ALKALINE HYDROLYSIS OF 4-HYDROXYBENZYL PHENYL SULFONES*

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During the base catalysed hydrolysis of 1-(4-hydroxy-3,5-ditert-butylphenyl)alkyl phenyl sulfones *I* 4-alkylidene 2,6-ditert-butyl-2,5-cyclohexadienones *II* have been proved as reaction intermediates. The proof was carried out spectrophotometrically in the UV region. On the basis of the analysis of reaction products, confirmed by kinetic measurements, a mechanism has been derived for this reaction.

In the preceding paper we investigated the structure of oligomeric compounds formed under the effect of aqueous bases on substituted 4-hydroxybenzyl phenyl sulfones and 4-hydroxybenzyl alcohols[1]. We supposed — as did some other authors in similar cases[2-5] — that the new bond is formed in two distinctly separated steps: in the first elimination of benzenesulfonyl group (or hydroxyl group) takes place under formation of 4-alkylidenecyclohexadienone onto which the corresponding anion is added in the second step (Scheme 1, *(A)*). However, for the explanation of the reactions of phenolic Mannich bases with nucleophiles a one-step mechanism has been formulated in which the transition state is reminding one of a bimolecular nucleophilic substitution[6] (Scheme 1, *(B)*). The decision as to which of the two mechanisms is indeed operative in the reactions of 2- or 4-hydroxybenzyl derivatives is very important for the chemistry of these compounds. The already published results either represented indirect proofs of the occurrence of the quinoid intermediate[4] or only hinted that some intermediate participates in the reaction[3]. The uncertainty in the interpretation of earlier results was due to inadequately selected substrates.

An unambiguous solution of this problem can be achieved only if the supposed intermediate is sufficiently stable to stand isolation or to be capable of spectrometric characterization. We considered that this requirement would be fulfilled in the case of 4-alkylidene-2,5-cyclohexadien-1-ones *II* substituted in the positions 2 and 6 with the bulky tert-butyl groups, which can be prepared crystalline (with the exception of 4-methylene derivative). As a model reaction we chose alkaline hydrolysis of 1-(4-hydroxy-3,5-ditert-butylphenyl)alkyl phenyl sulfones *I*.


