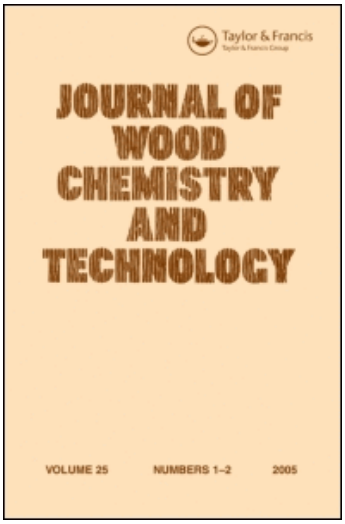

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EVIDENCE FOR INCREASED STERIC COMPRESSION IN *ANTI* COMPARED TO *SYN* LIGNIN MODEL QUINONE METHIDES[1]

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ABSTRACT

Two new lignin model quinone methides (QMs) have been characterised by ^{1}H and ^{13}C NMR techniques. It was shown that the QMs existed in solution as non-interconverting *syn* and *anti* isomers, in a ratio of 2:1. Evaluation of chemical shift data and nuclear Overhauser effects from these and previously synthesised QMs showed that the *anti* isomer was under greater steric strain than the *syn* isomer. Additional evidence for the increased steric strain was obtained from a relative kinetic study of the addition of primary amines to the QMs.

INTRODUCTION

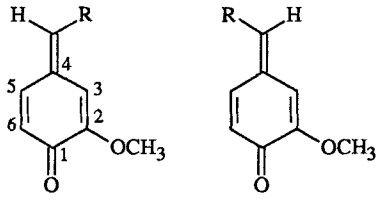
It is well established that *p*-quinone methides are key intermediates in alkaline-additive wood-pulping reactions. They have also been implicated as the biosynthetic precursors of lignin, lignans, neolignans, and flavanoids.[4] Generally, studies on quinone methides have been complicated by their instability under normal laboratory conditions. Often they are observed as transient species, or are stabilised by the addition of radical scavengers, or substitution of

stabilising groups.[5] QMs derived from 2-methoxy substituted lignin model compounds have been shown to be stable in solution for weeks, if oxygen is excluded. This stability, due to the presence of the electron-donating methoxy substituent, has allowed the synthesis and characterisation of a range of lignin model quinone methides.[6]

These QMs undergo addition reactions with nucleophiles such as water, hydroxide ion, hydrosulphide ion, alcohols, acids, amines, thiols and reduced species of anthraquinone at the electron-deficient α-carbon position.[6a,7] It is reactions of this type which are believed to be an important step in delignification reactions occuring in some wood-pulping processes.[8] Thus, quinone methides of this type play a major role in making one of the major industrial processes in the world a viable procedure.

It is widely believed that QM formation is the rate-determining step in most alkaline-additive wood delignification reactions,[8] yet few details are known of the mechanism of QM formation. Miksche[8] has shown that at pH > 11, rate = k[phenolate ion] for 4-hydroxy-3-methoxy benzyl alcohols, and that at room temperature the rate of formation of QMs from the phenolate anions of these benzyl alcohols is negligible - a temperature of 110 °C is required before $k = 10^{-3}$ min^{-1}. The rate of formation of QMs of 4-hydroxy-3-methoxybenzyl acetates or bromides, even at room temperature is much faster as the elimination of the acetate[7e] or bromide[6a] from the phenolate is more facile and appears to be concommittant with phenolate ion formation. Other studies[8,9] have indicated the pH dependence of the mechanism of addition of hydroxy compounds to QMs (the reverse reaction to QM formation). At pH < 4 a benzylic carbonium ion is thought to be the key intermediate, whereas at intermediate pH a plurality of mechanisms (QM vs carbonium ion) may exist.

In the literature pertaining to the synthesis and characterisation[6] of 2-methoxy substituted lignin model QMs, the preferred formation of the *syn* isomer (2:1 ratio compared to the *anti* isomer) of these compounds was noted.[6b,6c] Although a study on QMs with donor substituents on the exocyclic carbon has determined that low barriers to rotation about C4-Cα exist,[10] the situation was not clear for 2-methoxy substituted QMs. We wish to show here that the 2:1 ratio of *syn*:*anti* QMs **1-5** was observed under a wide range of conditions,



syn *anti*

and that the isomers did not interconvert under the conditions used.There was good evidence from nuclear Overhauser effects (n.O.e.) and relative kinetic treatments that the *anti* isomer was under greater steric strain than the *syn* isomer, possibly explaining the observed excess of the *syn* isomer.

