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Mechanism of decarboxylation of substituted salicylic acids. I. Kinetics in quinoline solution

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First-order rate constants for the decarboxylation of fourteen 4- and 5-substituted salicylic acids have been determined in quinoline solution in the temperature range 90–230 °C. Substituents have almost no effect on the rate constants, except those with large negative σ-constants: *p*-amino, *p*-hydroxy, *p*-ethoxy. The enthalpies and entropies of activation do not fit the isokinetic relationship, with the same three substituents deviating. It is suggested that the decarboxylation involves a preliminary ionization of the carboxyl group, followed by protonation of the aromatic ring of the anion so formed, and then loss of carbon dioxide. The isokinetic relationship fails because substituents affect all three steps differently, and the Hammett relationship fails because the substituent effect on the ionization is related to σ while that on the other two steps follows σ^+. The three substituents which deviate are those for which σ and σ^+ differ widely.

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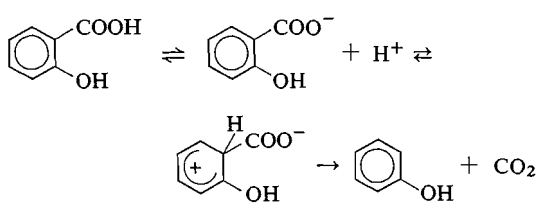
The decarboxylation of substituted salicylic acids in aqueous solution has been thoroughly investigated. Schubert and Gardner (1) showed that the decarboxylation of 2,4,6-trihydroxybenzoic acid in aqueous perchloric acid is first order with respect to 2,4,6-trihydroxybenzoate ion and to hydrogen ion, so that the slow step could be either a unimolecular decomposition of the free acid or a bimolecular reaction between the anion and the proton. Willi (2) found that the decarboxylation of 4-substituted salicylic acids obeys the Hammett relationship using σ^+, and that the rate is increased by electron-releasing substituents. He therefore concluded that the slow step is protonation of the anion in the 1-position of the aromatic ring. Lynn and Bourns (3) demonstrated that protonation and decarboxylation are sequential rather than concerted processes by showing that the ^{13}C-carboxyl kinetic isotope effect in the decarboxylation of 2,4-dihydroxybenzoic acid varies with buffer concentration. These results make it clear that the mechanism of decarboxylation of substituted salicylic acids in aqueous solution is the following:



In nonaqueous solution much less information is available. Brown, Hammick, and Scholefield (4) found that in resorcinol at 110–240 °C the first-order rates of decarboxylation increased as hydroxy groups were added to the 4- and 6-positions of salicylic acid, which suggested that here, too, protonation of the aromatic ring is an important part of the rate-determining process. Clark (5) studied the decarboxylation of 4-hydroxysalicylic acid in glycols and in quinoline and concluded that these solvents were acting as nucleophiles toward the carboxyl carbon.

The present work reports the rate and activation parameters for decarboxylation of 14 substituted salicylic acids in quinoline solution.

Experimental

Synthetic quinoline distilled from and stored over barium oxide was used throughout. Salicylic acid and the 4- and 5-amino, 4- and 5-hydroxy, 4- and 5-nitro, 4-ethoxy, 5-methyl, 5-chloro, and 5-bromo substituted salicylic acids were commercial products recrystallized to constant melting point from water, aqueous ethanol, or toluene. All melting points were determined in a Hershberg apparatus (6) using calibrated Anschütz thermometers. The preparation of the 4-methyl (7) and 4-bromo (8) acids has been previously described.

5-Methoxysalicylic Acid

This acid was prepared by methylating 5-hydroxysalicylic acid. To a solution of 7.1 g of 5-hydroxysalicylic acid in 40 ml of 10% sodium hydroxide solution was added in alternate small portions 12.1 g of dimethylsulfate and 40 ml of 10% sodium hydroxide solution. The mixture was refluxed for 4 h, cooled, and acidified. The precipitated crude 5-methoxysalicylic acid was refluxed with 10% sodium hydroxide solution, then reprecipitated with mineral acid. Recrystallization from benzene and from water produced 2.8 g (37%) of product with m.p. 145.7–146.2 °C (lit. (9), m.p. 143.5 °C).

