Kinetics of Polymerization of (+)-Catechin with Formaldehyde[1]

Preecha Kiatgrajai,[2a] J. D. Wellons,*[2b] Lawrence Gollob,[2a] and James D. White[2c]

Forest Research Laboratory and Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

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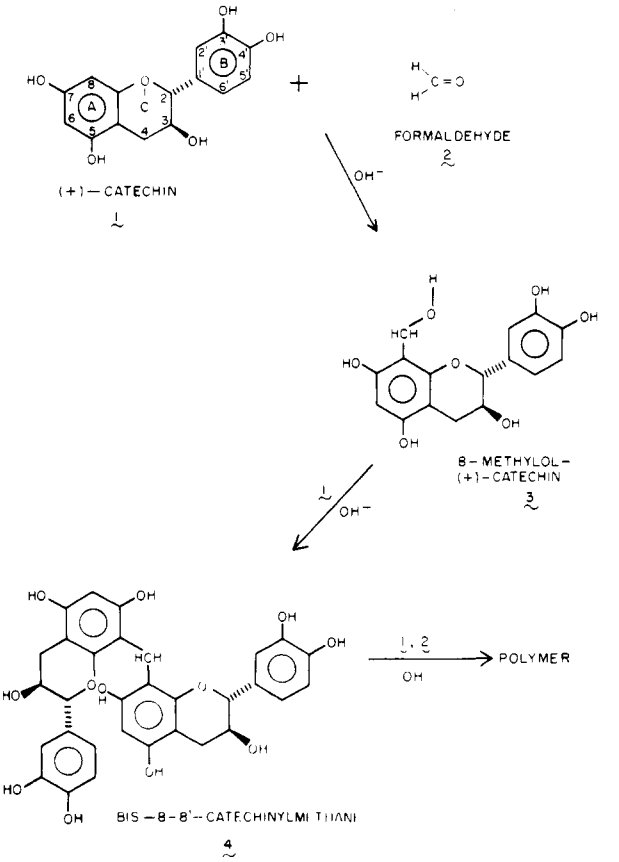
Rates of methylolation and condensation of (+)-catechin (1) with formaldehyde (2) in aqueous solution were measured over the pH range 6–9 and the temperature range 10–85 °C. First-order kinetics were observed for the rates of disappearance of 1 and 2 as well as for the increase in molecular weight via condensation. At lower pH, k(methylolation) $\simeq$ k(condensation), the reaction mixture consisting mainly of monomers and polymers. At pH 9, k(methylolation) > k(condensation), the reaction mixture containing mostly oligomers. Undesirable side reactions of 1 and 2 were much slower than those of 1 with 2. The polymerization of 2 with phenol was much slower than that with 1, suggesting that 1 cannot directly replace phenol in resin systems.

Many unsuccessful attempts have been made at formulating adhesives from phenol–aldehyde condensation products containing conifer bark tannins.[3] Although these tannin polymers have been shown to be copolymers of (+)-catechin (1, Scheme I) and its diastereomers, linked between the C-4 position of one unit and either the C-6 or C-8 position of the adjacent unit,[4] little else is known of their structure. Not surprisingly, a quantitative evaluation of the reactivity of these complex polymers with formaldehyde or methylolated phenol is difficult. The monomer 1, however, should serve as an adequate model for investigating the polymerization of tannins with formaldehyde.

Several factors could account for the difficulties encountered if (+)-catechin or condensed tannins replace phenol on condensation with formaldehyde. Rates of both the methylolation of (+)-catechin residues and the condensation of these methylol groups may greatly differ from those of the analogous reactions with phenol, or the polymerization reactions may be slow compared with rearrangement reactions that compete for the (+)-catechin[5] or with the Cannizzaro reaction of formaldehyde (2). We report here the rates of methylolation of 1 with 2 and of condensation of the methylol derivatives (e.g., 3) of 1 in aqueous solutions at pH 6–9 over the temperature range 10–85 °C.

