A Low-Temperature Internal Nucleophilic Aromatic Substitution Reaction on a β-O-4 Lignin Model Dimer†

Dexter L. Criss, Leonard L. Ingram, Jr., and Tor P. Schultz

Mississippi Forest Products Utilization Laboratory, Mississippi State University, Mississippi State, Mississippi 39762

Thomas H. Fisher* and Debbie B. Saebo

Department of Chemistry, Mississippi State University, Mississippi State, Mississippi 39762

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The major interunit bond in lignin is a β-O-4 link (see **1** in Scheme 1), an ether linkage joining the β-carbon of the side chain of one phenylpropane lignin unit with the phenolic oxygen of a second lignin unit.[1] The hydrolysis of this type of nonphenolic lignin ether linkage is believed to be the rate-limiting step in the bulk-phase alkaline hydrolysis of wood chips to pulp. We have conducted structure−reactivity studies on oxidative-cleavage reactions[2] and alkaline hydrolysis reactions[3] of various β-O-4 lignin models. During the latter studies we observed that lignin model compound **1** underwent an unusual base-catalyzed, room-temperature rearrangement reaction to **4** (containing an α-O-4 linkage). This rearrangement can be classified as either a 1,4 oxygen-to-oxygen aryl migration or an internal nucleophilic aromatic substitution reaction. We report here mechanistic studies on this rearrangement.

The rearrangement product **4** results from a migration of the B ring from the β-oxygen to the α-oxygen of the side chain, or in lignin terminology it is a β-O-4 to α-O-4 rearrangement. The identity of **4** was determined to be 2-(4-formyl-2-methoxyphenoxy)-2-(3,4-dimethoxyphenyl)-ethanol using ^{1}H, ^{13}C, CHCOR, COSY2Q, and INAPT NMR techniques. In the ^{1}H NMR, the α-H in **1** absorbs at 5.09 (m, 1H) ppm and the β-H at 4.17 (d, 2H) ppm, whereas in **4** the α-H was observed at 4.23 (m, 1H) and the β-H at 3.8 ppm. The β-H is underneath the three OMe H's but is clearly seen in the CHCOR spectrum. The chemical shifts of the α- and β-carbons in **1** and **4** have even more pronounced differences. The α-C absorbs at 72.4 ppm in **1** and at 83.1 ppm in **4**, a nearly 11 ppm downfield shift. The β-C shifts in the other direction (from 75.5 ppm on **1** to 67.5 ppm on **4**) because the B aryl ring has moved from the β- to the α-carbon. MS analysis of **4** gave major ions (*m*/*e*) of 151/152 and 180. These masses are assigned to the two ions formed from a scission of the α-C−O bond, one being vanillin, 151/152 mass, and the other the A ring ion with two side-chain carbons, which has a mass of 180.

Compounds **1** and **4** were separately reacted with 0.5 M NaOH in dioxane at rt to determine if they were in equilibrium. Samples were removed at 2, 20, 60, and 1020 min and analyzed by HPLC. After 1020 min, both **1** and **4** formed mixtures containing approximately equal amounts of **1** and **4**. This result suggests that the rearrangement is an equilibrium. Compound **1** appeared to rearrange slightly faster than **4**, since after 60 min **1** showed 28% rearrangement while **4** showed only 20% rearrangement. No rearrangement product was observed for either **1** or **4** under acidic conditions.

Intramolecular nucleophilic aromatic substitution reactions,[4] including vicarious nucleophilic aromatic substitution[5] of hydrogen, are known but not common. A stable σ-complexed spiro-Meisenheimer complex with a diazonium substituent was recently reported.[6] Only one literature example was found of a similar lignin-related rearrangement. In a study of nitrated kraft lignin, Lindeberg and Walding[7] prepared two lignin models similar to **1**: one model compound (**5**) contained 2-OMe,4-NO_2 groups in the B ring and the other (**6**) contained 2-OMe,5-NO_2 substituents on the B ring. β-Aryl ether **5** was found to rearrange to an α-aryl ether, while **6** did not rearrange but instead activated the replacement of the 2-OMe group with a OH on the B ring. A Meisenheimer complex was suggested[7] to be an intermediate in the rearrrangement, although no mechanistic evidence was presented. Alternatively, the rearrangement could occur through a nucleophilic, neighboring-group displacement to give an epoxide, which can open to either an α- or β-aryl ether. This latter mechanism must be considered since the initial step of the alkaline hydrolysis reaction of nonphenolic β-O-4 lignin models normally involves such a process.[3a,8]

The benzylic hydroxyl oxygen of **1** was labeled with ^{17,18}O, to provide mechanistic evidence on whether the rearrangement went through intermediate **2** or **3**, shown in Scheme 1. If the pathway proceeds through the spiro-Meisenheimer intermediate[4c] **2**, then **4a** would be obtained. Alternatively, if the neighboring-group epoxide pathway is followed, the rearrangement product of **1** would be **4b** with the labeled oxygen on the β-hydroxyl group.

