Adducts of Anthrahydroquinone and Anthranol with Lignin Model Quinone Methides. 4. Proton NMR Hindered Rotation Studies. Correlation between Solution Conformations and X-ray Crystal Structure

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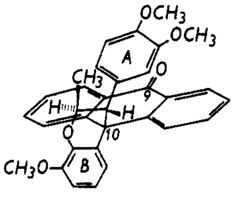
The acetylated anthrahydroquinone/lignin model quinone methide adduct *threo*-1-(4-acetoxy-3-methoxyphenyl)-1-(9,10-dihydro-10-hydroxy-9-oxoanthracen-10-yl)-2-(2-methoxyphenoxy)propane (1) exhibits hindered rotation in the proton NMR spectrum near room temperature. The spectral dispersion of aromatic and methoxyl protons caused by substantial shielding effects allows a detailed conformational assignment. X-ray crystallography of 1 reveals that the molecule exists in the solid state in a conformation very similar to that proposed in solution and that the single conformer in the crystalline state is the same as the major (62%) solution-state rotamer.

In earlier studies[1-5] of the catalytic delignification of wood by anthraquinone, adducts 1-4, representing proposed intermediates, were synthesized by reaction of anthrahydroquinone (AHQ) with lignin model quinone methides, followed by appropriate derivatization.

The proton NMR spectra[1,2,4,5] of these adducts were consistent with the "threo" conformation shown.[6,7] The threo stereochemistry has since been confirmed by a rigorous conformational analysis[2] of the dehydration product 5 and by independent synthesis[3] of both stereoisomers of 1.



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It was noted in the earlier papers[1-3] that some of these compounds exhibited hindered rotation phenomena[8-13] in their proton NMR spectra. The more detailed study presented here explores the similarity between the solid-state structure of 1 and its solution conformation.

Temperature-Dependent Proton NMR Spectra

Proton NMR spectra in $CDCl_3$ of 1 recorded at probe temperatures of −30, 7, 18, and 39 °C are shown in Figure 2.

At low temperature (−30 °C) the two rotameric forms are clearly distinguished and the spectrum has the appearance of being a composite of two isomers in a 62:38 ratio. As the temperature is raised, coalescence occurs at 7 °C, and at 39 °C the spectrum more closely resembles that of a single isomer, although some broadening of the A3 methoxyl is still apparent and the A2 and A6 protons are unresolved. At high temperatures, rotation is fast on the NMR time scale so an average spectrum is observed. In acetone-d_6 hindered rotation and the coalescence point occur at lower temperatures, so that ambient probe temperature spectra more closely resemble the high-temperature limit. The motion which is hindered is presumably the rotation of ring A about the C_α-C_{A1} bond. The ring A methoxyl can be either over ring C or ring D of the anthracenyl system. The predominant rotamer (62%) is that with the most highly shielded A3 methoxyl and is presumably the one shown in Figure 1a, with the A3-methoxyl over ring C. For steric reasons, it is anticipated that the methoxyl cannot approach ring D as closely in the other rotamer (38%).

Compounds 2, 3, and 5 exhibited similar behavior, as summarized in Table I.

Adduct 4 and its derivatives do not exhibit hindered rotation near ambient probe temperature whereas adducts with a γ-substituent do. Presumably a γ-substitution results in a more rigid conformation, with ring A in closer proximity to the anthracenyl ring; 10-substitution has a similar effect. Thus, whereas anthranol adducts (10-H) with a γ-substituent do not exhibit hindered rotation near room temperature, the corresponding AHQ adducts (10-OH) do, and compounds with a 10-OAc or 10-OMe but no γ-substitution also do. Attempts to prepare adducts with both large 10-substituents (OAc, OMe) and γ-substitution were unsuccessful because of severe steric crowding.

[†] Maintained at Madison, WI, in cooperation with the University of Wisconsin.

