

KINETICS OF THE BASE CATALYZED ISOMERIZATION OF SUBSTITUTED 4-ISOPROPYLIDENE-2,5-CYCLOHEXADIENONES

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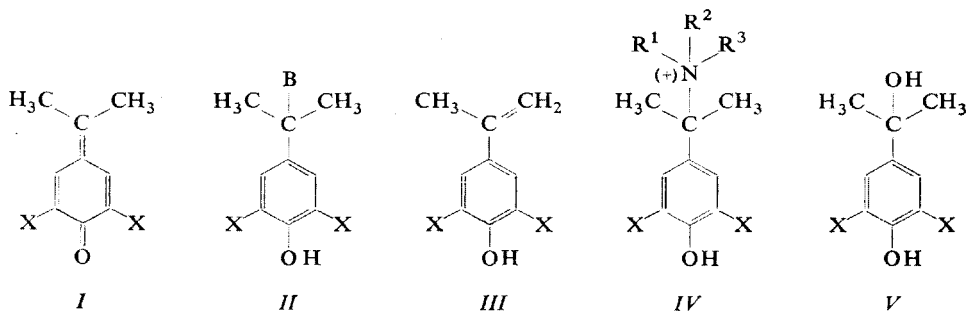
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Substituted 4-isopropylidene-2,5-cyclohexadienones *I* are smoothly transformed by tertiary bases in a nonpolar solvent into isomeric 4-isopropenylphenols *III*. The kinetics of the reaction is compatible with the base attack to the unprotonated form of the substrate as the rate-determining step. The isokinetic relationship and a Hammett-like relationship are approximately obeyed while the Brønsted equation is not.

The reactions of 4-alkylidene-2,5-cyclohexadienones (quinonemethides, *e.g.* *I*) are characterized by the tendency to restore the energetically more favourable aromatic system. The attack by a nucleophile may either result^{1,2} in its 1,6-addition, producing the 4-hydroxybenzyl derivative of the type *II*, or in the isomerization to 4-alkenylphenol *III*. The latter reaction may be formally denoted as 1,7 hydrogen shift; it proceeds very easily, *e.g.* already by the action of aluminium oxide³.

In this paper we are investigating kinetically the isomerization reaction *I* → *III* and have chosen conditions favouring it against the 1,6-addition, *viz.* a tertiary, sterically hindered base (mostly triethylamine), highly substituted substrate at the 4-position (4-isopropylidene derivatives, *Ia-d*) and non-hydroxylic solvent (1,2-dichloroethane). Even under this conditions the addition resulting in quaternary salts



In formulae *I-V* a X = H; b X = CH₃; c X = OCH₃; d X = t-C₄H₉.

must be considered as a possible side-reaction. The simple UV spectra of *I*, with a single intensive band⁴, enabled us to follow the kinetics according to the concentration of starting compounds. Of these only *Id* can be isolated in a state of purity; the remaining ones (*Ia-c*) have to be prepared *in situ* from the benzylic alcohols *V* through the corresponding chloride. In this way the hydrochloride of the amine used appears in the reaction mixture, and its effect on the reaction kinetics must be stated. Since this hydrochloride is also operative as the only proton donor, its effect is important from the point of view of the reaction mechanism.

EXPERIMENTAL AND RESULTS

Benzylic alcohols *Va-d* were described⁴. 1,2-Dichloroethane has been washed with 20% sodium hydroxide, dried with calcium chloride and rectified, b.p. 83°C. Triethylamine and other bases were of analytical purity.

Kinetic runs. A solution of benzylic alcohol *Va-c* (0.5 mmol) in 1,2-dichloroethane (20 ml) was saturated with dry hydrogen chloride under cooling⁴. The solution was evaporated *in vacuo* and diluted with 1,2-dichloroethane to a known concentration. This stock solution was further diluted for each kinetic run to the concentration of $1 \cdot 10^{-5}$ mol, thermostated and a known amount of base (30–1000× in excess) added. (In the experiments, specified in Table I, the known amount of the base hydrochloride was added in advance.) The absorbance was followed on

TABLE I

Kinetics of the Reaction of 4-Isopropylidene-2,5-cyclohexadienone (*Ia*) with Tertiary Bases B (1,2-dichloroethane solution, 20°C)