RESULTS AND DISCUSSION

During the quantitative control of the reaction of sulfones $Ia - Ic$ with sodium hydroxide we observed that 4-alkylidenecyclohexadienones $IIa - IIc$ indeed are formed in the first phase, and we isolated compounds IIa and IIb and compared their physical properties with those of authentic samples. Quinonemethide IIc is rather reactive and we identified it by comparison of its UV spectra only. Unless removed from the reaction immediately after their formation quinonemethides $IIa - IIc$ underwent two further parallel reactions. In the first the nucleophilic character of the hydroxyl ions by the addition[5] of which 4-hydroxybenzyl alcohols $IIIe - IIIc$ were formed, played a role. In the second the hydroxyl ions acted as bases and isomerized[7] the quinonemethides IIa and IIb to vinyl phenols IIa and IVb. If the alcohols $IIIa$ and $IIIb$ were allowed to stand in basic medium for several hours they also afforded vinyl phenols IVa and IVb. Simultaneously we proved the presence of quinonemethides IIa and IIb spectroscopically in the reaction mixture. We were unable to prove the conversion of vinyl phenols IV to quinonemethides II or carbinols III, and hence we consider the reaction $II - IV$ as irreversible. The mechanism of alkaline hydrolysis of 4-hydroxybenzyl phenyl sulfones may be expressed by Scheme 2.
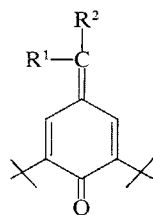
We endeavoured to confirm the proposed mechanism by kinetic measurements of the hydrolysis of sulfone Ib. The easy preparation of quinonemethide IIb enabled us to simplify the kinetically rather complex scheme $I \rightleftarrows II(+V) \leftrightharpoons III$ to the system
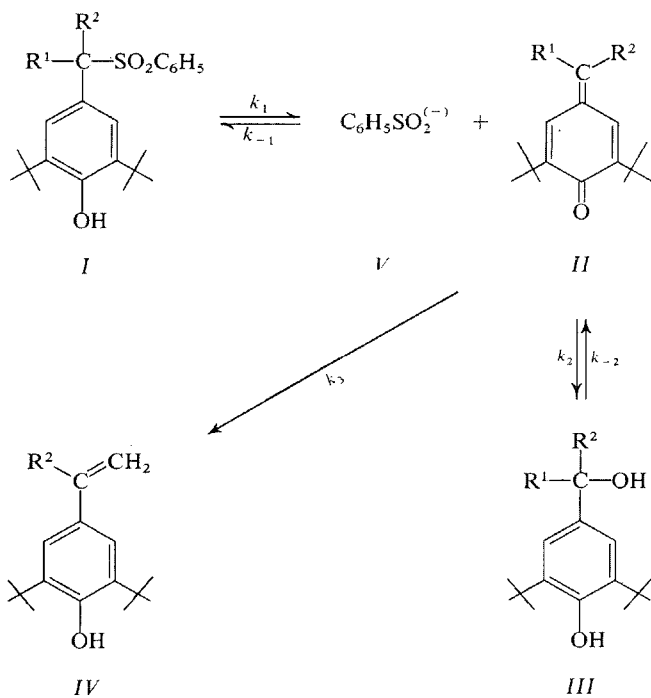$$\searrow IV$$
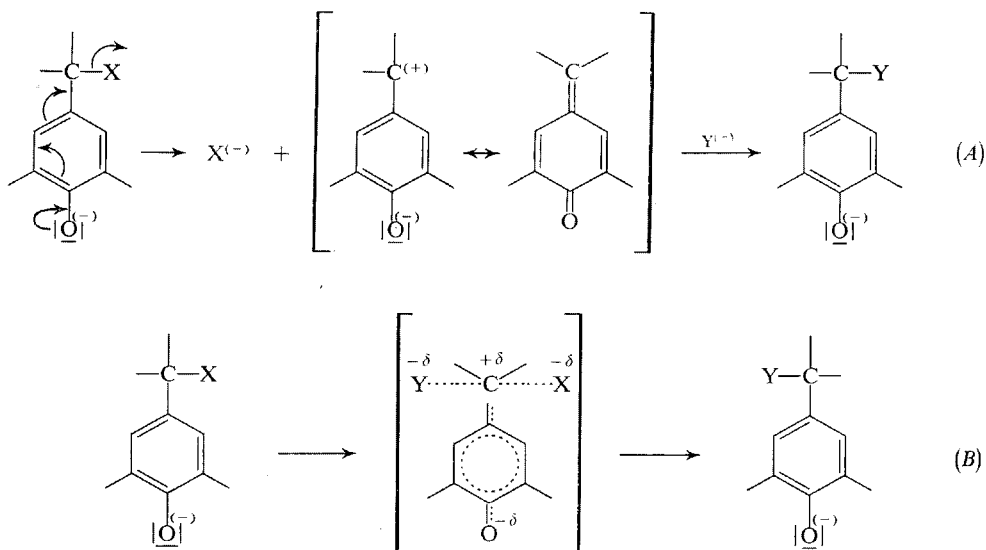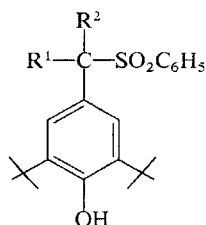
SCHEME 1

Ia, IIa; $R^1 = R^2 = CH_3$
Ib, IIb; $R^1 = H$; $R^2 = CH_3$
Ic, IIc; $R^1 = R^2 = H$

II

SCHEME 2

$III \rightleftarrows II \rightarrow IV$. The relative value of the equilibrium constant of the reaction $I \rightleftarrows II +$ $+ V$ may be obtained by the comparison of the two systems.

The rate equations for the reduced system can be written (under the pseudo first order conditions) in the following form:

$$d[II]/dt = -k_2[II] - k_3[II] + k_{-2}[III], \tag{1}$$

$$d[III]/dt = k_2[II] - k_{-2}[III], \tag{2}$$

$$d[IV]/dt = k_3[II]. \tag{3}$$

The time dependence of the loss of quinonemethide *II* was followed continually by spectrophotometry at 305 nm. The concentration of carbinol *III* in the reaction mixture was determined discontinually, after reaction with 2,6-dibromobenzoquinone-4-chloroimine[8]. From the relation $[II]_0 = [II] + [III] + [IV]$ (index 0 indicates the starting quinonemethide concentration) we could calculate the vinyl phenol *IV* concentration. The concentration dependences obtained are given in Fig. 1.