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(7) While the anthracenyl ring system is drawn planar, it was recognized[1] that the central ring would pucker to minimize steric interactions between the 10-substituents and the *peri*-hydrogen atoms at C-4 and D-5.
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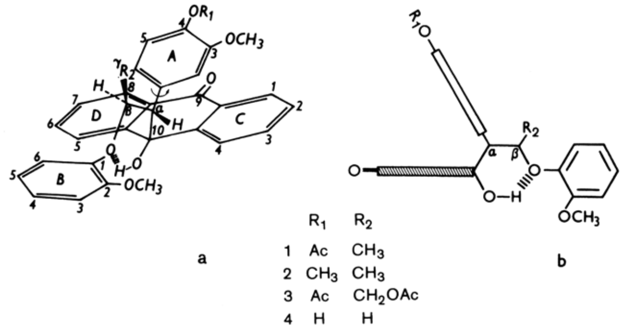
Table I. ^{1}H NMR Chemical Shift Data at High and Low Temperatures for Ring A Protons

compd	1			2			3			5		
temp, °C	39	−30		20	−40		19	−49		18	−13	
rotamer[b]		A	B		A	B		A	B		A	B
solvent[a]	C	C	C	Ac	C	C	C	C	C	Ac	Ac	Ac
H-2	5.55	5.61	5.42	5.60	5.50	5.32	5.57	5.55	5.48	5.1, 5.5[c]	5.09	5.42
H-5	6.52	6.64	6.49	6.39	6.43	6.31	6.51	6.62	6.47	6.35	6.40	6.35
H-6	5.55	5.44	5.75	5.57	5.42	5.73	5.59	5.50	5.72	5.1, 5.5[c]	5.48	5.07
3-OMe	3.37	3.33	3.46	3.36	3.40	3.52	3.36	3.29	3.43	3.25	3.16	3.27

[a] C = $CDCl_3$, Ac = acetone-d_6. [b] A = major rotamer, B = minor rotamer. [c] A2 and A6 protons are broad humps.[2]



	R_1	R_2
1	Ac	CH_3
2	CH_3	CH_3
3	Ac	CH_2OAc
4	H	H

Figure 1.

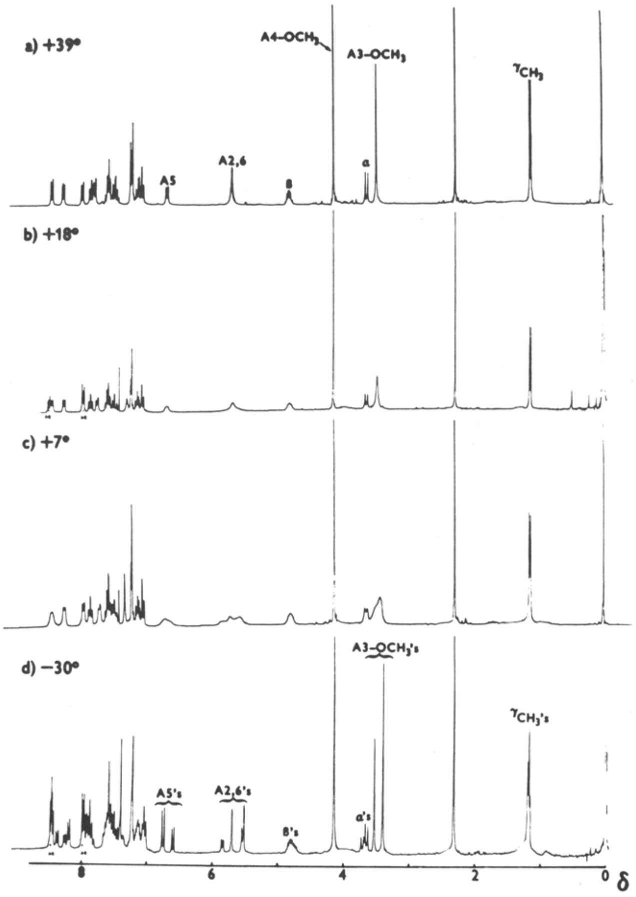


Figure 2. 270-MHz ^{1}H NMR spectra of 1 at different temperatures.

NMR lineshape methods have been used to study rate processes with activation energies of 20–100 kJ/mol (5–25 kcal/mol).[8] Analysis of the temperature-dependent NMR spectra allows the free energy difference between the major (A) and minor (B) rotamers (ΔG_{AB}), the activation energies ($\Delta G^{\ddagger}_A$, $\Delta G^{\ddagger}_B$), and the rate constants for the rotation (k_A, k_B) to be determined. However, analysis of the rate processes for the coalescing singlet A3 methoxyl peaks is complicated by the nonequal population distribution of the two rotamers, and the nonequality of the T_2 relaxation times at the two sites. The validity of approximate analysis methods has been examined by Kost et al.,[14] who found that the method of Shanan-Atidi and Bar-Eli[15] gave extremely close agreement with the full lineshape analysis method. The values obtained, Table II, were in good agreement with a partial lineshape analysis by the method of Nakagawa.[16]

Table II. Parameters of Hindered Rotation from A3-Methoxyl Peak Coalescence in 1[a]

$k_A = 42/s$
$k_B = 70/s$
$\Delta G_{AB} = 280$ cal/mol = 1.2 kJ/mol
$\Delta G^{\ddagger}_A = 14.25$ kcal/mol = 59.6 kJ/mol
$\Delta G^{\ddagger}_B = 13.97$ kcal/mol = 58.4 kJ/mol

[a] Parameter symbols are those used in ref 15. $\Delta P = 0.625 - 0.375 = 0.25$ (relative concentration (integral) difference). $T_c = 7$ °C = 280 K (coalescence temperature). $\Delta\nu = 35.3$ Hz (frequency difference in low temperature limit).