Base	[B] mol l ⁻¹	[BH ⁺] mol l ⁻¹	k_{obs}^a s ⁻¹	k^b mol ⁻¹ l s ⁻¹
Triethylamine	3.58 10 ⁻⁴	1 10 ⁻⁵	4.26 10 ⁻⁴	
Triethylamine	3.58 10 ⁻⁴	3.58 10 ⁻⁴	4.15 10 ⁻⁴	
Triethylamine	7.17 10 ⁻⁴	1 10 ⁻⁵	9.51 10 ⁻⁴	
Triethylamine	1.79 10 ⁻³	1 10 ⁻⁵	2.43 10 ⁻³	1.35
Triethylamine	7.17 10 ⁻³	1 10 ⁻⁵	9.61 10 ⁻³	
Triethylamine	8.97 10 ⁻³	1 10 ⁻⁵	1.21 10 ⁻²	
N-Methylpiperidine	3.58 10 ⁻²	1 10 ⁻⁵	3.65 10 ⁻²	1.02
N-Methylmorpholine	3.58 10 ⁻²	1 10 ⁻⁵	5.58 10 ⁻³	1.56 10 ⁻¹
4-Chloroquinuclidine	3.58 10 ⁻²	1 10 ⁻⁵	5.38 10 ⁻³	1.50 10 ⁻¹
4-Cyanoquinuclidine	3.58 10 ⁻²	1 10 ⁻⁵	1.89 10 ⁻⁴	5.27 10 ⁻³
Pyridine	3.58 10 ⁻²	1 10 ⁻⁵	3.81 10 ⁻³	1.07 10 ⁻¹
Pyridine	3.58 10 ⁻²	3.58 10 ⁻⁴	3.81 10 ⁻³	1.07 10 ⁻¹
4-Methylpyridine	3.58 10 ⁻²	1 10 ⁻⁵	7.11 10 ⁻⁴	1.98 10 ⁻²
2,4,6-Trimethylpyridine	3.58 10 ⁻²	1 10 ⁻⁵	3.69 10 ⁻⁴	1.03 10 ⁻³

^a Observed pseudo-first-order rate constants, ^b second-order rate constants.

a Specord UV VIS spectrophotometer at the wavelength corresponding to the absorption maximum of a given quinonemethide⁴. Since the extinction E_{∞} is virtually zero, the apparent first-order rate constants were obtained as the slopes of the plots in E vs. time. They were converted to the second order rate constants by dividing by the concentration of the base, or by plotting against this concentration, respectively; the resulting values are listed in Tables I and II. The activation parameters and constants of the isokinetic relationship were calculated according to the published program⁵.

In the case of di-tert-butyl derivative the kinetic runs were performed with the pure isolated compound⁴ *Id* and triethylamine. In this case the kinetics were followed by the concentration of the starting compound (absorbance at 326 nm) as well as of the product *IIIId* (absorbance at 263 nm). The whole absorption curves are reproduced in Fig. 1.

Preparative experiments. These were performed at the conditions similar to those used in kinetic runs. A solution of the benzylic alcohol *Va-d* (0.300 g) in 1,2-dichloroethane (100 ml) was converted to the chloride as above and triethylamine (2 ml) added. After the colour disappeared, the completeness of the reaction was checked by thin-layer chromatography, the solution was washed with water, dried with magnesium sulphate and evaporated. The crude product (c. 0.30 g \approx 100%) was investigated by mass spectroscopy and then purified by crystallization or converted to the benzoyle derivative.

4-Isopropenylphenol (*IIIa*), m.p. 76–78°C (hexane), lit.⁶ m.p. 80.5°C. 4-Isopropenylphenyl benzoate m.p. 116–117°C (ether-hexane); for $C_{16}H_{14}O_2$ (238.3) calculated: 80.65% C, 5.92% H; found: 80.35% C, 5.90% H. 2,6-Dimethoxy-4-isopropenylphenol (*IIIc*), m.p. 33–34°C (hexane), lit.¹ m.p. 27–28°C. 2,6-Di-tert-butyl-4-isopropenylphenol (*IIIId*), m.p. 78–79°C, lit.³ m.p. 77–78°C.

