NOTE

DEUTERIUM EXCHANGE IN SESAMOL

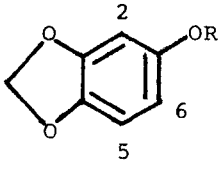
Richard K. Hill, Niteen A. Vaidya, and Gerald H. Morton
Chemistry Department, University of Georgia, Athens, GA 30602

SUMMARY

Trifluoroacetic acid-catalyzed exchange of sesamol in $^{2}H_2O$ results in rapid exchange of H-6 and slower exchange of H-2. The deuterium atoms introduced are retained during conversion to the methyl and allyl ethers.

Key Words: Sesamol, Deuterium Exchange.

Samples of the Bowers synthetic juvenile hormone mimic[1] 1 labeled with tritium in the aromatic ring were required for metabolic studies[2]. To ascertain the feasibility of hydrogen exchange in the parent phenol, sesamol (3,4-methylenedioxyphenol, 2), we have carried out model studies of deuterium exchange in sesamol so that rates and position of exchange could be followed by nmr spectroscopy.



1 R = $-CH_2CH=C(CH_3)-CH_2CH_2-CH(O)C(CH_3)-CH_2CH_3$

2 R = H

3 R = CH_3

4 R = $-CH_2-CH=CH_2$

In the nmr spectrum of sesamol, the aromatic protons appear as a group (Fig. 1) between δ6.0-6.8, distinct from the methylene signal at δ5.87 and the hydroxyl signal at δ5.9 ($CDCl_3$). At 300 cps scan width the signals are sufficiently separated to permit the assignment shown in Fig. 1. This aromatic pattern is essentially unaltered in the spectra of the methyl ether 3 and the allyl ether 4.

While the ortho and para hydrogens of phenols are subject to exchange under both acidic and basic conditions[3], preliminary experiments with sesamol in $NaO^{2}H$-$^{2}H_2O$ showed slow exchange of H-6 and only modest recovery of sesamol,

0362-4803/82/101265-04$01.00

Received July 28, 1981
Revised June 6, 1982

so attention was turned to acid catalysis. Warming a solution of sesamol in [$^2H_6$]acetone with dilute trifluoroacetic acid (TFA) in ^2H_2O caused complete exchange of H-6 within 90 minutes, before any exchange at H-2 or H-5 could be detected. The course of exchange was readily apparent from the nmr spectrum; replacement of H-6 by deuterium results in loss of the pair of doublets at δ 6.22 as well as collapse of the remaining aromatic signals to virtual singlets (Fig. 1b).

More concentrated TFA solutions (20%) effected complete exchange of H-6 in 2 minutes at 70°C. After another 3.5 hours 70% of H-2 had been replaced by deuterium, but the intensity of the H-5 signal was undiminished. Sesamol was recovered in 85% yield by evaporation of the solvents and sublimation of the residue. Raising the TFA concentration to 50% allowed complete exchange of H-6 within 10 minutes at room temperature and 90% exchange of H-2 in 165 minutes at 75°, still with no H-5 exchange, but the stronger acid caused some deterioration of the sample and less than 50% was recovered.

It was important to show that the isotope introduced by exchange would not be washed out from these labile positions during the preparation of ethers of sesamol. As expected, diazomethane converted dueterated sesamol into methyl ether 3 with no loss of deuterium. As a closer model for the Williamson synthesis of the allylic ether 1, deuterated sesamol was treated with allyl bromide and sodium ethoxide in ethanol. Allyl ether 4, isolated in 54% yield after 2-hour reflux, showed no nmr signal due to H-6. These Williamson conditions thus do not disturb the deuterium atoms at exchangeable locations.

In summary, this study has shown that trifluoroacetic acid catalysis allows complete exchange of the labile H-6 and appreciable exchange of H-2, and that the isotope remains secure during preparation of the methyl and allyl ethers. The finding that H-6 undergoes exchange more rapidly than H-2, even though both are ortho to the phenol, is consistent with the earlier observation[4] that the β hydrogens of methylenedioxybenzene are exchanged eight times more rapidly than the α in electrophilic detritiation.

EXPERIMENTAL

NMR spectra were recorded on a Hitachi Perkin Elmer R-20A spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard.

Deuterium exchange: Two representative experiments are described.