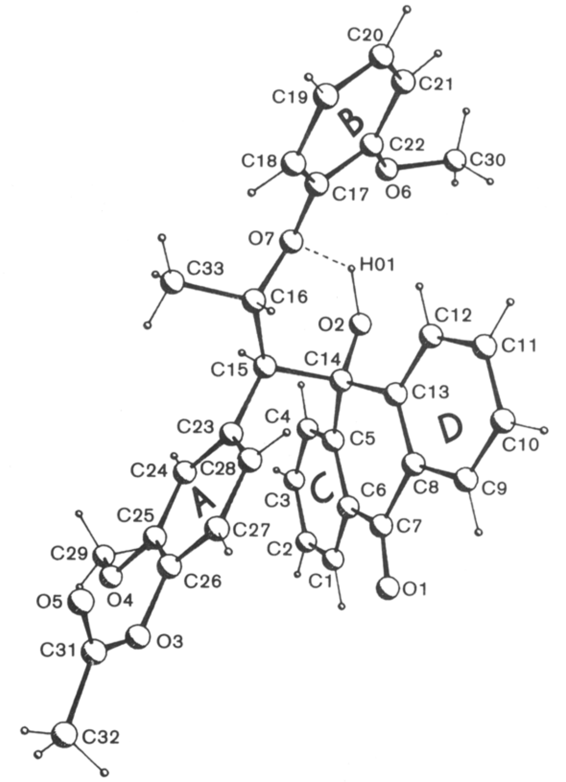


Figure 3. X-ray crystal structure atom-labeling scheme for 1.

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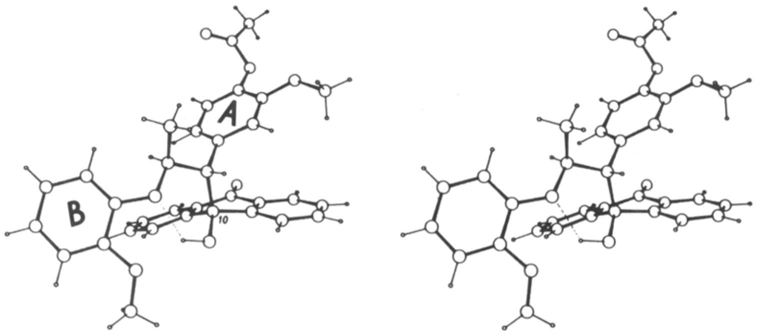

Figure 4. Stereographic projection of the molecular structure of 1.

Table III. Calculation of Predicted Chemical Shifts and Comparison with Observed Chemical Shifts in 1

	$P_C{}^a$	$Z_C{}^a$	$P_D{}^a$	$Z_D{}^a$	$\Delta_{J/B}{}^b$	$\delta_0{}^c$	$\delta_{predicted}{}^d$	$\delta_{obsd}{}^e$ major	$\delta_{obsd}{}^e$ minor
H2	1.062	3.095	5.520	2.199	1.18	6.90	5.72	5.61	5.42
H5	4.708	3.712	2.729	4.090	0.26	6.95	6.69	6.64	6.49
H6	4.482	2.302	1.277	2.750	1.33	7.00	5.67	5.44	5.75
A3-OMe[f]	1.597	4.269	7.638	2.761	0.43	3.80	3.37	3.33	3.46

[a] P is the distance in Å from the center of the plane (of ring C or D) to the projection of the atomic coordinate on that plane. Z is the vertical distance (Å) from the plane to the atom. [b] Johnson/Bovey shielding values from eq 6, ref 18, using an average C–C distance = 1.39 Å, spacing = 0.918 ring radii. [c] Unperturbed chemical shifts, from spectra of lignin models.[5] [d] $\delta_{predicted} = \delta_0 - \Delta_{J/B}$. [e] δ_{obsd} from Table I. [f] The geometric center of the methoxyl hydrogens is used.