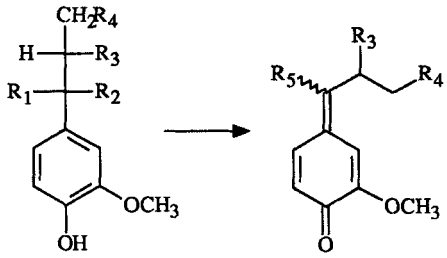
RESULTS AND DISCUSSION

The various routes to QMs **1-6** are summarised in Table 1. Comparison of entries (a)-(d) with (e) suggests a non-dependence of the *syn*:*anti* ratio on the benzylic leaving group, and entries (a)-(i) show that the ratio was independent of the side-chain stereochemistry. The ratio also remained unchanged whether the bromides were diastereomerically pure (>9:1 *threo*:*erythro*) or 1:1 mixtures. QMs formed in $CDCl_3$, CCl_4, or C_6D_6 showed no variation in the *syn*:*anti* ratio (entry (g)). QM **6**, formed via a free-radical mechanism, gave the same 2:1 ratio of isomers as QMs **1-5** (entry j). The above evidence suggested that the ratio of the isomers was independent of the structure of the side-chain on the methylenecyclohexadienone moiety, independent of the solvent (to some extent), and independent of free-radical *vs* ionic formation pathways. Thus it seemed likely that the preference for the *syn* isomer was arising after the leaving group had been eliminated.

Variable temperature ^1H NMR experiments showed no change in the ratio of isomers from -10 °C to +80 °C. Also, the formation of **2** was carried out at 0 °C and +50 °C; in both cases there was no observable change in the ratio of the isomers.[11] From this evidence it seemed that the *syn*:*anti* ratio did not reflect a pair of interconverting isomers at dynamic equilibrium.

TABLE 1

Various Routes to Quinone Methides **1-6**



Entry	Phenol Substitution				Reaction[a]	QM[b,c]
	R_1	R_2	R_3[d]	R_4		
(a)	Br	H	OAr	OH	(i)	**1 a**
	H	Br	OAr	OH	(i)	**1 a**
(b)	Br	D	OAr	OH	(i)	**1 b**
	D	Br	OAr	OH	(i)	**1 b**
(c)	Br	H	OAr	H	(i)	**2 a**
	H	Br	OAr	H	(i)	**2 a**
(d)	Br	D	OAr	H	(i)	**2 b**
	D	Br	OAr	H	(i)	**2 b**
(e)	OAc	H	OAr	OAc	(ii)	**3 a**
	H	OAc	OAr	OAc	(ii)	**3 a**
(f)	H	Br	Ar'	OTBDMS	(iii)	**4 a**
	Br	H	Ar'	OTBDMS	(iii)	**4 a**
(g)	H	Br	Ar"	OTBDMS	(iii),(iv)	**5 a**
	Br	H	Ar"	OTBDMS	or (v)	**5 a**
(h)	D	Br	Ar"	OTBDMS	(iii)	**5 b**
	Br	D	Ar"	OTBDMS	(iii)	**5 b**
(i)	OAc	D	Ar"	OTBDMS	(ii)	**5 b**
(j)	isoeugenol				(vi)	**6**[e]

[a](i) $NaHCO_3/D_2O/CDCl_3$ (ii) $NaOD/D_2O/CDCl_3$(iii) $K_2CO_3/D_2O/CDCl_3$ (iv) $K_2CO_3/D_2O/CCl_4$ (v) $K_2CO_3/D_2O/C_6D_6$ (vi) Ag_2O/CCl_4. [b] **a** R_5 = H, **b** R_5 = D [c] All 2:1 *syn:anti* [d] Ar = 2-CH_3O-C_6H_4 Ar' = 3,4-$(CH_3O)_2$-C_6H_3 Ar" = 2,3-$(CH3O)_2$-C_6H_3. [e] **6** = 2-methoxy-4-(allylidene)-cyclohexa-2,5-dienone.