(a) A mixture of sesamol (117 mg), trifluoroacetic anhydride (0.2 mL), ^2H_2O (0.6 mL) and [$^2H_6$]acetone (0.2 mL) was warmed in an nmr tube at 75°C. The nmr spectrum showed disappearance of the H-6 signal at δ6.22 after one

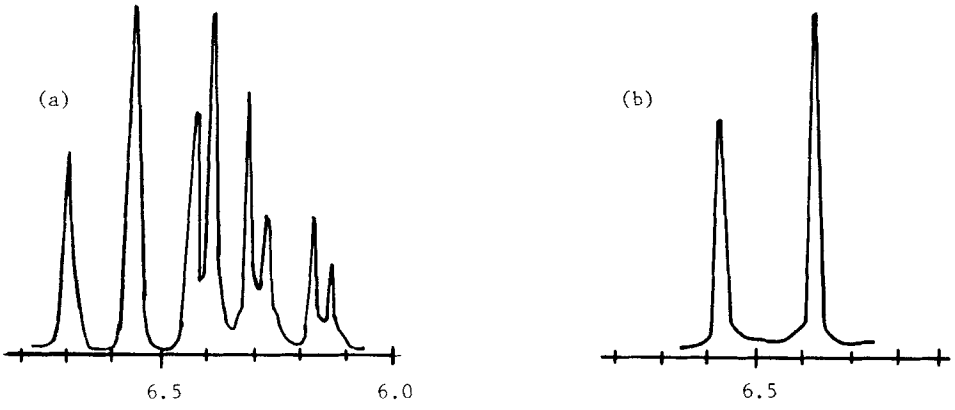


Figure 1. (a) Aromatic region of nmr spectrum of sesamol.
(b) Same region after exchange with TFA-^2H_2O.

Assignments: H-6: δ 6.22 J_o = 8.0 Hz, J_m = 2.4 Hz
H-2: δ 6.40 J_m = 2.4 Hz, J_p = 0.6 Hz
H-5: δ 6.63 J_o = 8.0 Hz, J_p = 0.6 Hz

minute. After 3.5 hr the mixture was concentrated at reduced pressure and the residue sublimed to give 100 mg of sesamol. The nmr spectrum showed no signal for H-6 and 70% exchange of H-2.

(b) A mixture of 1.0 g of sesamol, 5 mL of trifluoroacetic anhydride, 5 mL of ^2H_2O and 5 mL of tetrahydrofuran was heated to 100°C for 4 hr. The mixture was distributed between ether and 10% $NaHCO_3$. The ether layer was concentrated, after drying with Na_2SO_4, to afford 0.70 g of sesamol, with the nmr spectrum shown in Figure 1b.

Preparation of methyl ether 3. A solution of 0.40 g of sublimed sesamol in 10 mL of ether was treated with an ethereal solution of 10 mmol of diazomethane. After stirring for 8 hr at 25°C, the solution was washed with 25 mL of 10% NaOH, then washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residual oily ether 3 (0.25 g, 57%), had nmr absorption ($CDCl_3$) at δ 3.75 (s, 3H), 5.9 (s, 2H), and the three-proton multiplet of the aromatic region shown in Figure 1a.

Preparation of allyl ether 4. A modification of the procedure of Beroza[5] was used. To a solution prepared by dissolving 0.05 g of sodium in 10 mL of absolute ethanol was added a solutionof 0.35 g of sesamol and 0.25 g of allyl bromide in 15 mL of ethanol. The mixture was stirred at reflux for 2 hr, then poured into ice-water and extracted with two 25-mL portions of ether. The extracts were washed successively with 5% NaOH, 5% H_2SO_4, water, and brine, then dried over Na_2SO_4 and concentrated. The oily ether 4 (0.20 g, 54%) had nmr absorption ($CDCl_3$) at δ 4.35 (m, 2H), 5.2-6.15 (m, 3H), 5.8 (s, 2H), and the same three-proton multiplet shown in Figure 1a.

References

1. Bowers, W.S.-Science 164: 328 (1969).
2. See, e.g. (a) Morello, A., Repetto, Y., White, R.A., Hill, R.K., and Agosin, M.-Microsomes, Drug Oxidations, and Chemical Carcinogenesis (Coon, M.J. et al., eds,) Academic Press, New York, 1980, p. 773; (b) Morello, A. and Agosin, M.-Biochem. Pharmacol. 28: 1533 (1979); (c) Repetto, Y., Morello, A., and Agosin, M.-Chem. Biol. Interactions 24: 177 (1979).
3. Thomas, A.F.-Deuterium Labeling in Organic Chemistry, Appleton-Century-Crofts, New York, 1971, pp. 204-209.
4. Czernohorsky, J.H., Richards, K.E., and Wright, G.J.-Aust. J. Chem. 25: 1459 (1972).
5. Beroza, M.-J. Agr. Food Chem. 4: 49 (1956).

Acknowledgments. This research was supported in part by research grant AI-13633 from the National Institutes of Health, to whom the authors express their appreciation. We gratefully acknowledge helpful discussions with Prof. M. Agosin.