

**KINETICS AND MECHANISM OF THE FORMATION
OF 4-BENZYLIDENE-2,5-CYCLOHEXADIEN-1-ONES
BY ALKALINE HYDROLYSIS OF 4-HYDROXYBENZYL
PHENYL SULFONES***

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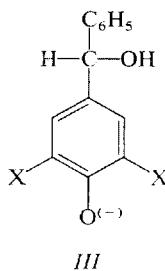
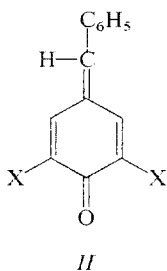
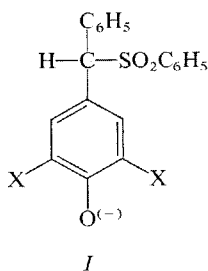
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4-Hydroxybenzyl phenyl sulfones *I* afford with hydroxyl ions in aqueous acetonitrile the corresponding 4-hydroxybenzyl alcohols *III*. In this two-stage reaction, the 4-benzylidenecyclohexadienones *II* are intermediates. The reaction kinetics correspond to a system of consecutive irreversible reactions. The reactivity of sulfones *I* may be correlated with the Hammett σ_m constants and that of 4-benzylidenecyclohexadienones *II* with σ_p^0 constants. Both reactions obey the isokinetic relationship.

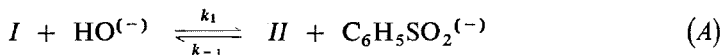
Recently¹, the 4-alkylidene-2,6-di-tert-butyl-2,5-cyclohexadien-1-ones (*p*-quinone methides) have been unequivocally demonstrated in this Laboratory as intermediates of the basic hydrolysis of 1-(4-hydroxy-3,5-di-tert-butylphenyl)alkyl phenyl sulfones. In this connection, the relationship between the reactivity of 4-hydroxybenzyl phenyl sulfones and *p*-quinone methides and the substitution of the benzyl (or methide) carbon atom by methyl groups has also been examined. Unfortunately, the attempted utilisation of 4-methylene-, 4-ethylidene-, and 4-isopropylidenecyclohexadienones in investigations on the relationship between their electrophilic reactivity and substitution at positions 2 and 6 did not meet with success. The required quinone methides are either extremely unstable or cannot be prepared in solvents suitable for kinetic measurements. Moreover, the occurrence of side reactions (dimerisation, isomerisation) did not allow to obtain reliable kinetic data. We have therefore focussed our attention to 4-benzhydrylidencyclohexadienones (*p*-fuchsones) that can undergo the addition reactions only² and that are stable enough (owing to the presence of two phenyl groups on the methide carbon atom) to be stored in crystalline state for a long period of time³. However, the reactivity of fuchsones proved to be too low. Furthermore, the synthesis of the required triarylmethyl phenyl sulfones failed. Finally, observations have been made use of from the preparation⁴ of 2,6-disubstituted

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benzylidene-2,5-cyclohexadien-1-ones *II*. The starting sulfones *I* that are readily accessible from the corresponding benzhydryl alcohols and benzylidenecyclohexadienones react readily with hydroxyl ions without any formation of by-products. The UV spectra of the starting sulfones *I* and the final phenyl(4-hydroxy-3,5-dialkylphenyl)-methanols *III* markedly differ from the bathochromically shifted spectra of cross-conjugated intermediates. Sodium hydroxide has been again used as the reagent, the hydroxyl ions of which act as a base in the reaction with 4-hydroxybenzyl phenyl sulfones and as a nucleophile in the reaction with benzylidenecyclohexadienones.



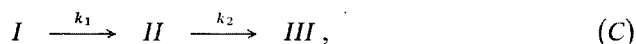
Contrary to 4-alkylidene-2,5-cyclohexadienones, the 4-benzhydrylidene-2,5-cyclohexadienones do not possess any hydrogen atom in the α -position with respect to the methide carbon atom and cannot thus afford vinylphenols by a prototropic 1,7-rearrangement⁵. The general scheme¹ of a base-catalysed transformation of 4-hydroxybenzyl phenyl sulfones may be thus simplified to a system of two consecutive reactions (A) and (B):