An explanation for the excess of the *syn* isomer may be found in consideration of the NMR data reported in this and other papers.[6b,6c] It has been shown that a steric interaction exists between Hβ and H3 in the *syn* isomers, and Hβ and H5 in the *anti* isomers of compounds **1-3**.[6b] This interaction was manifested in the ^{1}H NMR spectra by deshielding of the H3 *syn* and H5 *anti* protons, and hence downfield shifts in their resonances relative to the resonances from the non-compressed protons H3 *anti* and H5 *syn*. The ^{13}C NMR spectra showed corresponding shielding of the C3 *syn* and C5 *anti* carbons, with upfield shifts relative to the resonances from C3 *anti* and C5 *syn*. Other evidence was obtained from the homonuclear ^{1}H n.O.e. enhancement of the H3 *syn* and H5 *anti* resonances on irradiation of the Hβ resonances.

Consideration of the appropriate ^{1}H NMR data for **5a** shows that the downfield shift in the H3 *syn* resonance, relative to that of H3 *anti* is less than the downfield shift of H5 *anti* relative to H5 *syn* (Table 2). These differences were mirrored in the ^{13}C spectra, with the upfield shift of C3 *syn* relative to C3 *anti* being less than that of C5 *anti* relative to C5 *syn*. Also of note, in a difference n.O.e. experiment, was the larger enhancement of the H5 *anti* resonance (15%) when Hβ *anti* was irradiated, compared with that observed in the H3 *syn* resonance (10%) when Hβ *syn* was irradiated. These results suggest that the extent of through space interaction between Hβ *anti* and H5 *anti* was greater than that between Hβ *syn* and H3 *syn* - the greater interaction in the *anti* isomer may be attributable to a shorter distance between Hβ and H5 in the *anti* isomer compared to that between Hβ and H3 in the *syn* isomer - hence the *anti* isomer may be under greater steric strain than the *syn* isomer.

It is possible that the influence of the methoxyl group on the C2-C3 double bond length may cause some distortion in the cyclohexadienone ring. Such a distortion could lead to a decrease in the internuclear distance between Hβ *anti* and H5 *anti* compared to Hβ *syn* and H3 *syn*.[12] If the formation of the QMs was under product development control, the favoured transition state would be that leading to the more stable (less sterically crowded) *syn* isomer. A 2:1 ratio suggests that the energy difference between the 2 isomers is very small, and in the transition state leading to their formation one can envisage the possibility of the two isomers interconverting through a common transition state, either by rotation about the developing C4-Cα double bond, or via microscopic reversibility of the leaving group elimination.

TABLE 2

Chemical Shift Evidence for Steric Compression between Hβ and H3 in *syn*-**5a** and Hβ and H5 in *anti*-**5a**.

Nucleus	δ_1		δ_2		$\delta_1 - \delta_2$
	compressed		non-compressed		
^1H	*s*-H3	6.73	*a*-H3	6.29	0.44
	a-H5	7.64	*s*-H5	7.06	0.58
^{13}C	*s*-C3	104.1	*a*-C3	111.9	-7.8
	a-C5	132.7	*s*-C5	141.8	-9.1

TABLE 3

Relative Rates of Addition of Amines to **1b**, **2b**, and **5b**.

QM	RNH_2	No. additions	k_{anti}/k_{syn}
1 b	R = $-(CH_2)_2OH$	13	1.3 ± 0.1
2b	R = $-(CH_2)_2OH$	7	1.4 ± 0.2
2b	R = $-C(CH_3)_3$	10	1.4 ± 0.2
5 b	R = $-(CH_2)_2OH$	5	1.4 ± 0.3

Relative Rate of Addition of Amines to QMs

To test our hypothesis that the *anti* isomer may be under greater steric strain than the *syn* isomer, the relative rates of addition of primary amines to **1b**, **2b**, and **5b** were determined. It was thought that the proposed greater interaction present in the *anti* isomer may lead to this isomer reacting slightly faster with nucleophiles than the *syn* isomer, owing to the relief of steric strain. Primary amines were chosen as the most suitable nucleophiles, since the rate of addition of amines to QMs has been shown to be fast and irreversible.[4a] By adding a *ca.* 0.1 mole-equivalent aliquot of the amine to the QM (in $CDCl_3$ solution in a 5mm NMR tube) and measuring the *syn*:*anti* ratio, it was possible to determine the relative rate of addition of the amine to each isomer. This procedure was repeated until the QM was consumed. The results are summarised in Table 3. Although the errors inherent in the determination are large, the slightly faster addition of the amines to