The kinetic equations $(1)-(3)$ were modelled on the analogue computer MEDA 40 TA. The approximate rate constant values were used as starting points, calculated both from equation (2) under the assumption that $d[III]/dt = 0$ at the moment when the concentration of carbinol *III* is at maximum then

$$k_2/k_{-2} = [III]/[II], \tag{4}$$

and also from the initial rates of formation of carbinol *III* and vinyl phenol *IV*, *i.e.*

$$k_2 = (d[III]_0/dt)[II]_0^{-1}, \tag{5}$$

$$k_3 = (d[IV]_0/dt)[II]_0^{-1}. \tag{6}$$

The rate constant values were improved by a cyclic change of parameters. A good agreement of the computer generated curve for sulfone *Ib* with the experimental results (Fig. 1) confirms the correctness of the proposed mechanism. The constants determined by the analogue computer have the values $k_2 = 1.264$ min^{-1}, $k_{-2} = 0.141$ min^{-1} and $k_3 = 0.018$ min^{-1} for 0.0195M-NaOH.

Since k_2 is by an order of magnitude higher than k_{-2} and k_3 equation (1) can be expressed, with a good approximation, in the form

$$d[II]/dt \approx -k_2[II] \approx -k_{obs}[II], \tag{7}$$

where k_{obs} means the observed rate constant of the decrease in quinonemethide *II* concentration. Its value, 1.255 min^{-1}, does not practically differ from the value obtained for k_2 by the computer. The complete rate equation for quinonemethide *II* (Scheme 2) has the form

$$d[II]/dt = k_1[I] - k_{-1}[II][V] - k_2[II] + k_{-2}[III] - k_3[II], \tag{8}$$

which under the assumptions leading to equation (7) may be reduced to

$$d[II]/dt \doteq - k'_{obs}[II] , \qquad (9)$$

where k'_{obs} is observed rate constant of the pseudo first order for the concentration decrease of quinonemethide *II* generated from sulfone *I*. From Scheme 2 it follows that

$$d[I]/dt = -k_1[I] + k_{-1}[II][V] , \qquad (10)$$

and from the comparison of equations (1), (7)−(9) and (10) the following expression is obtained:

$$d[I]/dt = (k_{obs} - k'_{obs})[II] = \Delta k[II] . \qquad (11)$$

The Δk values are experimentally accessible from the linear dependencies of the rate constants k_{obs} and k'_{obs} on the concentration of base (Fig. 2). The value $1/\Delta k$ represents then the relative equilibrium constant of the separated reaction $I \rightleftarrows II + V$ $(K = 1/\Delta k = k_1/k_{-1})$.

From Fig. 2 it follows that the value of Δk for alkaline hydrolysis of sulfones *Ia − Ic* is independent of the base concentration. Hence, the absolute value of the equilibrium constant K is affected by substituents R^1 and R^2 only. From Table I
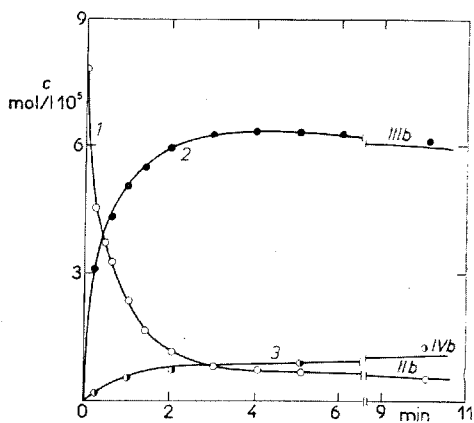

FIG. 1

Time Dependence of the Concentration of Compounds *II*, *III* and *IV* (in 0·0195M-
-NaOH)

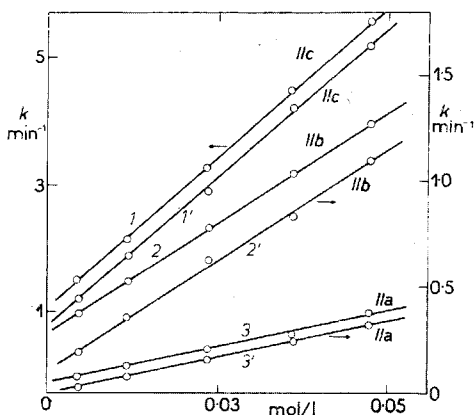———— Calculated curves, ○, ●, ◑ experimental values.

