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Reactions of Lignin Model β-Aryl Ethers with Acetyl Bromide

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Summary

The reactivities of several softwood lignin model compounds with acetyl bromide have been examined in a number of good lignin solvents. Primary (γ-)alcohols acetylate more rapidly than phenolic hydroxyls, whereas benzylic (α-)hydroxyls are converted to bromides via their acetates. Models treated under mild conditions with acetyl bromide cleanly produced acetylated α-bromo derivatives. Benzyl aryl ethers are cleaved rapidly and quantitatively to yield aryl acetates and acetylated α-bromo products. The rate order for the observed reactions is: primary (γ-)OH acetylation > benzyl aryl ether cleavage/bromination > benzylic secondary (α-)OH acetylation > benzylic acetate to benzylic bromide interconversion ≫ phenolic OH acetylation. These reactions are synthetically useful and have further potential in analytical methodologies.

Introduction

Acetyl bromide (AcBr) is familiar to lignin chemists for its ability to dissolve lignocellulosic materials in acetic acid. A rapid and simple method for lignin determination using AcBr (Johnson *et al.* 1961) has been widely applied (Dence 1992) and modified for various purposes (Bagby *et al.* 1973; Iiyama and Wallis 1988; Martin 1967; Morrison 1972). Iiyama and Wallis (Iiyama and Wallis 1989), observing the changes of UV-spectra and UV-specific absorption coefficients of lignin model compounds after AcBr treatment, proposed that AcBr acted as an acylating reagent similar to acetyl chloride, acylating hydroxyls (both aliphatic and phenolic) present in lignin to produce acetylated derivatives. [Nimz (Nimz 1966) had previously demonstrated aryl ether cleavage, bromination and acetylation of a phenylcoumaran model compound using AcBr]. It was also suspected that AcBr might acylate aromatic rings of lignin structural units in some cases in the presence of perchloric acid (Iiyama and Wallis 1989). Later, they examined the reactions of AcBr (with and without perchloric acid) with lignin model compounds and saccharides (Iiyama and Wallis 1990). They found that the rates of the various reactions were in the order *O*-acetylation > bromine substitution ≫ β-ether cleavage ≈ C-acetylation > demethylation. Their reactions of veratrylglycerol-β-guaiacyl ether **1b**, a 4-*O*-etherified β-ether model, gave rather complex arrays of products as determined by HPLC (Iiyama and Wallis 1990). The reactions included full acetylation, acetylation/α-bromination, and β-ether cleavage. Had we been aware of this manuscript we would probably not have chosen to explore the use of this reagent and would not have discovered the remarkable efficiency and selectivity that can be obtained under milder conditions than those described previously (Iiyama and Wallis 1990).

Selective methods for cleavage of α-ether linkages in lignin has recently become a focus of our group in attempts to differentiate between mechanisms for incorporation of ferulate into grass lignins during plant cell wall development (Ralph and Helm 1993). We recently showed that bromotrimethylsilane is an excellent selective reagent for benzyl aryl ether cleavage (Ralph *et al.* 1994a) and became interested in the potential of AcBr to more easily effect similar reactions in a broader range of solvents. This paper reports an investigation into the reactions of β-aryl ether lignin model compounds with AcBr in good lignin solvents aimed at better understanding the reaction and developing new methods for analysis of α-ether linkages in lignin. An unexpected benefit is the synthetic utility of these reactions.

Experimental

Acetyl bromide was purchased from Aldrich Chemical Co. and used without further purification. Commercial analytical reagent grade solvents were used as supplied.

Lignin model compounds **1a**, **1b**, **4b**, **6a** and **6b** (Fig. 1) were synthesized according to the standard methods described in the literature with only minor modification (Landucci *et al.* 1981; Meshgini and Sarkanen 1989; Ralph and Young 1981).

