# Neighbouring-group Participation by Phenolate in the Opening of an Epoxide Ring

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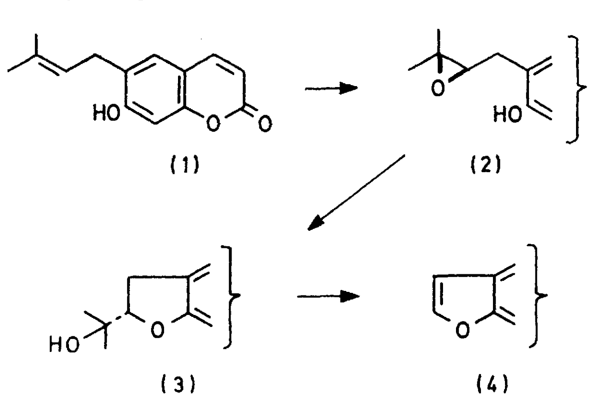
*o*-(2,3-Epoxypropyl)phenol has been detected by n.m.r. spectroscopy as an intermediate in the reaction of *o*-allylphenol with *m*-chloroperbenzoic acid to yield 2,3-dihydro-2-hydroxymethylbenzofuran. An impure sample of *o*-(2,3-epoxypropyl)phenol was isolated and the kinetics of its conversion into 2,3-dihydro-2-hydroxymethylbenzofuran in aqueous solution were studied. The rate shows a sigmoid dependence on pH and is proportional to the concentration of *o*-(2,3-epoxypropyl)phenolate.

BROWN and his co-workers,[1] in their work on the biosynthesis of furocoumarins [*e.g.* (4)] in cell cultures of *Ruta graveolens*, proposed a scheme which involves epoxidation of 7-de-*O*-methylsuberosin (1) to give the epoxide (2), which then undergoes opening of the epoxide ring with intramolecular nucleophilic displacement by the phenolic group to form (+)-marmesin (3).



This latter step is an example of neighbouring-group participation, and although many examples of participation in the opening of epoxide rings by alcohols,[2] esters,[3] and acids [4,5] are known there has been relatively little work on participation by phenolic groups.

We have studied the conversion of *o*-(2,3-epoxypropyl)phenol (5) into 2,3-dihydro-2-hydroxymethylbenzofuran (6). Owing to the extreme lability of *o*-(2,3-epoxypropyl)phenol [6] it was not possible to obtain it in a pure state, but the impurities in our sample should not have interfered with the kinetic investigation.

## EXPERIMENTAL

*o*-Allylphenol was prepared by the method of Claisen [7] (b.p. 217 °C; lit.,[7] 220 °C). 2,3-Dihydro-2-hydroxymethylbenzofuran was prepared by the method of Tinsley; [6] $\delta$ ($CDCl_3$) 3.0—3.3 (2 H, m), 3.6—3.9 (2 H, m), 4.6—5.1 (1 H, m), and 6.7—7.3 (4 H, m). Commercial *m*-chloroperbenzoic acid (93.0% pure) was used without further purification. Allylbenzene was a commercial sample which was purified by distillation.

*Reaction of* o-*Allylphenol with* m-*Chloroperbenzoic Acid.*—This reaction was followed in the n.m.r. spectrometer in a similar way to that described for the reaction of *trans*-stilbene-2-carboxylic acid.[5] The main features of the spectra of the starting materials were: *o*-allylphenol (0.64M) $\delta$ ($CDCl_3$) 3.42 (2 H, d), 5.2 (2 H, m), 5.7—6.5 (1 H, m), and 6.7—7.3 (4 H, m); *m*-chloroperbenzoic acid (0.9M) $\delta$ ($CDCl_3$) 7.2—8.2. The spectrum of the product, 2,3-dihydro-2-hydroxymethylbenzofuran, is given above. Equal volumes of the above solutions were mixed and after 35 min in the probe of the spectrometer (*ca.* 30 °C) the *o*-allylphenol had disappeared and a multiplet at $\delta$ 2.6—3.6 p.p.m. not ascribable to the benzofuran (6) had appeared. This $\delta$ value is similar to that (2.4—3.5) exhibited by the product from allylbenzene and *m*-chloroperbenzoic acid, presumably 2,3-epoxypropylbenzene. It was therefore concluded that the initial product of the reaction of *o*-allylphenol and *m*-chloroperbenzoic acid was *o*-(2,3-epoxypropyl)phenol. After 11 days at 30 °C the spectrum had changed to that of the benzofuran (6).