Crystal and Molecular Structure of 1

Small colorless plate-like crystals of 1 suitable for X-ray crystallography were obtained from acetone/pentane (see Experimental Section). Analysis showed that the crystal contains discrete molecules of $C_{33}H_{30}O_7$ with no unusual intermolecular contacts. Positional parameters, bond lengths, and bond angles are included as supplementary material; a diagram of the molecule showing the atom-labeling scheme is given in Figure 3.

The hydrogen-bonded 10-hydroxyl proton (HO1 on O2 in Figure 3) was located directly from the X-ray data. It is undoubtedly bonded to the guaiacyl oxygen (O7, Figure 3), as proposed earlier,[1,4] since the HO1–O7 distance is 1.81 Å; it may also be weakly bonded to the methoxyl oxygen (O6, Figure 3, 2.04 Å).

The conformation that the molecule adopts in the solid state, Figure 4, is very similar to that proposed from analysis of NMR data [1,4] for the solution conformation, Figure 1. The structure has ring A situated over the anthracenyl ring system, as observed recently for divanillylanthrone,[17] and shows strong H bonding between the 10-OH and the guaiacyl oxygen; the large dihedral angle (~180°) between H_α and H_β, confirms the threo configuration.

It is interesting to note that the molecule crystallized as a single conformer, the form which was assigned as corresponding to the major solution-state rotamer, i.e., that with the ring A3-methoxyl over ring C (compare Figure 1a, Figure 4).

From the X-ray data, the vertical and horizontal distances from the planes of rings C and D can be calculated. If it is assumed that rings C and D behave like independent benzene rings, approximate ^1H NMR shielding values may be calculated by the method of Johnson and Bovey,[18] Table III.

The shieldings predicted from the Johnson–Bovey treatment (using the X-ray data) agree very well with those obtained in the proton NMR of the *major rotamer*, lending support to the proposition that the major rotamer is the one with the A3-methoxyl over ring C (Figure 1a).

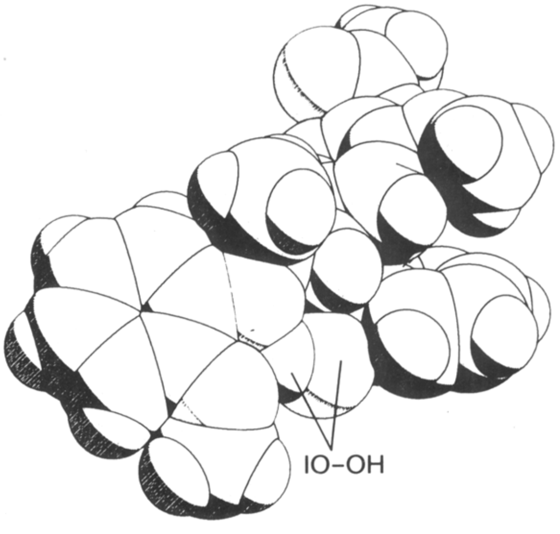

Figure 5. Space-filling model of 1 showing hindered 10-OH.

The X-ray data give information on the puckering of the anthracenyl ring system and on the orientation of the methoxyl and acetate groups which is not available from the NMR analysis. All aromatic rings (A, B, C, D) are planar to within ±0.02 Å. Atoms C7 and C14 (Figure 3) are in the plane of ring D, but C14 is slightly twisted (0.2 Å) out of the plane of ring C. The plane of the acetate group is at 54° with respect to ring A.

Recent interest in the orientation of aromatic methoxyl groups[19–21] prompts us to note our observations with lignin model derivatives. In the X-ray structure, Figure 3, each methoxyl carbon is oriented away from the ortho substituent, as expected. The C30 methoxyl is twisted so that C30 is 0.65 Å from the plane of ring B, while C29 is 0.22 Å from the plane of ring A. These orientations cannot necessarily be extrapolated to the solution conformation

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of the molecule. Like Makriyannis and Knittel,[19] we have found[5] that aromatic methoxyls with only one ortho substituent have ^{13}C NMR chemical shifts of 56.0 ± 0.5 ppm whereas 3,4,5-trimethoxybenzene derivatives have one resonance (presumably the 4-methoxyl carbon) at approximately δ 60. This may be attributable to an out-of-plane, nonconjugated conformation. In compound 1, the methoxyl shifts are δ 55.5 and 55.9.