The ^{17}O NMR of **1** labeled on the benzylic hydroxyl gave a peak at 20.6 ppm, which is in the hydroxyl region,[9] while the ^{17}O NMR of **4** had a peak at 90.6 ppm, indicating the presence of an ^{17}O aryl ether[9] (structure **4a** not **4b**). The MS of labeled **1** showed a small parent peak at *m*/*e* 332 and another small peak at *m*/*e* 334

* Corresponding author: phone, (601) 325-7612; fax, (601) 325-1618; e-mail, thf1@ra.msstate.edu.

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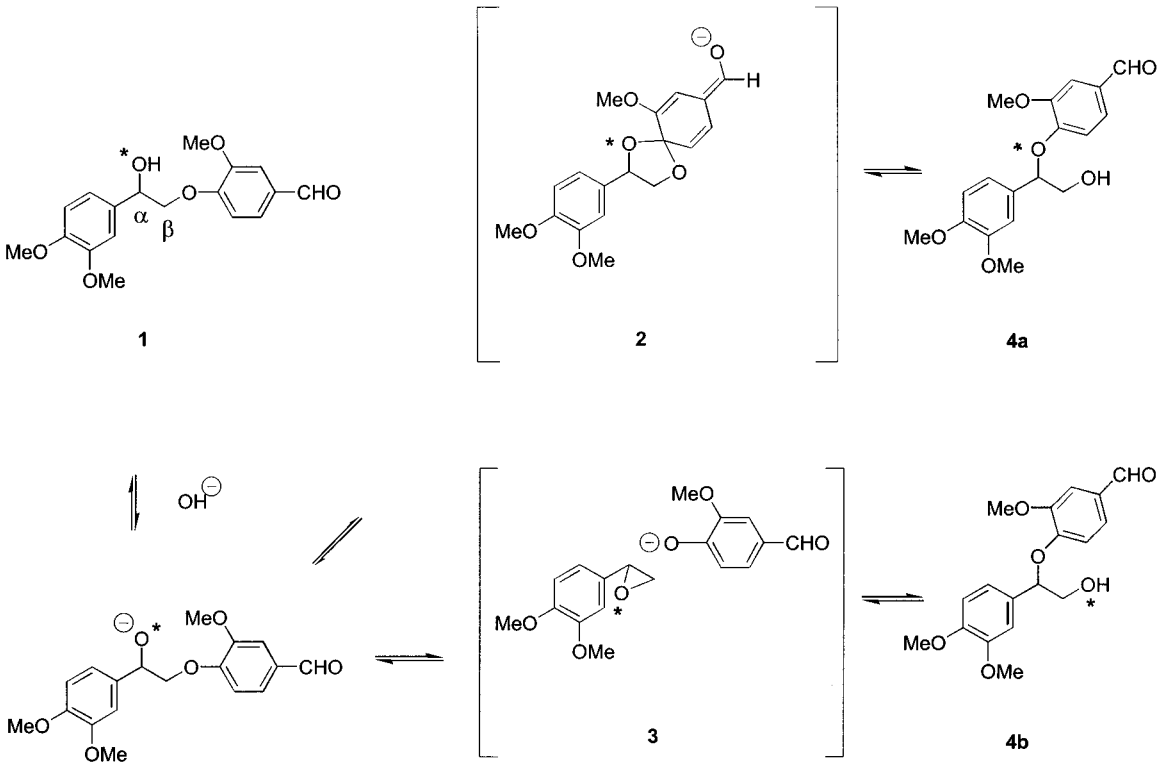
Scheme 1. Two Possible Mechanisms for Rearrangement of 1 to 4: Spiro-Meisenheimer Complex 2 or Epoxide 3[a]



[a] An asterisk (*) = $^{17/18}$O label.

(P + 2) of essentially equal intensity, indicating that **1** was labeled with approximately 50% ^{18}O. Dehydration of **1** gave an ion at *m/e* of 314 ($M^{\bullet+} - H_2O$) of 51% intensity with only a small (less than 2%) *m/e* 316 peak, further indicating that the label was on the hydroxyl group. The *m/e* 180 peak was accompanied by a significant ^{18}O (P + 2) peak, while the *m/e* 151/152 peaks had only small peaks at *m/e* 153/154. This result was expected since the label was on the 3,4-dimethoxyphenyl side chain. MS/direct probe of labeled **4** gave a *m/e* 180 peak, but no *m/e* 182 (P + 2) peak, and large peak intensities at *m/e* 153/154 along with the normally observed *m/e* 151/152 peaks. Consequently, on the basis of both the ^{17}O NMR and ^{18}O MS data, we conclude that the rearrangement product of labeled **1** is **4a**. Thus, the results are consistent with the proposed mechanism involving intermediate **2**.

Experimental Section

General Methods. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Labs of Knoxville, TN. Water (10% ^{18}O) was obtained from Aldrich, and water (10% ^{17}O, 70% ^{18}O) was obtained from Cambridge Isotope Labs. ^{1}H NMR spectra were run at 300 MHz, ^{13}C NMR at 75.6 MHz, and ^{17}O NMR at 40.8 MHz. The ^{17}O NMR spectra were collected into 16K data sets over a spectral width of 38.5 kHz using a 60° pulse, 15 000 scans, and 250 Hz line broadening. Mass spectra were obtained with either GC or direct probe sample introduction and EIMS at 70 eV. HPLC analysis used a 10 μm Econsil C-18 reverse-phase column with UV detector at 280 nm and a gradient elution using acetonitrile and water (1% acetic acid) starting with 25% acetonitrile for 5 min, then ramped to 95% acetonitrile over 10 min, and held for 5 min. The rearranged product **4** eluted slightly faster than **1**.