TABLE I

First-order rate constants ($k \times 10^4$ s^{-1}) for the decarboxylation of substituted salicylic acids in quinoline*

Substituent	k at temperature 93°	100°	110°	120°	126°	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
4-NH_2	*0.53*	*1.09*	*3.35*	*9.34*	*13.3*	28.5±0.8	−0.7±2.0

Substituent	k at temperature 130°	140°	150°	160°	170°	180°	190°	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
4-OH	*0.61*	*1.61*	*3.97*	*10.4*		*45.1*	*78.9*	29.5±0.5	−5.2±1.2
4-OEt	*0.13*	*0.40*	*1.02*	*2.78*	*5.81*	*14.6*	*29.7*	32.6±0.4	−0.5±0.9

Substituent	k at temperature 180°	200°	210°	220°	230°	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
H	*0.20*	*1.08*		4.86	*8.76*	33.4±0.4	−7.0±0.8
4-Me		3.61	6.86	12.9	*27.3*	30.7±0.8	−10.3±1.7
4-Br		3.39	6.40	11.3	*23.6*	29.3±0.9	−13.5±1.9
4-NO_2		*0.41*	0.86	2.16	4.73	38.2±0.8	+1.1±1.7
5-NO_2		*1.06*	1.99	3.93	7.89	30.7±0.8	−12.8±1.6
5-Me		1.36	3.10	5.83	*11.8*	32.9±0.8	−7.6±1.7
5-Br		1.51	3.40	6.34	*11.8*	31.1±0.9	−11.1±1.8
5-Cl		1.56	3.27	6.34	*12.1*	31.2±0.8	−10.9±1.6
5-OH		1.93	4.04	7.78	*18.2*	33.7±1.3	−5.2±2.6
5-NH_2		1.76	*3.69*	7.62	*15.9*	33.6±0.6	−5.6±1.2
5-OMe		2.23	4.53	8.43	*19.6*	32.6±1.2	−6.2±2.4

*Each rate constant is the average of two to five runs. The maximum deviation from the mean is about 3%. Numbers in italics were obtained gravimetrically; all others are manometric.

Rate Measurements

The apparatus for measuring rates of decarboxylation was similar to that previously described (10). The thermostat consisted of a 3 l round-bottom flask containing a refluxing liquid (*n*-butyl ether) into the vapors of which dipped the reaction vessel. The temperature, measured by a thermocouple in the reaction vessel, could be maintained to within ±0.05 °C by means of a manostat on the refluxing liquid. The manostat consisted of the flask containing the refluxing liquid and a ballast tank of about equal size connected to a vacuum pump through a solenoid gas valve. The gas valve was operated through a relay by a thermistor in the refluxing vapor.

The rate of carbon dioxide evolution was measured either gravimetrically as previously described (10) or manometrically. For manometric measurements the reaction vessel was modified to a bulb with a capillary neck. The reactant solution (10 ml of 0.1–0.2 *M* salicylic acid) was introduced through the capillary neck by means of a hypodermic syringe and allowed to come to thermostat temperature, then a mercury manometer was attached to the neck. Both manometric and gravimetric data were fitted by the least-squares method to the rate equation

$$\ln (x_i - x_t) = -kt + \ln (x_i - x_0)$$

where x_0, x_t, and x_i represent weight or pressure of carbon dioxide at times zero, t, and infinity respectively. The standard deviation of k within a run was about 1% and the maximum deviation of k from the mean of three to five runs was about 3%. Manometric and gravimetric rates agreed within experimental error so long as the rate constant was less than about 10^{-3} s^{-1}. At higher rates the evolution of carbon dioxide from solution was slower than the reaction.

Enthalpies and entropies of activation were calculated from a least-squares fit of the data to the equation

$$\ln \frac{k}{T} = \ln \frac{\mathbf{k}}{h} + \frac{\Delta S^{\ddagger}}{R} - \frac{\Delta H^{\ddagger}}{RT}$$

where **k** is the Boltzmann constant.

Results and Discussion

The decarboxylation of substituted salicylic acids in quinoline solution is a clean first-order reaction up to three half-lives for all 14 acids at all the temperatures investigated. Rate constants and activation parameters are shown in Table I.

Figure 1 shows a plot of the rate constants at 200 °C against σ^+. It is clear that the rates do not obey the Hammett relationship. Substituents having $\sigma^+ = -0.3$ or greater have very little effect on the rate, while 4-OH, 4-OEt, and 4-NH_2 substituents increase the rate of decarboxylation markedly. The fact that most substituents have little effect on the rate might be accounted for in one of three ways: (*a*) the substituents are insulated from the reaction site; (*b*) the substituents

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influence bond making and bond breaking in opposite senses so that cancellation occurs; or (*c*) the isokinetic temperature is near 200 °C (11). Considering the structure of the reactant, (*a*) is hardly possible; (*b*) and (*c*) may be aspects of the same phenomenon, that is, cancellation may occur at the isokinetic temperature only.