DISCUSSION

Reaction products. The isopropenylphenols *II* are produced as the only detectable product, as follows particularly from the following facts: The yields of the preparative

TABLE II

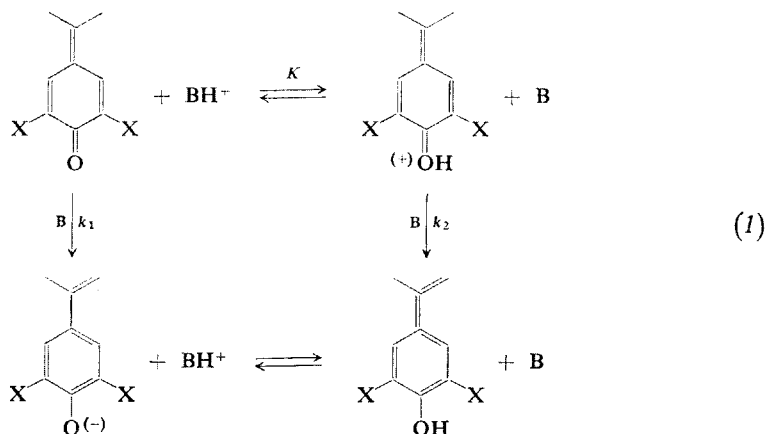
Kinetics of the Reaction of Substituted 4-Isopropylidene-2,5-cyclohexadienones *Ia-d* with Triethylamine (1,2-dichloroethane solution)

Temperature °C	Second order rate constants, mol l ⁻¹ s ⁻¹			
	<i>Ia</i>	<i>Ib</i>	<i>Ic</i>	<i>Id</i>
20	1.35	0.0440	0.0292	0.00790 (0.00805) ^a
30	1.73	0.0674	0.0351	0.0125
40	2.29	0.0790	0.0511	0.0180
50	2.71	0.107	0.0795	0.0260
60	3.74	0.133	0.108	0.0354
ΔH^\ddagger kcal	4.2	4.6	6.0	6.8
ΔS^\ddagger cal grad ⁻¹	-43.6	-48.9	-45.3	-45.0

^a The two values were determined from the decrease of *Id* and increase of *IIIId*, respectively.

experiments were 100% within the accuracy attained; mass spectra of the rough products did not exhibit any peaks of higher molecular weight (*e.g.* dimers). The reaction of compound *Id*, which only can be isolated as a pure substance, was followed kinetically from the concentrations of the product and of the starting product as well; the two determinations of the rate constant agree well (Table II). A sharp isosbestic point (Fig 1) shows the absence of any third component. The final spectrum of the reaction mixture agrees with the spectrum of pure *IIIId* in the presence of triethylamine. The same arguments also prove the irreversibility of the reaction; in addition no reaction was observed between *III* and a base.

Mechanism. In the presence of a base (in excess) and of its hydrochloride (in an almost stoichiometric amount with respect to the substrate) we consider the former to be the only operative proton acceptor and the latter the only proton donor. The two acid-base pairs present are in equilibrium (1) which is shifted to left and established much faster than the next step proceeds. With these assumptions it is only to decide whether the reaction starts from the unprotonated form of the substrate (k_1), or from the protonated form (k_2), or from both.



If the steps k_1 or k_2 are irreversible, the observed pseudo-first-order rate constants k_{obs} are expressed for the two possible paths, 1 and 2, respectively, as

$$\begin{aligned}
 (k_{\text{obs}})_1 &= \frac{[\text{B}]}{[\text{B}] + K[\text{BH}^+]} k_1[\text{B}] \cong k_1[\text{B}], \\
 (k_{\text{obs}})_2 &= \frac{K[\text{BH}^+]}{[\text{B}] + K[\text{BH}^+]} k_2[\text{B}] \cong Kk_2[\text{BH}^+].
 \end{aligned}$$

The data of Table I, concerning the reaction of *Ia* with triethylamine and with pyridine, decide in favour of the first possibility. The pseudo-first-order constants depend linearly on the concentration of the base (in a 30–1000 fold excess), so that k_1 is constant; on the other hand they do not depend on the concentration of the hydrochloride. The line in the k_{obs} vs $[B]$ plot (not shown) goes exactly through the origin, hence neither a fractional participation of the reaction path 2 was detected. The result could be anticipated with a view to the small values of the equilibrium constant K , which may be estimated to 10^{-17} or 10^{-11} for triethylamine or pyridine, respectively (from the basicities in water).