A sample of the crude epoxide for the kinetic investigation was prepared as follows. A solution of *o*-allylphenol (4.3 g, 0.032 mol) in chloroform (50 ml) was added to a solution of *m*-chloroperbenzoic acid (7.7 g, 0.045 mol) in chloroform (50 ml). The mixture was kept in a water-bath at 30 °C for 35 min and then poured on to ice–sodium carbonate solution. The chloroform layer was separated, washed with iced water, and dried ($MgSO_4$). The chloroform was carefully removed (rotary evaporator) with the temperature kept below 10 °C to yield a liquid which was about 47% *o*-(2,3-epoxypropyl)phenol, 33% *o*-allylphenol, and 20% 2,3-dihydro-2-hydroxymethylbenzofuran (n.m.r. spectrum). The kinetics of conversion of the 2,3-epoxypropylphenol into the benzofuran (6) were determined with this sample as it was thought that *o*-allylphenol and the product (6) would not interfere with the determination.

*Kinetic Measurements.*—Some preliminary experiments were carried out by repeatedly scanning the spectrum with a Unicam SP 800 spectrophotometer at 30 °C. Rate constants were determined by following the change in absorbance at the wavelength of largest absorbance difference. A Cary 16 spectrophotometer operating on-line to a

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[1] W. Steck, M. El-Dakhakhny, and S. A. Brown, *Tetrahedron Letters*, 1969, 4805; S. A. Brown, M. El-Dakhakhny, and W. Steck, *Canad. J. Biochem.*, 1970, **48**, 863; D. J. Austin and S. A. Brown, *Phytochemistry*, 1973, **12**, 1657.

[2] *Cf.* J. G. Buchanan and H. Z. Sable, ' Selective Organic Transformations,' ed. B. S. Thyagarajan, Wiley–Interscience, vol. 2, 1972, p. 52.

[3] J. G. Buchanan, *J. Chem. Soc.*, 1958, 2511; J. G. Buchanan and J. C. P. Schwarz, *ibid.*, 1962, 4770; J. G. Buchanan and R. M. Saunders, *ibid.*, 1964, 1791, 1796; J. G. Buchanan and R. Fletcher, *ibid.*, 1965, 6316; J. M. Coxon, M. P. Hartshorn, and W. H. Swallow, *Austral. J. Chem.*, 1973, **26**, 2521.

[4] G. Berti, *J. Org. Chem.*, 1959, **24**, 934; G. Berti and F. Bottari, *Gazzetta*, 1959, **89**, 2380.

[5] B. Capon, J. Farquarson, and D. J. McNeillie, preceding paper.

[6] *Cf.* S. W. Tinsley, *J. Org. Chem.*, 1959, **24**, 1197.

[7] L. Claisen, *Annalen*, 1919, **418**, 80.

Digico Micro 16P computer was used. Rate constants were calculated by a generalised least-squares method.[8] The reactions were first-order (the first, second, and third ' half-lives ' were all equal). Reactions were carried out in buffers of ionic strength 0.1M the pH's of which were determined with a Radiometer model 26 pH meter. The variation of $k_{obs}$ with pH was fitted to equation (i) by a generalised least-squares method.[8]

## RESULTS AND DISCUSSION

A preliminary investigation of the conversion of *o*-(2,3-epoxypropyl)phenol into 2,3-dihydro-2-hydroxymethylbenzofuran was carried out at *ca.* 30 °C by scanning the spectrum in (*a*) acetate buffer, pH 4.9 (no reaction detected after 2 h), (*b*) imidazole buffer, pH 7.14 (half-life 30 min), (*c*) Tris buffer, pH 8.45 (half-life 5 min), and (*d*) 0.1M-sodium hydroxide (reaction complete in *ca.* 30 s). The kinetics of the reaction

$$k_{obs} = k/(1 + 10^{-pH}/K_a) \qquad \text{(i)}$$

were therefore measured in the pH range 8.10—13.09 at 15 °C. No buffer catalysis was detectable at pH 8.45 in Tris buffer. The variation of rate constant with pH follows equation (i) (see Table) with $k = 7.28 \times 10^{-2}$ s$^{-1}$ and $K_a = 9.00 \times 10^{-11}$ mol l$^{-1}$ (p$K_a$ = 10.05). This value of $K_a$ is close to that expected for ionisation of phenolic group of *o*-(2,3-epoxypropyl)phenol, as the p$K_a$ value of *o*-cresol is 10.28 at 25 °C.[9] The possibility that the reaction is reversible was checked by adding 15 μl of a stock solution of 2,3-dihydro-2-hydroxymethylbenzofuran in dioxan to 2.5 ml of 0.1M-sodium hydroxide. No change in absorbance at 300 nm was detected; hence the cyclisation must go to completion. The only reasonable mechanism for this reaction on the basis of these results is a direct nucleophilic displacement of alkoxide anion by phenolate (Scheme). The displacement of a strongly basic alkoxide anion by the more weakly basic phenolate is presumably made possible by the strain of the epoxide ring. The alternative mechanism, which involves nucleophilic displacement by phenolate with specific acid catalysis, is clearly unimportant as the pH–rate profile is of the wrong type.