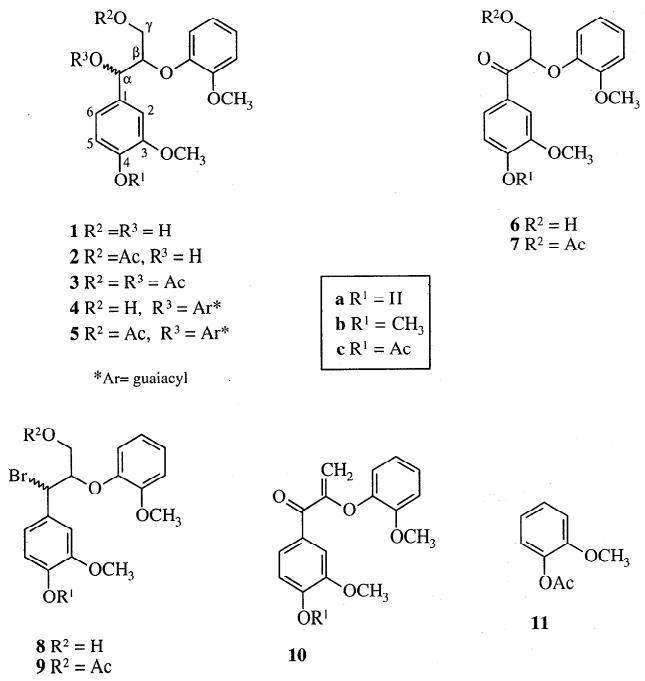

Fig. 1. Lignin model compounds and products resulting from AcBr treatment.

Compounds **2a–5b** and **7b–11** were obtained as described below by the treatment of lignin model compounds with AcBr. Their selected NMR data are listed in Table 1. Full data are reported in the recently released NMR Database of Model Compounds for Lignin and Related Plant Cell Wall Components (Ralph *et al.* 1994b).

^{1}H and ^{13}C NMR spectra were recorded under standard small-molecule conditions on a Bruker AMX-360 instrument in acetone-d_6; the central solvent peaks were used as internal reference (^{1}H, 2.04 ppm; ^{13}C, 29.80 ppm).

Table 1. ^{13}C NMR chemical shifts (in acetone-d_6) for side chain carbons of model compounds and their derivatives from AcBr treatment

Compound	C_α		C_β		C_γ	
	threo	*erythro*	*threo*	*erythro*	*threo*	*erythro*
1a	73.70	73.81	88.58	86.70	61.68	61.80
1b	73.73	73.71	88.20	86.54	61.75	61.82
2a	73.71	73.06	84.07	83.15	64.06	63.93
2b	72.29	73.92	83.45	82.45	63.90	63.61
3a	75.86	–	80.97	–	63.84	–
3b	74.77	75.70	80.84	80.27	63.81	63.23
3c	75.37	74.45	80.68	80.18	63.58	62.89
4b	81.00	81.07	86.13	85.19	61.89	61.72
5b	81.14	80.96	81.72	81.89	64.27	63.91
6a	195.64		83.69		64.11	
6b	195.95		83.81		64.10	
7a	195.10		80.50		64.66	
7b	194.29		79.97		64.84	
7c	195.08		80.40		64.62	
8b	56.04	54.25	85.08	84.93	62.04	61.57
9a	56.15	54.21	81.53	81.36	64.48	63.99
9b	53.92	55.94	81.46	81.33	64.45	64.01
9c	54.92	52.67	81.23	80.97	64.23	63.93

General procedure for AcBr treatment of lignin model compounds

To 0.05 to 0.20 mmoles of lignin model compound in 2 ml of solvent (acetic acid, 1,4-dioxane, or DMF) was added 2.0 to 6.0 equivalents of AcBr *via* syringe. The mixture was kept at room temperature with gentle stirring and monitored by t.l.c. Reactions times ranged from a few minutes to overnight. Reaction was terminated by addition of water (for DMF) or evaporation of solvents (for 1,4-dioxane and acetic acid).