FIG. 2

Dependence of the Observed Rate Constants for the Decrease in Concentration of Quinonemethides *IIa − IIc* on the Concentration of Sodium Hydroxide

1, 2, 3 k_{obs}, *1′, 2′, 3′* k'_{obs}).

TABLE I
Reactivity of Sulfones *Ia — Ic* during Alkaline Hydrolysis[a]

Sulfone	Δk	K
Ia	0·05	20·00
Ib	0·17	5·88
Ic	0·29	3·45

[a] 0·0195 M-NaOH.

it follows that the order of reactivities of sulfones is *Ia* > *Ib* > *Ic*, expressed by their ability to liberate alkylidenecyclohexadienones *II*.

The difference in the reactivities of sulfones *Ia — Ic* in dependence on the presence of the methyl groups is probably determined by the $+I$ and $+E$ effect of the methyl group, which decrease the activation energy of the first equilibrium step of the reaction by compensation of the positive charge on the benzyl carbon in the transition state. As for the reactivity of cyclohexadienones *II* the situation is just the opposite irrespective of whether the formation of alcohols *III* or vinyl phenols *IV* is in question. This is also confirmed by the ratio of rate constants during the reaction, for example with 0·02M-NaOH (Fig. 2), which gives the order *IIa* : *IIb* : *IIc* = 1 : 4·18 : 17·24.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Samples for analysis were dried at room temperature and 0·1 Torr for 8 hours.

Compounds used. Phenyl sulfones *Ia — Ic* were prepared[9] from corresponding alcohols and sodium benzenesulfinate in acetic acid according to Jerkeman and Lindberg[4]. Alkylidenecyclohexadienones *IIa* and *IIb* were prepared from corresponding alkyl phenols by oxidation with potassium ferricyanide in alkaline medium[10]; *IIa* had m.p. 102·5°C (lit.[10] 103·5—105·5°C), *IIb* had m.p. 90—91°C (lit.[11] 91°C). Methylenecyclohexadienone *IIc* was prepared *in situ* by dehydrohalogenation of 4-hydroxy-3,5-ditertbutylbenzyl chloride with triethylamine[12]. 2,6-Di-tert-butyl-4-vinyl phenol *IV* was prepared by isomerization of ethylidenecyclohexadienone *IIb* with triethylamine[7], m.p. 43—44°C. For $C_{16}H_{24}O$ (232·3) calculated: 82·72% C, 10·41% H; found: 82·53% C, 10·25% H.

Preparative hydrolysis of sulfone Ib. A solution of sulfone *Ib* (0·374 g; 1 mmol) in acetonitrile (10 ml) was hydrolysed with 0·02M-NaOH (200 ml) at room temperature. After one hour the reaction mixture was acidified with a saturated citric acid solution, then extracted with chloroform (6 × 50 ml), the extract was dried over magnesium sulfate and evaporated *in vacuo*. The crude product contained two compounds only, which were isolated by preparative thin layer chromatography on silica gel. Alcohol *III* (153 mg) when crystallized from light petroleum–ether had m.p. 102—103°C (lit.[13] 98—101°C), vinylphenol *IV* (75 mg) had after crystallization from hexane m.p. 43—44°C (lit.[7] 44—45°C).

Kinetic measurements. The reaction of sulfones *Ia — Ic* and alkylidenecyclohexadienones *IIa* to *IIc* with hydroxyl ions was followed by spectrophotometry (SPECORD UV VIS, Zeiss, Jena). The cell of the apparatus (quartz, optical path 1 cm, volume 2 ml) served as a reaction vessel. Into a solution of sodium hydroxide (1·5 ml; the concentrations used were 0·0137M, 0·0195M, 0·039M and 0·049M), kept at $20 \pm 0\cdot1°C$, 50 μl of a store solution of cyclohexadienone *IIa — IIc* or sulfone *Ia — Ic* in purified[14] acetonitrile were added under rapid stirring. The starting concentration of the substrate was in all instances $2 - 4 \cdot 10^{-4}M$. The loss of cyclohexadienones *IIa — IIc* was followed at 282 nm, 305 nm and 324 nm, respectively. The values of rate constants of pseudo first order k_{obs} and k'_{obs} were reproducible within the $\pm3\%$ limits. The concentration changes of product *III* were followed by the method of Larsson and Lindberg[8], measuring the extinctions of indophenol formed from alcohol *III* and 2,6-dibromo-1,4-benzoquinone-4-chloroimide at 555 nm. The accuracy of this method is $\pm5\%$.

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