimethyl derivative (**5**), the structure of which was confirmed by the independent synthesis of its racemic modification involving the "cross cou-