Scheme I



Results

The number of potential reaction sites on 1 had to be determined before selecting kinetic models for condensation of 1 and 2. By considering the ortho–para activitation normally resulting from a hydroxy group on benzene, we expected the C-6 and C-8 positions of 1 to be more reactive than C-2′, C-5′, or C-6′. The change in concentration of 1 and 2 and in the molecular weight of the polymer with time at various mole ratios of reactants (Figure 1) suggested that 1 clearly had ambient reactivity. At a 2:1 mole ratio of 2 to 1, all of 1 was consumed, and polymer formed rapidly, but no more than half of 2 was consumed, even after long reaction times. Conversely, at a 1:2 mole ratio of 2 to 1, all of 2 was consumed, but only two-thirds of 1 reacted, and most of what formed were dimers. Results similar to Figure 1 were obtained over a range of pHs (6–9) and temperatures (10–85 °C), suggesting that the optimum mole ratio of 2 to 1 was 1:1, i.e., that 1 was bifunctional in a methylolation/condensation reaction system. This postulate agrees with results of both Hillis and Urbach[6] and Hemingway and Megraw,[7] who report the C-6 and C-8 positions of 1 to be much more reactive than C-2′, C-5′, or C-6′.

Kinetics of Methylolation. As expected, the initial rates of disappearance of 1 and 2 apparently were first order. When the logarithm of the concentration of 1 or 2 was plotted as a function of time (first-order model), a straight line (r > 0.95) was obtained for up to 50% consumption of starting material. Equations for the second-order model had much lower correlation coefficients. A

(1) (a) Taken in part from the Ph.D. thesis of P.K., Oregon State University, 1980. (b) Paper 1611, Forest Research Laboratory, School of Forestry, Oregon State University.

(2) (a) Forest Research Laboratory. (b) To whom correspondence should be addressed at Georgia-Pacific Corp., Decatur, GA 30035. (c) Department of Chemistry.

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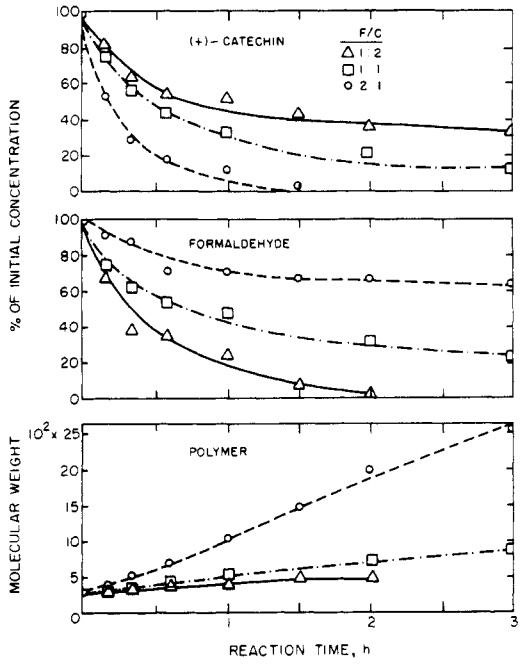

Figure 1. Rates of (+)-catechin (C) and formaldehyde (F) consumption and polymerization at pH 8 at 55 °C.

plot of the logarithm of the first-order rate constants for the disappearance of 1 or 2 vs. reciprocal absolute temperature (Figure 2) also had an $r > 0.95$.

To further verify that these reactions were first order, we determined the rates of disappearance of 1 and 2 at four initial concentrations (0.3, 0.6, 0.9, and 1.2 g/L of 1, 1:1 mole ratio of 2 to 1, pH 8). The rates were constant except for slightly low values at the lowest concentration of 1. At low initial concentrations, 1 slightly buffered the solution, requiring proportionally less NaOH to adjust the pH. Thus, the NaOH concentration was not constant. In addition, the run at lowest concentration approached the analytical limit for formaldehyde.

Kinetics of Condensation. Because 1 was found to be ambident under our study conditions, linear polymers resulted, and the rate of condensation could be determined from the relationship between the concentration of the residual reactive groups and the increase in degree of polymerization (DP).

The condensation to form a linear polymer can be expressed as in eq 1, where C and M represent, respectively,

$$C + M \xrightarrow{k'} \text{polymers} + H_2O \quad (1)$$

the total number of reactive carbon (C) and methylol (M) groups on 1 for the system. The rate constant for condensation (k') could not be calculated from C and M directly because these quantities could not be easily determined. However, each (+)-catechin, methylolcatechin, or partly condensed polymer contains two functional groups, one at each chain end. Each condensation reaction reduces the total number of reaction sites in the system by two. Therefore, for determination of the reaction order for the rate of condensation with respect to the total number of both types of functional groups (f), either first- or second-order models may be used as follows:

First Order

$$-df/dt = k_1'f \quad (2)$$

$$\ln (f_0/f) = k_1't \quad (3)$$

$$\ln (DP) = K_1't \quad (4)$$

Second Order

$$-df/dt = k_2'f^2 \quad (5)$$

$$f_0/f = f_0k_2't + 1 \quad (6)$$

$$DP = 2C_0k_2't \quad (7)$$

where f = total number of condensable functional groups at any instant, f_0 = initial number of condensable functional groups = $2C_0$, C_0 = initial number of molecules of 1 in the system, DP = number-average degree of polymerization, t = reaction time, k_1' = first-order rate constant for condenstion, and k_2' = second-order rate constant for condensation.