Workup: When the solvent was DMF, water was added and the product was extracted with ethyl acetate. The organic phase was washed with water followed by saturated NH_4Cl (2X), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The gravimetric yield was determined and the product was characterized directly by NMR. When acetic acid or 1,4-dioxane were used as solvent, the solvent was removed on a rotatory evaporator at $<40\,°C$, and evaporated several times following addition of acetone (to remove all traces of solvent before NMR characterization).

Results and Discussion

Acetyl bromide can effect three types of reactions of value to lignin chemists; acetylation, benzylic bromination, and α-ether cleavage. With the correct choice of solvents and conditions, these reactions are selective and significantly cleaner than those that result under the conditions used in lignin determination methods based on AcBr (Iiyama and Wallis 1990).

Acetylation of hydroxyls

Acylation of alcohols and phenols with acyl halides using basic or acidic catalysts is well known, although AcBr is only rarely used for preparative reactions. From the results summarized in Table 2, it is evident that the primary γ-OHs of the model compounds were readily acetylated by AcBr treatment. Although the secondary benzylic hydroxyls, when treated with AcBr in AcOH or 1,4-dioxane, were also acetylated, they subsequently formed α-bromo derivatives in almost quantitative yield (as discussed below). Phenolic OHs were acetylated more slowly than primary (γ-) or secondary benzylic (α-)OHs. When AcBr treatments of model compounds **1a, 1b** were performed in DMF, a basic polar aprotic solvent, the major products were peracetate derivatives, although α-bromides were also obtained. It is likely that most of these reactions can be considered to be acid-catalyzed since small amounts of water in samples will produce HBr. For compounds with α-carbonyl groups, i.e. **6a**, **6b**, acetylation of the γ-OH was extremely rapid. Elimination products **10** were produced quickly and became significant if AcBr treatment in AcOH or 1,4-dioxane exceeded 10 min.

Bromination of benzyl alcohols

Zawadowski (Zawadowski 1968) observed bromination of benzylic hydroxyls with AcBr, and Iiyama and Wallis (Iiyama and Wallis 1990) proposed that

bromides were formed among the products of their reactions (although they were not authenticated). Bromotrimethylsilane (TMSBr) and HBr are known to effectively form benzyl bromides from the benzyl alcohols, and these bromides have been utilized in schemes to generate lignin model quinone methides (Johansson and Miksche 1972; Ralph and Adams 1983). Model compounds **1a** and **1b**, representatives of structural elements predominant in softwood lignins, were completely converted to acetylated α-bromo derivatives **9b** and **9c** after AcBr treatment in acetic acid or 1,4-dioxane (Table 2). This observation confirms the nature of the products proposed by Iiyama and Wallis (Iiyama and Wallis 1990). The cleanliness of AcBr reactions is illustrated by Figure 2, a ^{1}H NMR spectrum of the crude total product from AcBr treatment of **1a**. AcBr is therefore synthetically useful for selective bromination of benzylic hydroxyls in the presence of other primary or secondary hydroxyls. Additionally, if stereochemical integrity is not a problem, AcBr may be used to selectively acetylate primary and/or phenolic hydroxyls in the presence of benzylic hydroxyls because the resulting benzylic bromide can be readily hydrolysed (acetone/water) back to the benzylic hydroxyls without impacting the acetates.

In order to determine the relative rates of acetylation and bromination reactions, we examined the products obtained from reactions terminated after 60 min, 90 min, and overnight (O/N) (Table 2). It was found that the acetylation of γ-OH proceeded faster than that of benzylic OH during the AcBr treatment in acetic acid. The α-bromo product is formed *via* the α-acetate intermediate **2** (e.g. **2b** from **1b**). Therefore, Iiyama and Wallis observation (Iiyama and Wallis 1990) of diacetates is simply an indication of too short a reaction time (or that bromides were partially hydrolyzed in subsequent work-up). Treatment of *threo* model compound **1a** with AcBr in AcOH or 1,4-dioxane resulted in a mixture of 2 diastereomers (about 1 : 1) of α-bromo derivatives **9b** suggesting an S_N1 reaction via the benzyl carbonium ion. Functional group interconversion (acetate to bromide) will occur from free-phenolic or 4-etherified compounds but is very slow from 4-*O*-acetates. No bromide formation was observed when the fully acetylated compound **1c** was used (Table 2). This could be because little HBr is produced when reacting compounds with no hydroxyls; much of the reactivity is presumably attributable to HBr. The completeness of reactions in dioxane or acetic acid implies that phenolic acetylation by AcBr is much slower than benzylic alcohol acetylation. In DMF, phenolic acetylation must be significantly faster and bromination from the acetate must occur slowly since only the acetates are observed after treatment of **1b** for 90 min whereas 25 % of the product is bromide **9b** after 12 h (Table 2).

