A Bimolecular Alternating Inter-Intramolecular Chain Propagation Leading to Cyclocopolymerization

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SUMMARY

This paper includes a report of the original studies which led to postulation of the cyclocopolymerization mechanism. Conditions for the copolymerization experiments, involving copolymerization of a wide variety of 1,4-dienes and alkenes, are reported in addition to the spectral and analytical evidence obtained in support of the proposed structures. Also included are some of the physical properties of the copolymers and some additional chemical evidence in support of the structures.

INTRODUCTION

Although a number of papers have been published from this laboratory [1] dealing with the subject of cyclocopolymerization, the observations which led to the original proposal and the evidence obtained to support this proposal have not been published. Two papers were presented which included some details of the early experiments [2, 3], and a review paper [4] was published which included only the structure of the divinyl ether (DVE)-maleic anhydride (MA) copolymer and a limited number of
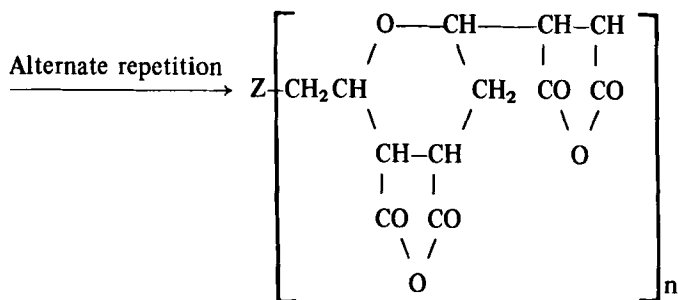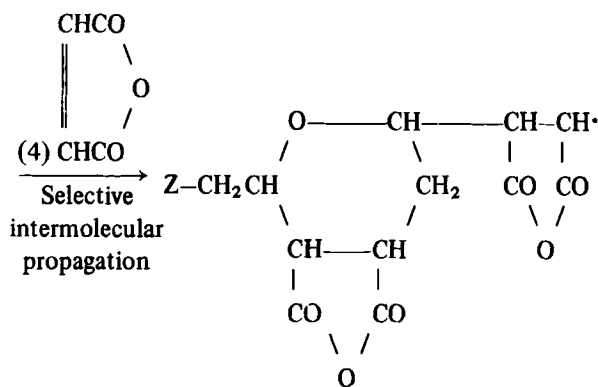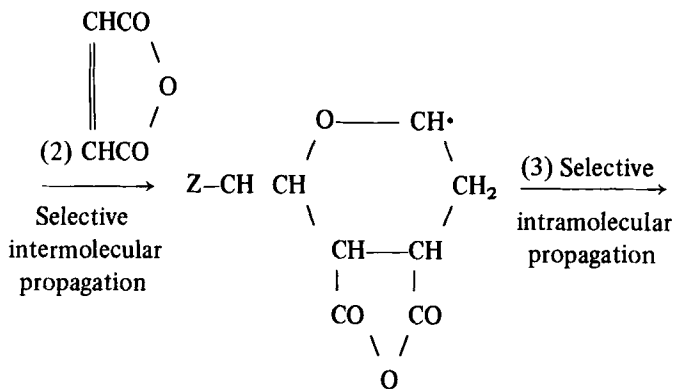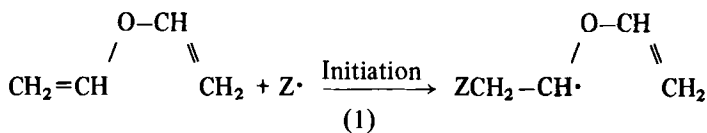
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219

intrinsic viscosity values of some of the other copolymers. Even though the DVE-MA copolymerization was observed to yield soluble, noncross-linked copolymer [2] before the postulation of the alternating intra-intermolecular chain propagation (now known commonly as "cyclopolym-erization") to explain the failure of 1,6-dienes to yield cross-linked polymers [5], it was only after unquestionable evidence had been obtained for the cyclopolymerization mechanism [6] that a plausible explanation for this most unusual behavior in the copolymerization of 1,4-dienes with alkenes was forthcoming. A satisfactory mechanism for this unusual behavior must account for (1) the failure of the system to cross-link in accordance with the widely accepted (at the time) theory of Staudinger [7]; (2) the essential absence of carbon-carbon double bond content in the copolymer; (3) polymer composition equivalent to a diene-olefin molar ratio of 1:2; and (4) essentially quantitative conversion of monomers to copolymer.