Since the order of magnitude of the forward reaction rates of conversions (A) and (B) is different enough, the system may be solved as two separate reactions. The forward reaction rate of step (A) is as high that the reaction course can be examined by the "stopped flow" technique only. Although the reactions of quinone methides with heteronucleophiles are generally reversible, the equilibrium constant of reaction (A) is so low (with equimolar concentrations of quinone methides *II* and the benzenesulfinate anion) that the usual expression for an irreversible reaction can be used in calculations. The rate constants k_2 were obtained from time dependence of the decrease of quinone methides *II* generated in situ from sulfones *I* under conditions

leading to the pseudofirst order. The applicability of this experimental arrangement was verified by rate measurement of the reaction of sodium hydroxide with quinone methides *Ib*–*IId* prepared previously from the corresponding 4-hydroxybenzyl phenyl sulfones⁴. The rate constant values obtained by both procedures were identical within limits of experimental error. The rate constant k_{-2} was determined in the case of the alcohol *IIId* only since the quinone methide is obtained most readily in the whole series. The observed value was as low ($8.26 \cdot 10^{-7} \text{ s}^{-1}$ at 25°C) that the reaction (*B*) can be considered to be irreversible. The small error (if any) which might be due to this simplification was circumvented in such a manner that the reaction was followed up to a 60% conversion only, *i.e.*, to the point when the reversible reactions cannot markedly affect the kinetic data. The rate constant values k_1 and k_2 are shown in Table I.

The separation of reaction steps (*A*) and (*B*) is advantageous from the experimental standpoint, but the thus obtained rate constant k_1 and k_2 are independent of each other. It is thus desirable to verify the validity of the whole mechanism. With the use of the rate equation (*C*), expressions (*I*), (*2*), and (*3*) are obtained:



$$d[I]/dt = -k_1[I], \quad (1)$$

$$d[II]/dt = k_1[I] - k_2[II], \quad (2)$$

TABLE I

Rate Constants (s^{-1}) of the Basic Hydrolysis of Substituted 4-Hydroxybenzyl Phenyl Sulfones *Ia*–*Ie* (in 1 : 1 acetonitrile–water)

Temperature, °C		15	20	25	30
<i>Ia</i>	k_1	0.34	0.65	1.15	2.15
	k_2	0.07	0.11	0.13	0.16
<i>Ib</i>	k_1	2.39	4.62	8.66	15.00
	k_2	$2.13 \cdot 10^{-3}$	$2.80 \cdot 10^{-3}$	$3.60 \cdot 10^{-3}$	$4.80 \cdot 10^{-3}$
<i>Ic</i>	k_1	6.03	9.62	18.23	28.87
	k_2	$3.74 \cdot 10^{-4}$	$5.40 \cdot 10^{-4}$	$7.80 \cdot 10^{-4}$	$1.10 \cdot 10^{-3}$
<i>Id</i>	k_1	$3.01 \cdot 10^2$	$4.95 \cdot 10^2$	$8.35 \cdot 10^2$	$13.86 \cdot 10^2$
	k_2	$2.63 \cdot 10^{-5}$	$4.06 \cdot 10^{-5}$	$5.73 \cdot 10^{-5}$	$8.42 \cdot 10^{-5}$
<i>Ie</i>	k_1	1.40	2.47	4.47	8.00
	k_2	$6.95 \cdot 10^{-4}$	$9.90 \cdot 10^{-4}$	$1.44 \cdot 10^{-3}$	$1.99 \cdot 10^{-3}$

$$d[III]/dt = k_2[II]. \quad (3)$$

For the concentration of the quinone methide *II* we obtain (4)

$$[II] = (k_1[I]_0/(k_2 - k_1)) (\exp(-k_1 t) - \exp(-k_2 t)), \quad (4)$$

where $[I]_0$ is the initial concentration of 4-hydroxybenzyl phenyl sulfone (*I*). Introducing the dimensionless quantities $\tau = k_1 t$ and $\varkappa = k_2/k_1$, we obtain

$$[I]/[I]_0 = \exp(-\tau), \quad (5)$$

$$[II]/[I]_0 = 1/(\varkappa - 1) (\exp(-\tau) - \exp(-\varkappa\tau)). \quad (6)$$

The reaction sequence (C) is valid when the calculated curve is in accord with the experimentally determined dependence of $[II]/[I]_0$ on $(1 - [I]/[I]_0)$. As shown on Fig. 1, this condition is very well fulfilled.