The rate constants calculated from eq 7 were more than 50–100 times greater than those for disappearance of 1 or 2. These constants could not be explained in terms of a

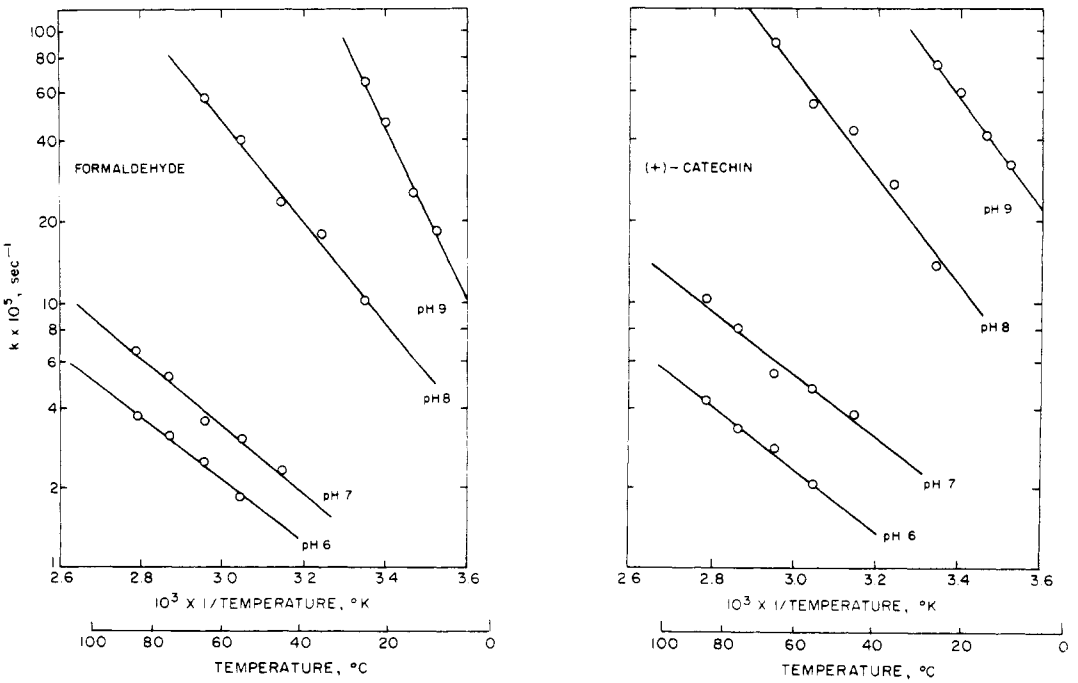

Figure 2. First-order rate constants (k) of (+)-catechin (C) and formaldehyde (F) disappearance at 1:1 F/C.

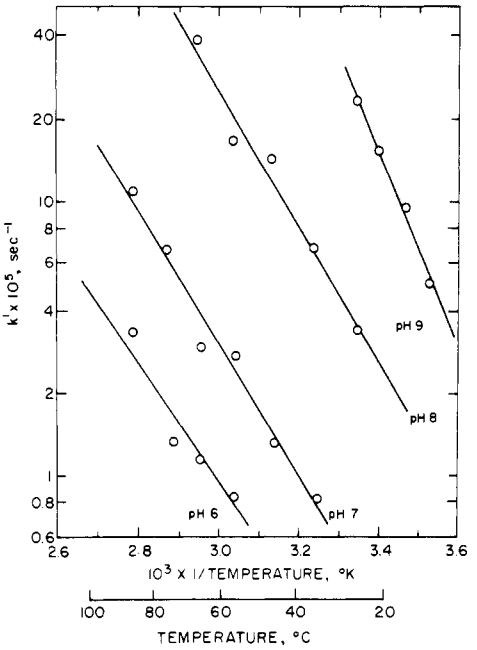

Figure 3. First-order rate constants (k') for condensation at 1:1 F/C.