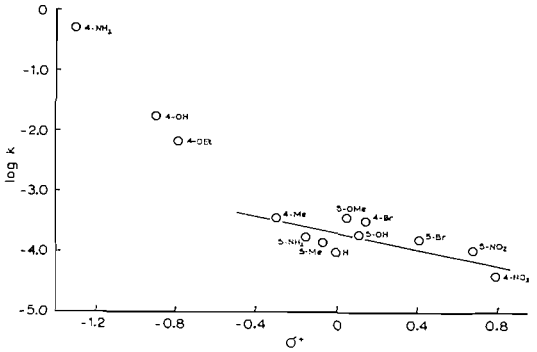


FIG. 1. Hammett plot of the rate constants for decarboxylation of salicylic acids in quinoline at 200 °C. Rate constants for the three points at upper left are calculated from the activation parameters. σ^+ values are from ref. 14.

Figure 2 is a plot of the isokinetic relationship, $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$. Once again the points for 4-OH, 4-OEt, and 4-NH_2 deviate from the rest. The remaining points show a considerable scatter but, including their experimental uncertainty, they all lie on a straight line with slope = 290 ± 50 °C. The isokinetic temperature is therefore too great to account for the lack of substituent effects at 200 °C. It is also worth noting that rate constants at 100 °C calculated from the activation parameters give a Hammett plot hardly distinguishable in shape from that at 200 °C.

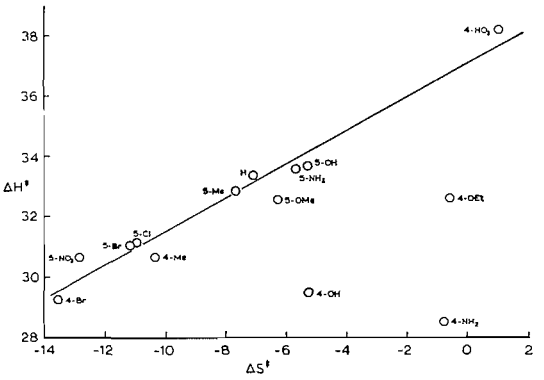
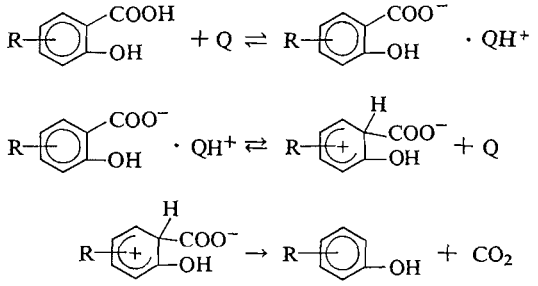


FIG. 2. Isokinetic plot for the decarboxylation of salicylic acids in quinoline.

However, even allowing for the difficulties in calculating and interpreting isokinetic temperatures (12), the 4-OH, 4-OEt, and 4-NH_2 points do not fall on the line. Deviations of this kind by a certain set of reactants from the isokinetic and Hammett relationships established by related compounds have often been taken to mean that these reactants use a different mechanism than the others (11). It can be shown that in the present case this is not necessarily so.

The first-order decarboxylation of salicylic acids in quinoline contrasts with that of substituted anthranilic acids in nitrobenzene which is second order (10). To determine whether the difference in order is a function of the acids or of the solvents, salicylic acid was decarboxylated in nitrobenzene at 200 °C. The reaction is second order with respect to salicylic acid with a rate constant of $2 \times 10^{-4}\ M^{-1}\ s^{-1}$. Conversely, a number of 4- and 5-substituted anthranilic acids have been found to decarboxylate by a first-order reaction in quinoline (13).

The bimolecular decarboxylation in neutral aprotic nitrobenzene solvent suggests that there is no convenient intramolecular route for the proton transfer from the carboxyl group to the aromatic ring which is part of the decarboxylation reaction; protonation is accomplished by transfer from one acid molecule to another. However, in the equally aprotic but basic solvent quinoline, the decarboxylation is first order. Quinoline must therefore be able to facilitate the proton transfer in a way that nitrobenzene cannot. Since quinoline is more basic than nitrobenzene it seems reasonable to suppose that it functions by accepting a proton from the carboxyl group; the quinolinium ion so formed could then serve as the protonating agent for the aromatic ring.



The ionization postulated for the first step has a dual function; it converts the aprotic quinoline into a protonating agent and converts the salicylic

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acid to the anionic form in which it is more readily subject to protonation, as has been demonstrated by the work in aqueous solution reviewed at the beginning of this paper.

In fact, the whole mechanism proposed here for decarboxylation in quinoline bears a strong formal resemblance to the mechanism which operates in aqueous solution, with quinoline and water playing analogous roles. However, the resemblance may be more apparent than real. In a medium of such low dielectric constant as quinoline ($\varepsilon = 9$) it is extremely unlikely that the ions formed in the first step would dissociate extensively. This probability has been shown in the equations by representing the ions as pairs (dot notation) rather than as separated entities. That dissociation is small is further indicated by the fact that adding quinolinium chloride has no effect on the rate of decarboxylation (13). The association of quinolinium and salicylate ions in ion pairs would, of course, greatly facilitate the proton transfer of the second step and thus compensate for the low concentration of ions. Whether the protonation and decarboxylation of steps 2 and 3 are actually sequential, as shown, or concerted is not evident at this point.