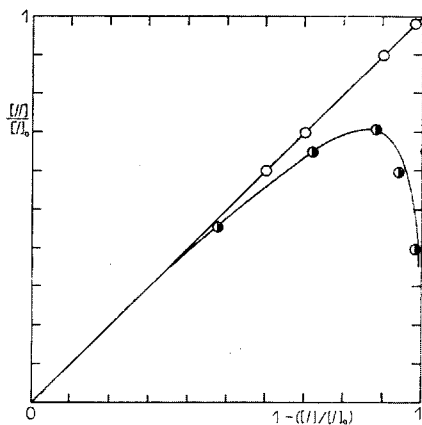
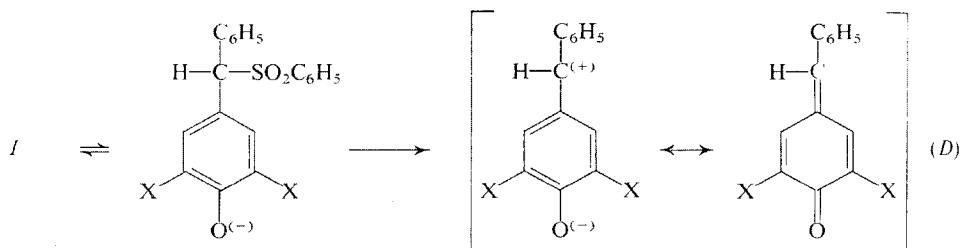


FIG. 1
Verification of the Validity of the Assumed
Hydrolysis Mechanism

Sulfone *Ia*, ○; sulfone *Ib*, ●; full lines
correspond to calculated curves.

It may be seen from data of Table I that the highest rate constant value for the first reaction step corresponds to the phenol of the lowest acidity ($X = \text{tert-C}_4\text{H}_9$). This observation is not unexpected because of certain resemblance to the carbocation formation by solvolysis of substituted benzhydryl alcohols⁶, $\text{Ar}_2\text{CHOH} \rightleftharpoons \text{Ar}_2\text{C}^{(+)}\text{H} + \text{HO}^{(-)}$. In both cases, the substrate reactivity is inversely proportional to the charge of the reaction centre in transition state and thus to the activation enthalpy (Table II). The high reactivity of the present sulfones according to the reaction (D) might be ascribed to compensation of the carbocationic character by a strong +E and +I effect of the ionised hydroxyl, the difference in reactivities being determined by the +I effect of the substituent X. Owing to experimental conditions that guarantee a total dissociation, the preceding phenol-phenoxide equilibrium need not be considered.

In the case of the chloro and bromo sulfones *If* and *Ig*, we did not succeed to trap the corresponding intermediate *II*. According to a rough estimation based on a correlation of the rate constant k_1 logarithms with the sum $2\sigma_X^m + \sigma_{\text{O}(-)}^p$ ($\rho = -6.82$; $r = 0.809$), the rate constant belonging to substituents Cl and Br should be at least six orders of magnitude lower than that for $X = \text{H}$. Since, however, the second reaction ($\rho = 8.16$; $r = 0.963$) exhibits a high and positive value of the reaction constant ρ , it is obvious that $k_2 \gg k_1$ and that the intermediate cannot be trapped under such conditions. The relatively low reactivity of sulfones *If* and *Ig* is also confirmed by preparative experiments in which a portion of the unreacted starting sulfones was recovered from the reaction mixture even after a reflux for 1 h. The highest deviation from the regression straight line for the first reaction step is shown by the sulfone *Ie*, the corresponding dienone *IIe* of which is more stable (k_1 is higher) than it could be expected from the σ_m constant for the OCH_3 substituent. This effect might be *inter alia* ascribed to an inaccurate value of the σ constant for the OCH_3

TABLE II

Activation Parameters for the Reaction of 4-Hydroxybenzyl Phenyl Sulfones *I* and 4-Alkylidene-cyclohexadienones *II* with Hydroxyl Ions

Compound	ΔH^\ddagger kcal mol ⁻¹	ΔS^\ddagger cal K ⁻¹	Compound	ΔH^\ddagger kcal mol ⁻¹	ΔS^\ddagger cal K ⁻¹
<i>Ia</i>	20.59	10.88	<i>Id</i>	17.12	12.28
<i>IIa</i>	8.63	-33.65	<i>IId</i>	12.73	-35.20
<i>Ib</i>	20.73	15.24	<i>Ie</i>	43.32	91.59
<i>IIb</i>	8.69	-40.51	<i>IIe</i>	11.67	-32.40
<i>Ic</i>	17.93	7.31			
<i>IIc</i>	11.89	-32.85			

group since this value can vary in a wide range depending on the solvent⁷. Reaction rate constants for the second step may be well correlated with σ_p^0 constants (or, $2\sigma_p^0$, with respect to the presence of two substituents). For a formal *meta* position, such a correlation is not unusual⁸⁻¹⁰.