second-order reaction because the rate of condensation could not be larger than that of the preceding methylolation. In fact, when formaldehyde was reacted with phenol under conditions similar to those used here, methylolation was sufficiently faster than condensation that significant amounts of methylol compounds accumulated.[8]

When one functional group (e.g., the methylol group) is much lower in concentration than the other functional group with which it condenses, the reaction can be expected to follow the first-order rate law (eq 4). The high correlation coefficients ($r > 0.92$) both for the regressions of log DP vs. time (up to at least a DP of 1.5–2) and of the logarithm of the first-order rate constants for condensation vs. reciprocal absolute temperature (Figure 3) supported the first-order model. Other support came from the observation that first-order rate constants were independent of initial concentration. These rates of condensation were further confirmed by comparing them to the rates of disappearance of 1 and 2. The rate of disappearance of 2 (methylolation) plus the rate of condensation was equal to or slightly less than the rate of disappearance of 1, at a 1:1 mole ratio of 2 to 1, in most experiments, a result that was expected because 1 was consumed by both methylolation and condensation reactions.

At conversions of 1 in excess of 50% (e.g., DP > 2), the rate of condensation was lower than that predicted from first-order kinetics. This deviation could have resulted from either of two factors. First, the gel permeation chromatography (GPC) columns used in this study did not adequately resolve higher (DP > 5) molecular weight fractions and could have biased those larger DPs toward low values. Alternatively, if one of the two reaction sites on 1 (e.g., C-6 or C-8) was more reactive, that one would initially react more frequently, resulting in a decreased rate at higher conversions.

Discussion

Rates of methylolation (disappearance of 2) and condensation should be free from errors resulting from side reactions of the monomers. The primary side reaction of 2 is self-oxidation–reduction (Cannizzaro reaction) in alkali to produce methanol and formic acid and is usually significant at temperatures of 40–60 °C at pH >12.[9] After analyzing aqueous solutions of 1 and 2 at the highest temperature and pH combinations (25 °C at pH 9, 55 °C at pH 8), we found that 1 and 2 were stable for more than 5 h as long as both were not present in the solution. The primary side reactions of 1 are epimerization to (+)-epicatechin and rearrangement of the epimers to catechinic acid, but these two reactions occur at rates approximately 1/20 and 1/80, respectively, of those of condensation of 1 with 2.[5]

Rates of methylolation and condenstion were strongly pH and temperature dependent. The rate of condensation nearly equaled that of methylolation at pH 6 and 7, resulting in a reaction mixture consisting mostly of monomers and polymers with low concentrations of dimers, trimers, and tetramers (Figure 4). At pH 9, the rate of methylolation was almost 3 times that of condensation, resulting in significant accumulations of dimers, trimers, and tetramers in the reaction mixture. As temperature increased at every pH, rate of condensation increased more than that of methylolation. Thus, high temperatures favored condensation, whereas low temperatures favored methylolation. A similar increase in the proportion of methylolation to condensation occurred at higher pH and lower temperatures in phenol–formaldehyde condensations.[10]

The activation energies for methylolation of 1 and for condensation were in the ranges of about 6–18 and 10–17 kcal/mol, respectively. These values were slightly less than those previously reported for methylolation and condensation of other phenolics with formaldehyde. Activation energies were 18–31 kcal/mol for self-condensation of saligenin with phenol in the absence of solvent, with and without catalyst,[11] 14 and 16 kcal/mol for methylolation and condensation, respectively, in the reaction of *m*-cresol with formaldehyde in aqueous solution at an initial mole ratio of 1:0.87:0.024 *m*-cresol/formaldehyde/triethanolamine,[12] and 19–21 kcal/mol for methylolation of resorcinol with formaldehyde without catalyst at a pH of about 4.[13] But because reaction rates were lower for these other phenolics than for 1, the slightly lower activation energies for the (+)-catechin and formaldehyde reactions seemed reasonable.

The kinetics of condensation suggested that the two reactive sites of 1 (C-6 and C-8) might differ in reactivity. However, if they differed greatly, condensation initially would involve only the more reactive site, forming dimers. Subsequent condensation of the less reactive site would convert pairs of dimers into tetramers. The observation that major concentrations of trimers are a normal component in the molecular weight distribution verified that the two reactive centers in 1 must not differ dramatically in their reactivity with formaldehyde.