Effect of the base. An investigation of various tertiary bases is restricted by the condition that they must not add to form the quaternary salts *IV*, in addition weak bases ($\text{p}K < 5$) are insufficient to generate the quinonemethide *I* from its precursor. Several bases complying with these conditions react with rate constants only roughly parallel to their base strength, so that a Brønsted plot (Fig. 2) is far from linearity. It seems that steric effects play an important role, e.g. pyridine reacts relatively fast compared with 2,4,6-trimethylpyridine. However, the steric effects cannot explain fully the observed scatter. At any rate, the Brønsted coefficient β would be rather low, c. 0.4, showing moderate transfer in the transition state.

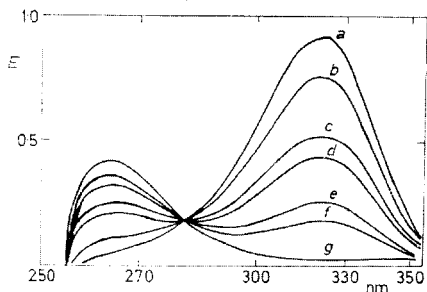


FIG. 1

Kinetics of the Reaction of *Id* with Triethylamine Yielding *III*d, as Followed by UV Spectroscopy

The curves *a*–*g* correspond to the reaction time from 0 to ten hours.

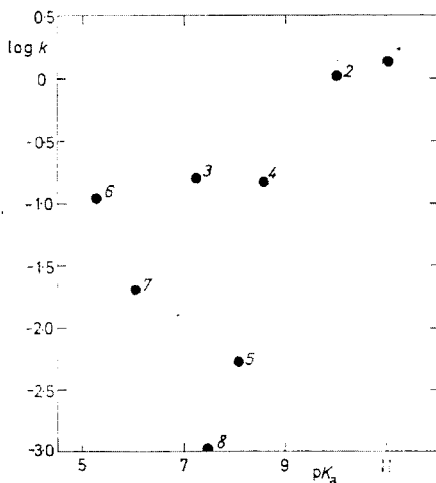


FIG. 2

Brønsted Plot for the Reaction of *Ia* with Various Bases

1 Triethylamine, 2 N-methylpiperidine, 3 N-methylmorpholine, 4 4-chloroquinuclidine, 5 4-cyanoquinuclidine, 6 pyridine, 7 4-methylpyridine, 8 2,4,6-trimethylpyridine.

Substituent effects. The choice of substituents is also very restricted, this time mainly owing to the instability of some derivatives. The set of four compounds is, of course, insufficient for any safe conclusion, but it seems that the rate constants are best correlated with the σ_p^0 constants (the values of $2\sigma_p^0$ have been applied with respect to two substituents, $\rho \approx 5-6$). The use of σ_p is compatible with the formal *meta* position of the substituents, since no aromatic system is actually involved. The constants σ_p may be applied for olefinic systems in general⁷ and more particularly for quinones⁸; they do not express more than that inductive and mesomeric effects are equally important. Steric effects are apparently negligible. The high absolute value of ρ may comply with the character of a conjugated olefin rather than of an actual *meta* derivative of benzene; for the latter a value of ρ c. 1.5 would be expected.

Activation parameters. The temperature dependence was followed for the reaction of the four substrates *Ia-d* with triethylamine (Table II). The remarkably low entropies of activation may be interpreted by a considerable loss of degrees of freedom in the transition state⁹; it concerns clearly the triethylamine moiety. The similar values of the activation parameters for the four reactions suggest further the same reaction mechanism⁹. This conclusion is supported in a more convincing manner by the existence of an isokinetic relationship (linear relationship between the ΔH^\ddagger and ΔS^\ddagger values). A statistical analysis⁵ yielded a standard deviation of 0.026 log units without the isokinetic constraint. This value represents either deviation from the Arrhenius law or the experimental error; the latter possibility is more probable. This would correspond to a 6% accuracy of the rate constant, understandable in view of the instability of the starting compounds. By the isokinetic constraint the standard deviation rises only insignificantly to 0.032 log units, while the differences in reactivity between individual reactions are represented by a standard deviation 30× higher. The isokinetic temperature β is negative -1060 K.

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