Finally, it is interesting to comment on the resistance of the 10-hydroxyl group of compounds such as 1 to acetylation, even under forcing conditions, and the failure[1] to prepare the 10-OMe analogue from 10-methoxyanthrone (oxanthrone methyl ether, 9-oxo-10-methoxydihydroanthracene) and the appropriate γ-methyl or γ-hydroxymethyl quinone methide. A space-filing representation, Figure 5, indicates the inaccessibility of the H-bonded 10-OH in this rather rigid structure.

In summary, it has been demonstrated that proton NMR gives detailed insight into the solution conformation of compounds such as 1. In these compounds, the conformations in solution clearly resemble the solid-state structure and it has been shown that the most stable rotamer in solution is the sole conformer observed in the solid state.

Experimental Section

The preparation and full spectral details of compounds 1–5 have been reported previously.[1–5]

Proton NMR spectra were determined in $CDCl_3$ or acetone-d_6 on a Bruker WH270 FT spectrometer, with tetramethylsilane as internal reference. Temperature measurements to ±0.1 °C were made by inserting an NMR tube containing solvent and a thermocouple into the probe and measuring the equilibrium temperature before and after a spectrum was recorded.

Crystal and Molecular Structure of $C_{33}H_{30}O_7$. A colorless plate-like crystal of dimensions 0.25 × 0.225 × 0.07 mm was obtained by slow diffusion of pentane through a porous clay disk (from a flower pot) into a solution of 1 in acetone. Preliminary precession photography indicated the triclinic crystal class. Lattice parameters were obtained from the setting angles of 25 reflections centered on an Enraf-Nonius CAD4 diffractometer using Cu K_α X-rays. Details are available as supplementary material.

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Registry No. 1, 90990-69-5; 2, 90990-70-8; 3, 90990-71-9; 4, 90990-72-0; 5, 84064-68-6.

Supplementary Material Available: Details of the crystal data solution and refinement, tables of positional parameters, bond lengths, and angles, thermal parameters, and coordinates of calculated hydrogen positions (8 pages). Ordering information is given on any current masthead page.

Oxidatively Catalyzed Nucleophilic Aromatic Substitution. Further Studies on the $S_{ON}2$ Reaction

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The oxidation of several electron-rich fluoroarenes in the presence of a nucleophile, usually acetate ion, has been investigated. Two substrates, 1- and 2-fluoronaphthalene, have been shown to undergo a formally nonoxidative fluorine/acetoxy exchange induced by chemical oxidants such as benzoyl peroxide, potassium peroxydisulfate, and copper(III). The mechanism is believed to involve electron-transfer chain catalysis according to the $S_{ON}2$ mechanism. On electrochemical oxidation of these substrates, the major reaction pathway observed was oxidative substitution of hydrogen. The catalytic efficiency of the anodically initiated title reaction is also improved at higher temperatures; e.g., anodic acetoxydefluorination of 4-fluoroanisole takes place with a current efficiency of 590% at 78 °C. We also give the first example of an intramolecular although not catalytic $S_{ON}2$ reaction.

Electron-transfer reactions involving radical ion intermediates are becoming increasingly important when considering organic reaction mechanisms. One class of this type of reactions is electron-transfer chain (ETC) reactions,[1] i.e., initiation by reductants or oxidants. The $S_{RN}1$ reaction[2] is a well-known example of a reductively initiated reaction and, on the oxidative side, catalyzed cycloaddition reactions[3] provide entries into hitherto unrealized transformations.

We have recently studied oxidatively induced nucleophilic substitutions on aromatic halides, another possible class of ETC reactions. The first example of this formally redox neutral reaction was discovered by us in 1976;[4] oxidation of 4-fluoroanisole in the presence of acetate ion gave 4-acetoxyanisole.

In 1980, Alder[5] proposed the existence of the $S_{ON}2$ mechanism:

$$\mathrm{Ar{-}X} \xrightarrow{-e} (\mathrm{Ar{-}X})^{+\cdot} \quad \text{initiation} \tag{1}$$

$$(\mathrm{Ar{-}X})^{+\cdot} + \mathrm{Nu}^- \rightarrow (\mathrm{X{-}Ar{-}Nu})\cdot \xrightarrow{-X^-} (\mathrm{Ar{-}Nu})^{+\cdot} \tag{2}$$

$$(\mathrm{Ar{-}Nu})^{+\cdot} + \mathrm{ArX} \rightleftharpoons \mathrm{Ar{-}Nu} + (\mathrm{Ar{-}X})^{+\cdot} \quad \text{propagation} \tag{3}$$

Evidence for the participation of this mechanism in the

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