To determine which site on 1 was the most reactive toward formaldehyde, we chromatographed the dimer peak identified on the GPC on a μ-CN Bondapak column, separating it into three peaks. Two of these peaks each accounted for about 25% of the peak area of dimer,

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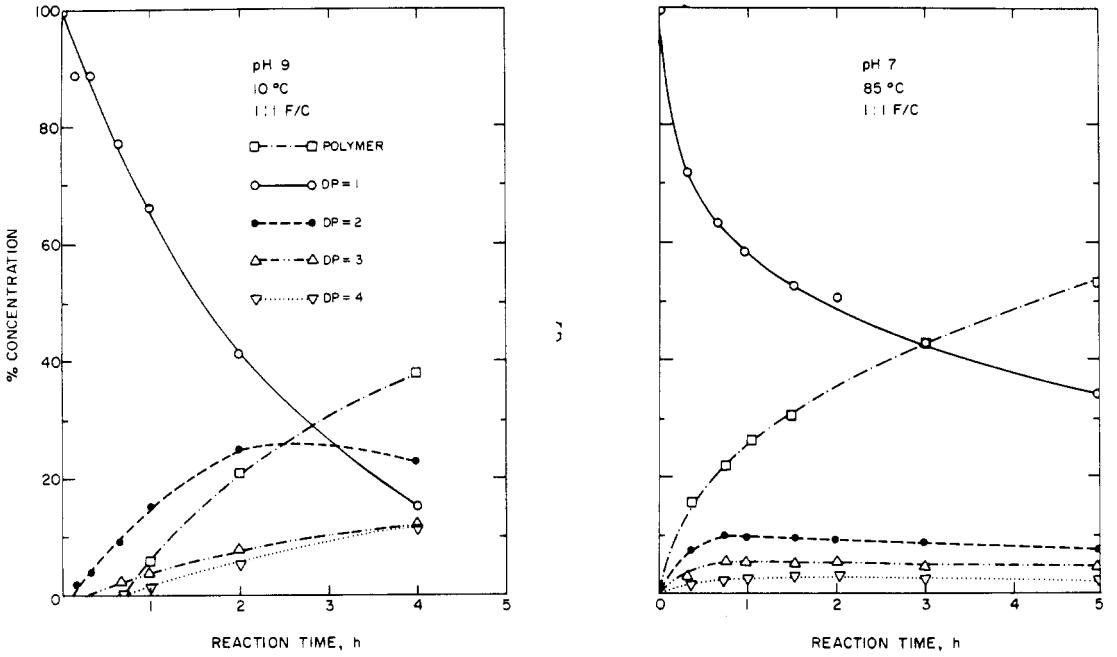

Figure 4. Distribution of monomers, dimers, trimers, tetramers, and polymers from the reaction of (+)-catechin (C) with formaldehyde (F).

whereas the larger peak was about 50% of the total peak area. Only the major peak was cleanly separated from all other components. This component was isolated and identified from its proton NMR spectrum to be bis(8-catechinyl)methane (4). The ^{1}H NMR spectrum of 4 was identical with that of 1 except for the appearance of methylene bridge protons at δ 3.60, the disappearance of the phenolic hydroxy proton signal (presumably shifted downfield to $\delta > 10$), the replacement of the doublet due to C-6 (δ 5.90) with a singlet at δ 5.98, and the disappearance of the C-8 doublet (δ 6.05). A recent study by Hundt and Roux[14] demonstrates that substitutions for either the C-6 or C-8 proton of 1 cause a downfield shift of the signal for the remaining aromatic proton in ring A. Thus, the singlet at δ 5.98 confirms that the dimer is symmetrical with a methylene group bridging the C-8 carbons of the two monomer units and that the C-8 position of 1 is, therefore, more reactive than the C-6 position.

Finally, the rate of reaction of 1 with 2 was compared to that of phenol with 2 at pH 9, 25 °C, and a 1:1 initial mole ratio of 2 to phenol. The first-order rate constants for disappearance of phenol and 2 were 1.4×10^{-5} and 1.1×10^{-5} s^{-1}, respectively. These rates of disappearance were only slightly larger than the rate of *o*-methylolphenol formation (1.05×10^{-5} s^{-1}) reported by Freeman and Lewis[15] for a solution with a 1:3:1 mole ratio of phenol/2/NaOH. From these data, the rate of polymerization of phenol with 2 appeared to be about 1/60 of that of 1 with 2. Thus, a major difficulty in using 2 to partly replace phenol seems to be that they differ dramatically in reactivity.