TABLE 4

^{1}H NMR Data for QMs **4** and **5**
a) Chemical Shift

QM[a]	Me_2Si	^{t}BuSi	OCH_3	γ^b	β	α	H3	H5	H6	B ring
s-**4 a**	-0.02 -0.01	0.828	3.77 3.86 3.94	.	4.11[c]	6.55[d]	6.61[e]	7.08	6.42[e]	6.75-6.90
a-**4 a**	-0.01	0.825	"	.	4.20[c]	6.60[d]	6.30[e]	7.58[f]	6.48[e]	"
s-**5 a**	-0.01 -0.02	0.820	3.85 3.83 3.75	.	4.56[c]	6.59[d]	6.73[e]	7.06[f]	6.39[e]	6.82,7.03[g]
a-**5 a**	-0.01	0.81	"	.	4.63[e]	6.64[d]	6.29[e]	7.64[f]	6.47[e]	"
s-**5 b**	-0.01	0.82	"	.	4.56[e]	-[h]	6.73[i]	7.05[e]	6.39[i]	"
a-**5 b**	-0.01	0.81	"	.	4.63[e]	-[h]	6.29[i]	7.64[e]	6.47[i]	"

b) Coupling Constants

QM	$J_{\alpha\beta}$	$J_{\beta\gamma_1}$	$J_{\beta\gamma_2}$	J_{35}	$J_{3\alpha}$	J_{56}	$J_{5\alpha}$	$J_{6\alpha}$
s-**4 a**	9.9	.	.	2.3	<0.3[j]	9.7	<0.3[j]	0.3
a-**4 a**	10.1	.	.	1.8	<0.3[j]	9.7	<0.3[j]	1.4
s-**5 a**	8.6	.	.	2.2	0.5	8.2	<0.3[j]	0.5
a-**5 a**	7.9	.	.	2.0	<0.3[j]	8.3	0.4	1.5
s-**5 b**	-[h]	6.5	6.8	2.3	-[h]	9.5	-[h]	-[h]
a-**5 b**	-[h]	6.5	6.8	2.0	-[h]	9.8	-[h]	-[h]

[a] *s* = syn, *a* = *anti*, [b] Hγ resonances overlapping methoxyl resonances, [c] multiplet, [d] dddd, [e] dd, [f] ddd, [g] B ring resonances overlapping H5 *syn*, [h] not observed, [i] doublet, [j] not fully resolved

the *anti* isomer was consistently observed, strengthening our case for the relief of steric strain hypothesis.

EXPERIMENTAL

NMR Methods

All NMR spectra were recorded on a Bruker AC200 FT NMR spectrometer. For the nOe determination, the sample was first degassed using the freeze-thaw technique.[13] The difference nOe experiment was carried out using the Bruker pulse microprogram NOEDIFF. Irradiation was applied with a power of 60 μW for 5 seconds, and a delay between each acquisition of 3 seconds. The parent phenolic precursors[14] and the QMs **1**-**3**[6a,7e] and **6**[14g] were synthesised as described previously. QMs **4a** and **5a** have previously been formed *in situ*[14h] with no reported ^{1}H NMR data. Assignments of the ^{1}H NMR resonances for each isomer of QMs **1**-**3** have been reported previously.[6b] The relevant ^{1}H data for **4** and **5** are reported in Table 4. ^{13}C NMR data for **5a** have been presented elsewhere.[15] As the QMs were only stable in solution, elemental or mass spectral analyses were not possible.