Table 2. The products from reactions of lignin model compounds with acetyl bromide in some good lignin solvents

Model compound	Solvent	Time	AcBr (eq.)	Products ratios
1a	Acetic acid	60 min	6	**9c** (> 98)
		O/N	6	**9c** (> 98)
	1,4-dioxane	60 min	6	**9c** (8) + **9a** (92)
		O/N	6	**9c** (> 98)
	DMF	60 min	6	**9c** (17) + **3c** (58) + **3a** (17) + **2a** (6)
		O/N	6	**9c** (18) + **3c** (76) + **3a** (6)
1b	Acetic acid	90 min	4	**9b** (59) + **2b** (41) + **3b** (trace)
		O/N	4	**9b** (> 98)
	1,4 dioxane	90 min	4	**9b** (> 98) + **3b** (< 1)
		O/N	4	**9b** (> 98)
	DMF	90 min	4	**3b** (80) + **2b** (20)
		O/N	4	**3b** (75) + **9b** (25)
1c	1,4-dioxane	O/N	2	**1c** (no reaction)
4b	Acetic acid	8 min	4	**9b** (> 98) + **11** (> 98)
	1,4-dioxane	8 min	4	**9b** (> 98) + **11** (> 98)
	DMF	30 min	4	**5b** (> 97)
6a	Acetic acid	10 min	2	**7a** (> 94) + **10a** (< 6)
	1,4-dioxane	10 min	2	**7a** (93) + **10a** (3.5) + **7c** (3.5)
	DMF	10 min	2	**7a** (98) + **7c** (2)
6b	Acetic acid	10 min	4	**7b** (> 95) + **10b** (< 5)
	1,4-dioxane	10 min	4	**7b** (> 95) + **10b** (< 5)
	DMF	10 min	4	**7b** (100)