The activation parameters of both reactions summarised in Table II, are in accordance with the reaction mechanism proposed. The similarity of activation enthalpy and activation entropy values in the particular reaction series (separate reaction steps one and two) confirms the same mechanism for all substituents X. In the usual form, this result is presented on Fig. 2 by a linear dependence of rate constant logarithms for two different temperatures, confirming the validity of the isokinetic relationship¹¹. The statistic analysis¹² "without the isokinetic constraint" affords the standard deviation 0.179 and 0.019 log units for the first and second reaction step. These values may be more likely regarded as an experimental error due to the instability of the intermediate *II* than as a deviation from the Arrhenius law. "With isokinetic constraint", the standard deviation is negligibly increased to 0.226 and 0.0227 log units. The isokinetic temperature of the reaction step one is positive ($\beta = 536$ K) and that for the step two negative ($\beta = -23270$ K).

EXPERIMENTAL

Materials. The preparations of 4-hydroxybenzyl phenyl sulfones *Ia*–*Ie* have been reported earlier¹³. The sulfone *If*, m.p. 197–199°C (decomp.), was prepared analogously. For $C_{19}H_{14}Cl_2O_3S$ (393.3) calculated: 58.02% C, 3.59% H, 8.15% S; found: 58.25% C, 3.45% H, 8.17% S. The sulfone *Ig*, m.p. 210–212°C (decomp.). For $C_{19}H_{14}Br_2O_3S$ (482.2) calculated: 47.32% C, 2.93% H, 6.65% S; found: 47.51% C, 3.05% H, 6.60% S. The quinone methides *Iib*–*Iid* were prepared from the corresponding sulfones⁴. Solutions were prepared from purified¹⁴ commercial acetonitrile (middle fraction, b.p. 81.5°).

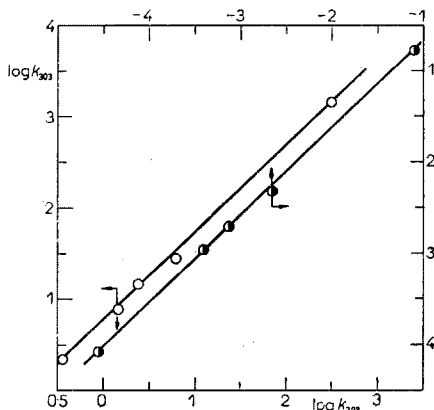


FIG. 2
Isokinetic Relationship for the Conversion
of Sulfones *I* to Alcohols *III*
Reaction (A), ○; reaction (B), ●.

Kinetic Measurements

Reaction (A). The $2 \cdot 10^{-5}$ M solution of the appropriate sulfone *Ia*–*Ie* (1 : 1 water–acetonitrile) was combined at 25°C with $2 \cdot 5 \cdot 10^{-2}$ M-NaOH in a mixing chamber of a Durrum Stopped Flow D 110 Spectrophotometer. The absorbance increase due to the formation of benzylidene-cyclohexadienones *II* was measured at 375 nm. The reaction half-time value was directly read on the screen of a Hewlett-Packard 1207 oscilloscop. Each measurement was repeated at least three times. The error of measurement was lower than $\pm 3\%$. The rate constants were calculated from the relationship $k_1 = 0.693/t_{1/2}$.

Reaction (B). Solutions (the same concentrations and solvents as in reaction *A*) of sulfones *Ia*–*Ie* or quinone methides *Iib*–*Iid* and sodium hydroxide were combined in a cell of a Specord UV-Vis spectrophotometer (Carl Zeiss, Jena). The absorbance decrease of the benzylidenecyclohexadienones *II* was monitored at 375 nm. The rate constants k_2 were obtained from the plot $\log A$ vs time (for $A_\infty = 0$).

Hydrolysis of sulfones *If* and *Ig*. A mixture of the dichloro sulfone *If* (395 mg), 0.25M-NaOH (10 ml), and tetrahydrofuran (90 ml) was refluxed for 2 h, cooled down, neutralised with saturated aqueous citric acid, and processed as usual. Chromatography on silica gel (20 g) in ether–light petroleum (1 : 1) yielded 137 mg of the unreacted sulfone *If* and 161 mg of phenyl(4-hydroxy-3,5-dichlorophenyl)methanol, m.p. 146–147°C. For $C_{13}H_{10}Cl_2O_2$ (269.1) calculated: 58.02% C, 3.74% H; found: 58.32% C, 3.60% H. The analogous hydrolysis of the dibromo sulfone *Ig* (485 mg) yielded 195 mg of phenyl-(4-hydroxy-3,5-dibromophenyl)methanol, m.p. 165–166°C (reported¹⁵, m.p. 164°C) along with 287 mg of the unreacted starting sulfone *Ig*.

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