Experimental Section

High-pressure liquid chromatography (HPLC) was performed with a Waters Associates ALC/GPC 244 instrument either with a μ-Bondapak-CN column (4 × 300 mm, ~3000 theoretical plates) or with μ-Styragel gel permeation columns (1 ft, 1000 Å; 2 ft, 500 Å; 1 ft, 100 Å; in series). Eluent was monitored at 280 nm, and peak areas were determined with a Hewlett-Packard 3370B integrator. NMR spectra were recorded on a Varian FT-80A instrument. Molecular weights of standards were determined by vapor-pressure osmometry (VPO) on a Wescan Instruments Model 232A.

Kinetic Measurements. (+)-Catechin (1) was purified as described previously,[5] whereas 2 was obtained from Georgia-Pacific Corp. as a 50% solution (unstabilized) and was stored at 60 °C. A solution of 180 mg (0.63 mmol) of 1 and 300 mL of distilled water in a 500-mL three-necked boiling flask was purged with N_2 and heated to the reaction temperature in a constant-temperature circulating bath. A 1–4% solution of 2 in water was added to the reaction mixture, the amount and concentration depending on the desired mole ratio of 2 to 1, the appropriate amount of 0.05 or 0.1 N NaOH was added immediately to adjust the pH, and the reaction was started. Solutions of pH 6, 7, 8, and 9 were reacted at temperatures ranging from 10 to 85 °C, and 22-mL samples were removed from the reactions at intervals. A portion (2 mL) of each sample was diluted with 7 mL of cold methanol, neutralized with acetic acid to pH 6–7, if necessary, and stored briefly in the freezer for analysis of molecular weight and concentration of 1. The remaining 20 mL of sample was used to determine the concentration of 2.

The percent concentration of 1 in the mixture was determined by injecting 15 μL of dilute solution (aqueous methanol) into the HPLC instrument and eluting it from μ-Bondapak-CN columns with 2-propanol/water/acetic acid (1:99:2 v/v/v) flowing at 1 mL/min. The peak for 1 was base-line resolved from methylolcatechin and dimers, which were the only other compounds eluting from this column. The peak area of 1 was converted to mass with a response factor determined from injecting a known mass of 1 into the mobile phase.

The percent concentration of 2 in the mixture was determined by titrating with hydroxylamine hydrochloride.[16] A 20-mL sample from the reaction flask was neutralized immediately (pH 5–7), cooled to room temperature, and then acidified to pH 3.4 (the pH of 0.5 N hydroxylamine hydrochloride in water) with 0.01 N HCl. A 50-mL aliquot of 0.5 N hydroxylamine hydrochloride was added to the acidified sample; the reaction was allowed to proceed for 0.5 h at ambient temperature and then back-titrated to pH 3.4 with 0.033 N NaOH.

Number-average molecular weights ($\bar{M}_N$) of the reactants were determined by GPC. A diluted 15-μL sample used to determine concentration of 1 was injected into the HPLC instrument and

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eluted from the μ-Styragel GPC columns with tetrahydrofuran–methanol(95:5 v/v) flowing at 1 mL/min. A linear calibration of log $\bar{M}_N$ vs. elution volume (milliliters) was constructed from 1 ($\bar{M}_N$ = 290), 4 ($\bar{M}_N$ = 620), a tannin trimer[17] ($\bar{M}_N$ = 866), and polystyrene molecular weight standards ($\bar{M}_N$ = 3600, 17 500, and 35 000) purchased from Waters Associates (Lots No. 116, 41022, and 76, respectively). $\bar{M}_N$ was determined for the phenolic standards by VPO in acetone/water azeotrope (88.5:11.5 v/v). During GPC, distinct peaks eluted from samples of the reaction mixture at the proper elution volumes for monomer, dimer, trimer, tetramer, and, occasionally, pentamer, but higher molecular weights merged into a continuous distribution. The mass of material eluting at each molecular weight or elution volume was determined from the area under that fraction of the peak, assuming that the UV_{280} extinction coefficient was independent of molecular weight. This assumption was supported by the fact that the total peak area per mass injected remained constant throughout the reaction. For polydisperse samples, $\bar{M}_N$ was calculated as $\bar{M}_N = \sum N_i M_i / \sum N_i$, where M_i is the molecular weight of the ith fraction and N_i the moles of sample eluting in that fraction.