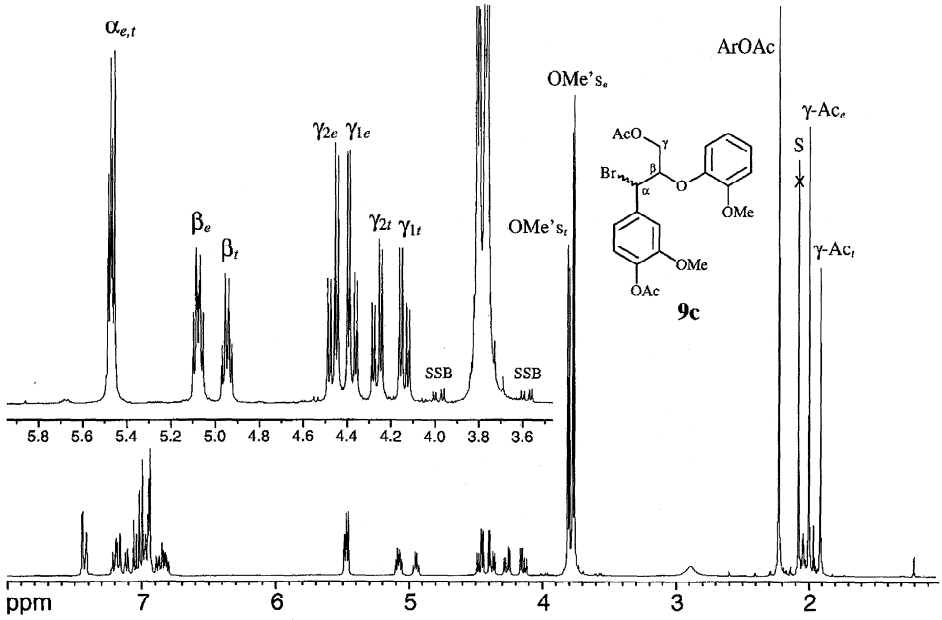

Fig. 2. Proton NMR spectrum of crude total product from AcBr treatment of **1a** producing bromides **9c**. *t = threo, e = erythro*, SSB = spinning sidebands, S = solvent residue (acetone). No bromide degradation or β-ether cleavage was detectable after several days in AcBr.

The cleavage of non-cyclic benzyl aryl ethers

The presence and quantity of non-cyclic benzyl aryl ether (α-*O*-4) substructures in lignin have been controversial. Methods for distinguishing α- from β-ethers are becoming more important because of the fundamentally different mechanisms for their formation (nucleophilic addition to quinone methides *vs* radical coupling) and their biochemical implications (Ralph and Helm 1993). There are several methods used to cleave and quantitate benzyl aryl ether substructures. Perhaps the simplest uses mild acid hydrolysis (Lai and Guo 1992). The increase in phenolic content is measured following reaction conditions which do not appear to cleave β-ethers. Recently, we developed a bromotrimethylsilane (TMSBr) method which works superbly on lignin model compounds (Ralph *et al.* 1994a) but is not effective for quantitative analysis of α-aryl ether linkages in lignin. This is because the reagent rapidly reacts with water and lignin has very low solubility in totally anhydrous solvents that are compatible with TMSBr (e.g. dioxane). We assumed that AcBr would efficiently cleave non-cyclic benzyl aryl ethers although this was not specifically mentioned as a solubilizing mechanism by Iiyama and Wallis (Iiyama and Wallis 1990). Since writing this manuscript we have been reminded of a report (Nimz 1966) indicting that even cyclic benzyl aryl ethers are efficiently cleaved. AcBr has been used for the cleavage of simple cyclic ethers under more drastic conditions. For example, refluxing simple cyclic ethers with AcBr and Lewis acid catalysts yielded acetoxy bromoalkanes (Veejendra and Alex 1986).

In this study we found that the benzyl aryl ether model compound **4b** was cleaved rapidly and cleanly, without impacting the β-ether after > 12 h. NMR spectra of the products showed that the α-bromo acetylated product **9b** and 2-methoxy phenyl acetate **11** were formed essentially quantitatively in AcOH or 1,4-dioxane (Table 2). The mechanism of α-ether cleavage by AcBr presumably follows an S_N1 process resulting in a mixture of α-bromo diastereomers **9b**. The possibility that the cleavage reaction follows an S_N2-like mechanism with fast isomerization can not be ruled out; anchimerically assisted reactions followed by bromide isomerization have recently been observed in this laboratory (Ralph et al. 1994a).

Conclusion

The relative rates of reactions observed between AcBr and β-aryl ether lignin model compounds under mild conditions is: primary (γ-)OH acetylation > benzyl aryl ether cleavage/bromination > secondary benzylic (α-)OH acetylation > benzylic acetate to benzylic bromide interconversion ≫ phenolic OH acetylation. Under these conditions, no β-aryl ether cleavage or demethylation (reported previously under harsher conditions (Iiyama and Wallis 1990)) were detectable. The cleanliness and reproducibility of these reactions suggests that lower reaction temperatures should be examined for AcBr lignin determination methods. The selective bromination of benzyl alcohols by AcBr is synthetically useful. Selective cleavage of benzyl aryl ethers by AcBr may provide a new technique for the analysis of α-aryl ether

linkages and for quantitating hydroxycinnamic acids that are passively incorporated to lignin. Such applications are being evaluated in our laboratory.

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