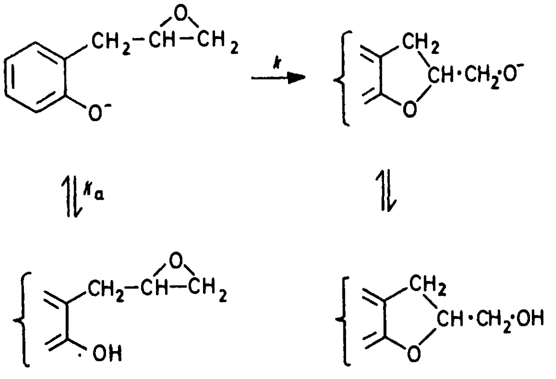
First-order rate constants for the conversion of *o*-(2,3-epoxypropyl)phenol into 2,3-dihydro-2-hydroxymethylbenzofuran in aqueous solution at 15 °C (*I* 0.1M)

| pH (Buffer) [b] | $10^3k_{obs}$/s$^{-1}$ | $10^3k_{calc}$/s$^{-1}$ [a] |
|---|---|---|
| 8.10 (Phosphate) [b] | 0.659 | 0.816 |
| 8.21 (Tris) [b] | 0.958 | 1.04 |
| 8.45 (Tris) [c] | 1.82 | 1.80 |
| 8.91 (Tris) [b] | 5.11 | 4.96 |
| 9.29 (Tris) [b] | 10.3 | 13.2 |
| 9.75 (2,2′-Iminodiethanol) [b] | 22.7 | 24.5 |
| 9.95 (2,2′-Iminodiethanol) [c] | 29.3 | 32.4 |
| 10.17 (2,2′-Iminodiethanol) [c] | 41.0 | 41.6 |
| 10.72 (Phosphate) [c] | 64.9 | 60.1 |
| 12.15 (NaOH) [c] | 69.0 | 72.1 |
| 13.09 (NaOH) [c] | 72.2 | 72.7 |

[a] Calculated from the equation $k_{calc} = k/(1 + 10^{-pH}/K_a)$ with $k = 7.28 \times 10^{-2}$ s$^{-1}$ and $K_a = 9.00 \times 10^{-11}$ mol l$^{-1}$. [b] Followed at 285 nm. [c] Followed at 300 nm.

The conversion of *o*-(2,3-epoxypropyl)phenol into the benzofuran (6) is an ' abnormal ' [10] epoxide ring opening. The strong preference for ring opening in an intramolecular process *via* the spiro-mode [11] therefore strongly outweighs the factors which favour intermolecular reaction *via* the normal mode. The achieving of a collinear transition state is more important in this system than the relative reactivities for nucleophilic attack on primary and secondary carbon.

An approximate value for the rate constant for normal ring opening by phenolate of an epoxide of this type was estimated from the results of Cavell *et al.*[12] and the relative nucleophilicity of the phenolate ion.[13] This value was *ca.* $10^{-5}$ l mol$^{-1}$ s$^{-1}$, and since the ' abnormal ' reaction usually occurs at less than one-tenth the rate of the ' normal ' reaction when there is no acid catalysis, the rate constant for the intermolecular abnormal ring opening by phenolate would be less than $10^{-6}$ l mol$^{-1}$ s$^{-1}$. Since the rate constant for the intramolecular reaction is $7.27 \times 10^{-2}$ s$^{-1}$, the effective molarity is greater than $7.27 \times 10^4$M.



(5) (6)

SCHEME

This work shows that the conversion of *o*-(2,3-epoxypropyl)phenol into the benzofuran (6) occurs rapidly in aqueous solution *via* the monoanion. The calculated rate constant at pH 7 is $10^{-5}$ s$^{-1}$ at 15 °C, which corresponds to a half-life of 165 min. This shows that if an epoxide similar to *o*-(2,3-epoxypropyl)phenol were formed in a plant it would be converted fairly rapidly into the corresponding benzofuran without enzymic catalysis; the configuration of the benzofuran would depend on the configuration of the epoxide. Whether this happens, or even whether an epoxide is an intermediate in the formation of dihydrobenzofurans in plants, is at present unknown.

[6/1980 *Received, 25th October*, 1976]

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[8] W. E. Wentworth, *J. Chem. Educ.*, 1965, **42**, 96, 162.

[9] G. Kortum, W. Vogel, and K. Andrussow, ' Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961, p. 429.

[10] *Cf.* R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737.

[11] S. Danishefsky, J. Dynak, E. Hatch, and M. Yamamoto, *J. Amer. Chem. Soc.*, 1974, **96**, 1256; *cf.* B. Capon and S. P. McManus, ' Neighboring Group Participation,' Plenum Press, New York, 1976, p. 54.

[12] E. A. S. Cavell, R. E. Parker, and A. W. Scapelhorn, *J. Chem. Soc.*, 1965, 4780.

[13] *Cf.* A. Streitwieser, *Chem. Rev.*, 1956, **56**, 583.