Although copolymers of certain 1,6-dienes with a number of well known olefinic monomers have now been reported [8], a fundamental assumption in copolymerizations of this type is that the intramolecular cyclization step involves only the 1,6-diene and all members of the cyclic structure are con-tributed by this comonomer. The DVE-MA copolymerization reported in this paper represents the first example of a cyclopolymerization in which more than one comonomer is involved in the cyclization step which results in formation of cyclic structures containing members contributed by more than one comonomer. The mechanism proposed as shown here assumes that one comonomer, the 1,4-diene, contributes four members to the developing cyclic structure while the other comonomer, the alkene, con-tributes the remaining two members.

The proposed structure for the DVE-MA copolymer is supported by (1) the elemental analysis for the copolymer obtained at high conversion is consistent; (2) the IR spectrum is essentially devoid of residual double bond absorption and contains characteristic absorption bands for cyclic anhydride and six-membered cyclic ether structures; (3) the copolymer composition of 1:2 molar ratio of DVE to MA is consistent with the known reactivity ratios of these types of monomers; and (4) the presence of the cyclic ether group has been confirmed by chemical evidence which involved cleavage by hydri-odic acid and incorporation of iodine into the polymer. Similar but not such extensive evidence has been obtained for the other copolymers reported.

An interesting property found to be associated with certain of these co-polymers, particularly the DVE-MA copolymer, is their physiological action. The DVE-MA copolymer has been found by the Cancer Chemotherapy National Service Center, National Institutes of Health, to be a promising

$$
\begin{array}{c}
\text{O--CH} \\
/ \quad \backslash\!\backslash \\
CH_2{=}CH \qquad CH_2 \;+\; Z\cdot \quad \xrightarrow{\text{Initiation}} \quad ZCH_2{-}CH\cdot \qquad CH_2 \\
(1)
\end{array}
$$

$$
\begin{array}{c}
\text{CHCO} \\
\| \quad \backslash \\
O \\
/ \\
(2)\ \text{CHCO} \\
\xrightarrow[\substack{\text{Selective} \\ \text{intermolecular} \\ \text{propagation}}]{}
\end{array}
\qquad
\begin{array}{c}
\text{O} \rule{1em}{0.4pt} \text{CH}\cdot \\
/ \qquad \backslash \\
Z{-}CH\ CH \qquad\qquad CH_2 \\
\backslash \qquad / \\
CH\rule{1em}{0.4pt}CH \\
|\qquad | \\
CO \quad CO \\
\backslash \ / \\
O
\end{array}
\qquad \xrightarrow[\substack{\text{intramolecular} \\ \text{propagation}}]{(3)\ \text{Selective}}
$$

$$
\begin{array}{c}
\text{CHCO} \\
\| \quad \backslash \\
O \\
/ \\
(4)\ \text{CHCO} \\
\xrightarrow[\substack{\text{Selective} \\ \text{intermolecular} \\ \text{propagation}}]{}
\end{array}
\qquad
\begin{array}{c}
\text{O}\rule{2em}{0.4pt}\text{CH}\rule{2em}{0.4pt}\text{CH-CH}\cdot \\
/ \qquad\qquad \backslash \qquad |\ \ | \\
Z{-}CH_2\,CH \qquad\qquad CH_2 \quad CO\ CO \\
\backslash \qquad\qquad / \qquad \backslash\ / \\
CH\rule{1em}{0.4pt}CH \qquad\quad O \\
|\qquad | \\
CO \quad CO \\
\backslash\ / \\
O
\end{array}
$$

$$
\xrightarrow{\text{Alternate repetition}} \quad Z\!\!\left[\!\!
\begin{array}{c}
\text{O}\rule{1.5em}{0.4pt}\text{CH}\rule{1.5em}{0.4pt}\text{CH-CH} \\
/ \qquad\quad \backslash \qquad |\ \ | \\
CH_2CH \qquad CH_2 \ CO\ CO \\
\backslash \qquad\quad / \qquad \backslash\ / \\
CH{-}CH \qquad\ O \\
|\ \ | \\
CO\ CO \\
\backslash\ / \\
O
\end{array}
\!\!\right]_n
$$

anti-tumor agent [9]. In certain tests, the weight of tumor developed by
the test animal was only 11% of that of the control animal. Also, more
recent results [10] have shown in both laboratory and clinical studies that
this copolymer possess the ability to induce interferon generation.