Isolation and Verification of Bis(8-catechinyl)methane. To improve the yield of dimers, we selected reaction times and conditions specifically. A solution of 1.1 g of 1 and 200 mL of distilled water at 22 °C was purged with N_2 and adjusted to pH 10 with 5% aqueous NaOH, and then 9.1 mL of 0.5% aqueous 2 was added, making the mole ratio of 2 to 1 equal to 1:2.5. After 5 min, the reaction was stopped by pouring the solution onto a slurry of 10 mL of 5% acetic acid, 20 mL of methanol, and 500 g of crushed ice and stirring for 5 min. The solution was filtered through glass wool, freeze–dried, redissolved in 750 mL of tetrahydrofuran, filtered through a fine-porosity Gooch crucible, diluted with water, evaporated under vacuum to a syrup, and freeze–dried again.

A 0.2% solution of this freeze–dried solid in methanol/water (1:9 v/v) was injected repeatedly into the HPLC instrument and eluted from μ-Bondapak-CN columns with methanol/water/acetic acid (10:90:5 v/v/v) flowing at 1 mL/min. This mobile phase, less polar than that used to assay 1, separated the dimer into three peaks. The major peak eluted between 9 and 11 mL and was collected in a flask wrapped in aluminum foil and chilled in ice–water. Reinjection of the isolate onto both the GPC and μ-Bondapak-CN columns verified that the fractionation was complete and that no further reaction had occurred during fractionation. A 12-mg sample of dimer was collected for VPO and proton NMR spectroscopy: $\bar{M}_N$ [$(CH_3)_2CO/H_2O$, 88.5/11.5 v/v] 620 ± 30; ^1H NMR [$(CD_3)_2CO$] δ 6.94 (s, 2, $H_{5'}$), 6.79 (s, 4, $H_{2',6'}$), 5.98 (s, 2, H_6), 4.69 (d, 2, J = 8, H_2), 4.07 (m, 2, H_3), 3.60 (s, 2, methylene bridge), 2.92 (dd, 2, J = 15, 5 Hz, H_4), 2.54 (dd, 2, J = 15, 8 Hz, H_4).

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Supplementary Material Available: Kinetic data from which Figures 2 and 3 were constructed (3 pages). Ordering information is given on any current masthead page.

(17) The tannin trimer was provided by Dr. R. W. Hemingway, USDA Forest Service, Alexandria, LA.

Stereochemical Evidence for Aryl Participation in the Ring Opening of Oxiranes. Ring-Opening Reactions of 1-Benzyl-1,2-epoxycyclohexane under Acidic Conditions

Paolo Costantino, Paolo Crotti, Maria Ferretti, and Franco Macchia*

Istituti di Chimica Organica e Chimica Farmaceutica della Facoltà di Farmacia, 56100 Pisa, Italy

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The reactions of 1-benzyl-1,2-epoxycyclohexane (1) have been investigated and compared with the ones of the corresponding methyl-substituted oxirane (3) in order to evaluate the possibility that an aryl group not directly linked to the oxirane ring can participate in the ring-opening processes. The acid-catalyzed ring-opening reactions of 1 are not completely anti stereoselective and give mixtures of syn and anti addition products accompanied by rearrangement compounds. The stereoselectivity and the amounts of rearrangement products vary noticeably with the reaction conditions. The results obtained and in particular the presence of substantial amounts of syn products observed in the ring-opening reactions of 1, markedly higher than those from epoxide 3, strongly suggest the incursion of aryl participation and have been rationalized through a mechanism implying the intermediacy of a phenonium-type ion.

The properties and the reactivity of some oxirane systems have been related in recent years to the carcinogenic and mutagenic activity of polycyclic arenes.[1] On the other hand, 1,2-epoxides have been found active as inhibitory agents[2] of mutagenesis and carcinogenesis. Therefore, a more detailed knowledge of the mechanism and stereochemistry of the ring opening of simple 1,2-epoxides appears to be useful in order to understand the more complex biological processes in which the more complex systems are involved.

The participation by neighboring aryl groups, and therefore the intermediacy of σ-bridged phenonium-ion-type intermediates, has been largely suggested and proved in the solvolyses of most β-arylalkyl systems.[3,4] However, the aryl participation in the ring opening of oxiranes has been put forward only in order to explain the syn stereo-

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