Relative Rate Determination

The QM (0.02-0.04 mmol) in $CDCl_3$ or C_6D_6 was treated with successive *ca.*0.1 mole-equivalents of the amine (in CCl_4) in the NMR tube. For each addition a quantitative ^{1}H spectrum was obtained and the *syn*:*anti* ratio determined by integration of the relevant H3, H5 and H6 resonances. By comparing integrals to that of CH_2Cl_2 added as an internal standard, an estimation of the amount of added amine could be determined, as well as the amount of each isomer present. The amount of each isomer reacting for each addition of a known amount of amine could then be calculated, and the result expressed as the relative ratio of the reaction rates k_{anti}/k_{syn}.

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REFERENCES

1. R.M. Ede, J. Ralph and L. Main, presented in part at the 4th International Symposium on Wood and Pulping Chemistry, Paris, April 1987. Proceedings 2, 171.

2. Author to whom correspondence should be addressed.

3. Present adress: Dairy Forage Research Centre, USDA, 1925 Linden Drive West, Madison, Wisconsin 53706, U.S.A.

4. See for example Oxidative Coupling of Phenols, W.I. Taylor and A.R. Battersby (eds), Marcel Dekker, New York, 1967.

5. P. Grunanger, in Methoden der Organischen Chemie, E. Mueller and O. Bayer (eds), G. Thieme Verlag, Stuttgart, Vol. VII/3b, p. 397.

6. (a) J. Ralph and R.A. Young, J. Wood Chem. Technol., 3, 183, 1983. (b) J. Ralph and B.R. Adams, J. Wood Chem. Technol., 3, 161 1983. (c) J. Ralph and R.M. Ede, Holzforschung, 42, 337, 1988.

7. (a) G. Leary, I.J. Miller, I.J., W. Thomas, and A.D. Woolhouse, J. Chem. Soc., Perkin Trans 2, 1737, 1977. (b) G. Leary and W. Thomas, Aust. J. Chem., 30, 2323, 1977. (c) J.A. Hemmingson and G. Leary, J. Chem. Soc., Perkin Trans. 2, 1584, 1975. (d) J.A. Hemmingson, Aust. J. Chem., 32, 225, 1979. (e) L.L. Landucci, and J. Ralph, J. Org. Chem., 47, 3486, 1982.

8. G.E . Miksche, in Chemistry of Delignification with Oxygen, Ozone, and Peroxides, J.S. Gratzl, J. Nakano and R.P. Singh (eds), Uni Publishers Co., Tokyo, p107, 1980.

9. (a) G.D. Cook and B.E. Norcross, J. Am. Chem. Soc., 78, 3797, 1956. (b) L. Ivnas and B.O. Lindgren, Acta Chem. Scand., 15, 1081, 1961. (c) B.O. Lindgren, Acta Chem. Scand., 17, 2199, 1963. (d) F. Nakatsubo, K. Sato, and T. Higuchi, Mokuzai Gakkaishi, 1976, 22, 29, 1976.

10. U. Berg and J. Sandstrom, Acta Chem. Scand., B32, 41, 1978.

11. These variable temperature experiments were limited by the instability of the QM above 60 °C and difficulties in preparing the QM at temperatures lower than 0 °C.

12. The reader may find molecular models useful in visualising this effect

13. J.H. Noggle and R.E. Shirmer, The Nuclear Overhauser Effect. Chemical Applications, Academic Press, New York, 1971.

14. (a) E. Adler, B.O. Lindgren, and U. Saedén, Svensk Papperstidn., 55, 245, 1952. (b) E. Adler, and E. Eriksoo, Acta Chem. Scand., 9, 341, 1955. (c) K. Kratzl, W. Kisser, J. Gratzl, and H. Silbernagel, Monatsch Chem., 90, 771, 1959. (d) F. Nakatsubo, and T. Higuchi, Holzforschung, 29, 193, 1975. (e) L.L. Landucci, S.A. Geddes, and T.K. Kirk, Holzforschung, 35, 67, 1981. (f) J. Ralph and R.A. Young, Holzforschung, 1981, 35, 165, 1981. (g) A. Zanarotti, J. Chem. Res. (M), 2625, 1983. (h) J. Ralph, R.M. Ede, L. Main, and N. Robinson, J. Wood Chem. Technol., 7, 133, 1987.

15. R. M. Ede, The Synthesis and Reactivity of β-Aryl Lignin Model Quinone Methides, D. Phil. Thesis, University of Waikato, Hamilton, New Zealand, 1987.