2-(4-Formyl-2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)ethanol (1). Ethanol **1** was synthesized according to the procedure of Collier et al.[3b] ^{1}H NMR (acetone-d_6): δ, ppm: 3.79, 3.81, 3.91, 4.17 (d, 2H, J = 5.8 Hz, H-β), 4.73 (d, 1H, J = 3.9 Hz, α-OH), 5.09 (m, 1H, H-α), 6.93 (d, 1H, J = 8.2 Hz), 7.03 (dd, 1H, J = 2.0, 8.2 Hz), 7.18 (d, 1H, J = 2.0 Hz), 7.18 (d, 1H, J= 8.2 Hz), 7.43 (d, 1H, J = 1.9 Hz), 7.50 (dd, 1H, J = 1.9, 82 Hz). ^{13}C NMR (acetone-d_6): δ 56.1, 56.2, 56.3, 72.4 (C-α), 75.5 (C-β), 110.9, 111.5, 112.6, 113.5, 119.4, 126.7, 131.4, 135.3, 149.9, 150.3, 151.0, 155.0, 191.2. Mp: 112−114 °C (lit.[3a] mp 113−114 °C).

[$^{17/18}$OH]-2-(4-Formyl-2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)ethanol (1). Synthesis of labeled **1** started with the dioxolane derivative **7** [2-(4-(1,3-dioxolan-2-yl)phenoxy)-1-(3,4-dimethoxyphenyl)-1-ethanone])[3a] under basic conditions to prevent colabeling the 4′-formyl. The protected ketone **7** (0.601 mmol), KOH (1.2 mmol), 1 mL of 10% ^{17}O water (containing about 70% ^{18}O), and 10 mL of dioxane were stirred at rt. After 4 h $NaBH_4$ (3.01 mmol) was added, and the mixture was stirred overnight. Then 10 mL of acetone was introduced, the mixture stirred for 30 min, and 100 mL of water with 5 drops HCl added. The mixture was extracted three times with CH_2Cl_2. The crude product was recrystallized from EtOH giving white crystals, mp 112−114 °C, 49% yield. Precise isotope enrichment could not be determined due to the presence of both ^{17}O and ^{18}O and the large P−1 peak typical of benzaldehydes but was estimated as approximately 50% ^{18}O and 7% ^{17}O. ^{1}H and ^{13}C NMR spectra were identical to those of nonlabeled **1**. ^{17}O NMR ($CDCl_3$): δ 20.1 (br s).

2-(4-Formyl-2-methoxyphenoxy)-2-(3,4-dimethoxyphenyl)ethanol (4). Compound **1**, 0.101 g, was dissolved in 2.5 mL of dioxane, and 5.5 mL of 0.5 N NaOH was added, with overnight stirring at rt. The mixture was extracted three times with CH_2Cl_2, washed with water, and dried. The mixture of isomers **1** and **4** was separated using open column silica gel chromatography. The column was slurry-packed with Waltman 60 A, 70−230 mesh, silica gel with the elution monitored by UV at 280 nm. The elution solvent was a 40:60 mixture of ethyl acetate:cyclohexane which was gradually increased to 70% ethyl acetate. The starting compound **1** eluted first. The eluted compound **4** had a single peak on HPLC. Attempts to recrystallize **4** were unsuccessful, and it was observed that **4** by itself or in solution slowly turned dark. MS direct probe (% intensity):

180 (25) [probably 1-(3,4-dimethoxyphenyl)ethan-2-one]$^{\bullet+}$, 152 (10), vanillin$^{\bullet+}$, 151 (100) [vanillin$^{\bullet+}$ − 1], 107 (10) [anisole$^{\bullet+}$ − 1]. ^{1}H NMR (acetone-d_6): δ 3.76, 3.79, 3.95, 3.8 (d, 2H, H-β), 4.23 (m, 1H, α-OH), 5.46 (dd, 1H, H-α), 6.89 (d, 1H, J = 8.2 Hz), 6.97 (dd, 1H, J = 2.0, 8.2 Hz), 7.08 (d, 1H, J = 8.2 Hz), 7.10 (d, 1H, J = 2.0 Hz), 7.36 (dd, 1H, J = 1.9, 8.2 Hz) 7.41 (d, 1H, J = 1.9 Hz). ^{13}C NMR (acetone-d_6): δ 29.80 (CD_3 of solvent is reference) 55.96, 55.99, 56.2, 67.5 (C-β), 83.1 (C-α), 110.8, 111.2, 112.5, 115.4, 119.7, 126.2, 131.3, 131.5, 150.1, 150.4, 151.3, 154.1, 191.2. ^{17}O NMR ($CDCl_3$): δ 90.6 (br s). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.08. Found: C, 64.41; H, 6.34.

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