EXPERIMENTAL

Copolymerization of Divinyl Ether with Maleic Anhydride. (1) The
apparatus consisted of a 500-ml three-necked flask equipped with a suitable
stirrer, pressure-equalizing dropping funnel, thermometer, and reflux con-
denser equipped for circulating ice water. To the top of the reflux con-
denser was attached a mercury pressure manometer and trap designed to
withstand about ½ atm internal pressure. All joints were wired or securely
clamped to accommodate the anticipated internal pressure. To 150 ml of
dry xylene in the flask was added 24.5 g (0.25 mole) of maleic anhydride
and 0.5 g of benzoyl peroxide. After solution was complete, the contents
of the flask were cooled to 0° and 8.75 g (0.125 mole) of divinyl ether (bp
28.3°) added through the dropping funnel. The flask and its contents
were heated to 50° by means of a water bath which resulted in the develop-
ment of about 6 in. mercury pressure in the manometer. After several
minutes the internal temperature had reached 63°. Polymerization was in-
dicated by the development of cloudiness in the previously clear solution.
The hot water bath was replaced by an ice bath to aid in the exothermic
reaction; however, polymerization occurred quite spontaneously, resulting
in much of the mercury being blown from the manometer into the trap.
The internal temperature was 122°. The polymer was produced as an
insoluble suspension which was removed by filtration and washed thoroughly
with hot xylene. After drying at 80°, the polymer weighed 33 g (99.2%
yield), indicating that the polymerization was complete within a short time.
    Since the copolymer was expected to be insoluble due to cross-linking,
an attempt to hydrolyze the anhydride rings and convert the material to
the sodium salt was made. However, when added to 10% aqueous sodium
hydroxide, the polymer dissolved completely and remained in solution when
neutralized with aqueous hydrochloric acid. The copolymer was also found
to be soluble in acetone.
    (2) The apparatus consisted of a 1-liter stirred autoclave since the pres-
sure developed in the above system indicated this change. To the cooled
autoclave was charged 49 g (0.5 mole) of maleic anhydride, 300 ml of dry
xylene, 1.0 g of benzoyl peroxide, and 17.5 g (0.25 mole) of divinyl ether.

The autoclave was heated to 50° and held for 1 hr after which the temperature was raised to 70° for 3 hr. After cooling, the suspended solid copolymer was isolated as in (1). Yield: 66 g; mp 350° (d); $[\eta]$ = 0.176 dl/g (DMF); $[\eta]$ = 0.174 dl/g (2N NaOH). Analysis calculated for $C_{12}H_{10}O_7$, C, 54.13; H, 3.76. Found: C, 53.99; H, 4.00. The IR spectrum of the anhydride form of copolymer exhibited the following bands (cm^{-1}): 1860 m (cyclic anhydride); 1100-1085 s, b (six-membered cyclic ether); and 950-920 m, b (COOH). The IR spectrum of the carboxylic form of the copolymer exhibited the following bands (cm^{-1}) 3450 s (OH stretching vibrations); 1850 m, 1740-

1710 s, b (C=O vibrations); 1668-1635 m, 1450-1400 m, b $(-C\overset{O}{\underset{O-}{\diagdown}}$ out-of-

plane deformations); 1230-1200 s (C–O stretching vibrations); 1100-1085 b, six-membered cyclic ether); and 950-920 m (OH out-of-plane deformation.[12]

An estimate of the molecular weight through use of the Staudinger constants reported by Kagawa and Fuoss [11] for polyacrylic acid in 2N NaOH, $[\eta]$ = 4.27 $\times$ $10^{-3}P^{0.69}$ (P = degree of polymerization), resulted in a value of P = 216. Using the value of 75.5 for the equivalent weight of the carboxylic unit of the copolymer gave a value of 16,300 for the molecular weight of the carboxylic form of the copolymer. Using the value of 66.7 for the equivalent weight of the anhydride form of the copolymer yielded a value of 14,400 for the molecular weight of the polyanhydride.

Copolymerization of Divinyl Ether and Fumaronitrile. To 75 ml of dry xylene contained in a suitable pressure vessel was added 9.75 g (0.125 mole) of fumaronitrile, 8.75 g (0.063 mole) of freshly distilled divinyl ether, and 0.5 g of benzoyl peroxide. The autoclave was heated with stirring for 4 hr. After cooling, the insoluble copolymer was removed by filtration and dried. Yield: 12.8 g. The IR spectrum of the copolymer (after purification by precipitating from an acetone solution with benzene) exhibited the following absorption bands (cm^{-1}): 2250 m, (–CN); 1625 vw (CH$_2$=CH–), 1735 m (–C≡N stretch); 1130-1085 s, b (six-membered cyclic ether); and 725 m (C–H). The copolymer was found to be soluble in acetone and DMF. Analysis calculated for $C_{12}H_{10}ON_4$: N, 24.8. Found: N, 20.25.