The proposed mechanism can also account for the poor fit of the data to the Hammett relationship shown in Fig. 1. An electron-attracting substituent, say, at R would tend to increase the rate of decarboxylation by increasing the concentration of ion pairs formed in the first step. At the same time it would hinder the protonation of the aromatic ring in step 2, and facilitate the loss of CO_2 in step 3. The overall effect of a substituent could be represented by the Hammett equation modified as follows:

$$\log \frac{k}{k_0} = \rho_1\sigma + \rho_2\sigma^+ + \rho_3\sigma^+$$

where the subscripts refer to the three steps in the proposed mechanism. This formulation assumes that the third step is the slow one. If it is actually fast, or if steps 2 and 3 are concerted, the third term will disappear. Hammett's σ is appropriate for the first step since it involves the ionization of a carboxyl group, whereas σ^+ is required for the second and third steps because they involve the formation and decay of positive charge on the aromatic ring. As indicated above, a substituent will have an opposite effect on step 2 to that on steps 1 and 3; ρ_2 will be negative while ρ_1 and ρ_3 will be positive. Consequently, if ρ_2 is approximately equal in magnitude to $\rho_1 + \rho_3$, the cancellation of substituent effects postulated earlier will be accomplished. Furthermore, the cancellation will be effective only for those substituents for which σ and σ^+ are the same; that is, for all the substituents used here except 4-OH, 4-OEt, and 4-NH_2. This immediately suggests that these three apparently aberrant groups may be included in the same mechanism.

To test this possibility, the modified Hammett equation may be rearranged to

$$\frac{\log k/k_0}{\sigma} = \rho_1 + (\rho_2 + \rho_3)\frac{\sigma^+}{\sigma}$$

and Fig. 3 shows a plot of the data in this form. There is a considerable scatter of points, as might be expected from the large uncertainty that appears in the variables of the rearranged equation when σ is small, and from the fact that the acidities of substituted salicylic acids in media of low dielectric constant show considerable deviations from the simple Hammett relationship used to describe step 1 (8). Nevertheless, a linear trend is evident and the points for the "aberrant" groups 4-OH, 4-OEt, and 4-NH_2 do not deviate more than the others. The slope and intercept of the best straight line through the points give $\rho_1 = +4$ and $\rho_2 + \rho_3 = -4$. The latter value is consonant with the large negative ρ's observed in other aromatic substitutions (14) and the former value is not unreasonable for the ionization of a carboxylic acid in quinoline, when it is remembered that ρ for this reaction changes from $+1$ to $+2$ on changing the solvent from water to ethanol (15).

The three-step mechanism can also explain the failure of the activation parameters to fit the isokinetic relationship. According to Leffler and Grunwald (11), substituent effects in which resonance plays a particularly large part, such as those for which σ^+ differs sharply from σ, often do not fit the isokinetic relationship. This is because the isokinetic temperature for the resonance contribution is not the same as that for the polar contribution to the substituent effect. It may also be pointed out that a similar argument applies to multistep reactions in general. The observed enthalpies and entropies are composite quantities made up of the enthalpies and entropies

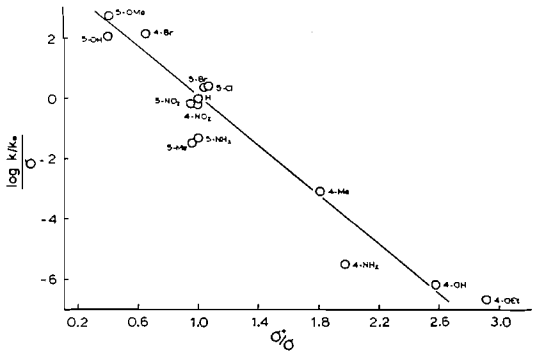

FIG. 3. Rate constants for decarboxylation of salicylic acids in quinoline at 200 °C plotted in a modified Hammett relationship. σ and σ^+ values are from ref. 14.

of the separate steps. Even though each individual step obeys the isokinetic relationship, the overall reaction will not do so unless all steps have the same isokinetic temperature.

In summary, then, it seems probable that all 14 substituted salicylic acids react by the same three-step (or two-step) mechanism. However, the data now available do not exclude the possibility that the reactive acids decarboxylate by a different mechanism than the others. Whether or not more than one mechanism applies, the fact that all the data can in principle be accommodated by a single mechanism illustrates once more (12) the danger of basing a change of mechanism on a break in the Hammett or isokinetic relationship.

Acknowledgment

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