Copolymerization of Divinyldimethylsilane and Maleic Anhydride. To 75 ml of dry benzene contained in a suitable reaction vessel was added 12.25 g (0.12 mole) of maleic anhydride, 7.0 g (0.063 mole) of divinyldimethylsilane, and 1.0 g of benzoyl peroxide. After heating with stirring at reflux temperature for 1 hr, the copolymer began to precipitate as a white powder. Heating was continued for 4 hr, after which the product was cooled, filtered, washed thoroughly with hot dry benzene, and dried. It

was soluble in DMF, DMSO, and aqueous NaOH. Analysis calculated for
$C_{14}H_{16}O_6Si$: C, 54.6; H, 5.2; Si, 9.1. Found: C, 54.6; H, 5.7; Si, 9.4.
The IR spectrum of the copolymer exhibited the following absorption
bands (cm^{-1}): 1860 m, 1780 s, 1730 s (cyclic anhydride); 1470 s, 1375 s
(Si–CH$_3$); 1250-1210 b, s (cyclic anhydride); 930 b (OH deformation);
840 b, m (Si–C); and 720 m (C–H). [η] (DMF, 30°) = 0.121 dl/g; [η]
(2 N NaOH, 30°) = 0.082 dl/g.

**Copolymerization of Divinylcyclopentamethylenesilane and Maleic
Anhydride.** By a procedure similar to that described above the for co-
polymer of divinyldimethylsilane with maleic anhydride, 9.5 g (0.063 mole)
of divinylcyclopentamethylenesilane was copolymerized with 12.25 g (0.125
mole) of maleic anhydride to yield 5.3 g (24.3% yield) of copolymer after
purification by precipitation from acetone with benzene. [η] (DMF, 30°)
= 0.106 dl/g. Analysis calculated for $C_{17}H_{20}O_6Si$: C, 58.6; H, 5.8; Si, 8.1.
Found: C, 57.9; H, 6.25; Si, 7.65. The IR spectrum of the copolymer
exhibited the following absorption bands (cm^{-1}): 1860 m, 1780 s, 1730 s
(cyclic anhydride); 1250-1220 b, s (C–O–C stretching vibration, cyclic
anhydride); 930-910 m (OH deformation); 780-760 m (Si–C); and 720
(C–H).

Copolymerization of Divinylsulfone and Maleic Anhydride. By a pro-
cedure similar to that described above for copolymerization of divinyldi-
methylsilane with maleic anhydride, 7.4 g (0.063 mole) of divinyl sulfone
was copolymerized with 12.25 g (0.125 mole) of maleic anhydride. [η]
(DMF, 30°) = 0.064 dl/g; [η] (2 N NaOH, 30°) = 0.052 dl/g. Analysis
calculated for $C_{12}H_{10}O_8S$: C, 45.9; H, 3.2; S, 10.2: Found: C, 50.8; H,
5.1; S, 7.6. The IR spectrum of the copolymer (after purification by pre-
cipitation from acetone solution with benzene) exhibited the following
absorption bands (cm^{-1}): 1860 m, 1780 s, 1730 s (cyclic anhydride);
1470 s (unidentified); 1375 s, 1290 s, b, 1120 s (C–SO$_2$–C); 1230-1210
(C–O–C stretching vibration, cyclic anhydride); 920-910 m (OH deforma-
tion); and 740-735 m (C–H).

Copolymerization of 1,4-Pentadiene and Maleic Anhydride. By the pro-
cedure described for copolymerization of divinyl ether and maleic anhydride,
8.5 g (0.125 mole) of 1,4-pentadiene and 24.5 g (0.25 mole) of maleic an-
hydride dissolved in 150 ml of dry xylene was copolymerized in a stirred
autoclave using 0.5 g of benzoyl peroxide as initiator. The yield of the co-
polymer was 33 g.

Copolymerization of Divinyldimethylsilane and Acrylonitrile. To 75 ml of dry benzene was added 6.7 g (0.125 mole) of freshly distilled acrylonitrile, 7.0 g (0.063 mole) of divinyldimethylsilane, and 1.0 g of benzoyl peroxide. The solution was heated at reflux temperature for 4 hr. After 1 hr, the copolymer began to precipitate as a light brown powder. After cooling, the benzene-insoluble copolymer was removed by filtration, washed thoroughly with hot benzene, and dried. It was found to be soluble in DMF. Analysis calculated for $C_{12}H_{18}N_2Si$: C, 66.0; H, 8.25. Found: C, 67.7; H, 6.41.

Copolymerization of Divinyl Ether and Vinyl Acetate. To 100 ml of distilled water in a pressure bottle was added 0.5 g of Aerosol OT, 0.1 g of potassium persulfate, 17.2 g (0.2 mole) of freshly distilled vinyl acetate, and 7.0 g (0.1 mole) of freshly distilled divinyl ether. The bottle was sealed and heated at 60-65° with constant agitation for 2 hr, after which the solution was cooled and the copolymer precipitated by the addition of a saturated solution of sodium chloride. After thorough washing, the copolymer was dried and was found to be soluble in most organic solvents. Analysis calculated for $C_{12}H_{18}O_5$: C, 59.5; H, 7.44. Found: C, 59.5; H, 7.71.

Copolymerization of Divinyl Ether and Acrylonitrile. Divinyl ether (7.0 g, 0.1 mole) was copolymerized with acrylonitrile (10.6 g, 0.2 mole) according to the procedure described above for divinyl ether and vinyl acetate. The yield of copolymer was 13.5 g. Analysis calculated for $C_{10}H_{12}ON_2$: C, 68.2; H, 6.82; N, 15.9. Found: C, 65.1; H, 6.23; N, 22.3. The analytical results indicate that the ratio of acrylonitrile in the copolymer is higher than the predicted diene: alkene ratio of 1:2 which can readily be explained by the high reactivity of the acrylonitrile radical with an acrylonitrile molecule.

Copolymerization of Divinyl Ether and Dimethyl Fumarate. Divinyl ether (7.0 g, 0.1 mole) was copolymerized with dimethyl fumarate (28.8 g, 0.2 mole) in 75 ml of dry benzene, using 1.0 g of benzoyl peroxide as initiator. The reactants were placed in a pressure bottle, and after exclusion of oxygen, the reaction vessel was heated at 60° for 2 hr with shaking. The resulting clear liquid was filtered, and the copolymer precipitated by the addition of an excess of methanol, after which the product was dried at 80° for 24 hr. It was soluble in both benzene and DMF, but insoluble in methanol. $[\eta]$ (DMF, 30°) = 0.123 dl/g.

Copolymerization of Divinyl Ether and Diethyl Maleate. Divinyl ether (7.0 g, 0.1 mole) was copolymerized with diethyl maleate (34.4 g, 0.2 mole) according to the procedure described above for copolymerization of divinyl ether and vinyl acetate. Yield of copolymer: 25.7 g, after precipitation from acetone solution with aqueous NaCl. The copolymer was soluble in acetone, benzene, DMF, dioxane, CCl_4, and ethyl ether. It was insoluble in heptane. $[\eta]$ (benzene, 30°) = 0.216 dl/g.

Copolymerization of Divinyl Sulfone with Dimethylfumarate. Divinyl sulfone (11.8 g, 0.1 mole) was copolymerized with dimethyl fumarate (28.8 g, 0.2 mole) according to the procedure described above for the copolymerization of divinyl ether with dimethyl fumarate. The copolymer was precipitated from the benzene solution by addition of excess ethyl ether. Yield: 34.4 g.

Reaction of Copolymer of Divinyl Ether and Maleic Anhydride with Hydriodic Acid. To 16.8 g (0.1 mole) of the DVE-MA copolymer was added 25 ml of 57% hydriodic acid. The copolymer dissolved by hydrolysis of the anhydride rings. The solution was refluxed for 6 hr. After cooling, the copolymer was isolated by evaporation of the water and excess hydriodic acid under vacuum on a water bath. The IR spectrum of the compound showed decreased absorption in the 1100-1085 cm^{-1} region of the spectrum and increased absorption in the 675-650 cm^{-1} region, indicating that some cleavage of the cyclic ether bond had occurred and the C–I bond introduced. Analysis calculated for $C_{12}H_{14}O_8I_2$: C, 26.7; H, 2.6: I, 47.0. Found: C, 47.5; H, 5.06; I, 5.19. These results indicate that only about 10% of the tetrahydropyran rings were cleaved but clearly support the proposed structure.

ACKNOWLEDGMENTS

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