

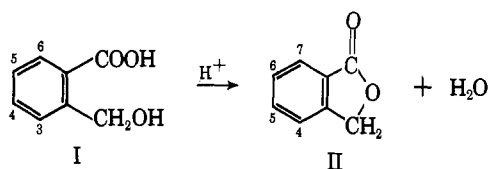
Steric Acceleration of the Lactonization of 2-(Hydroxymethyl)benzoic Acids^{1,2}

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Tirouflet reported that Cl, Br, or I in the 4- or 5-position of 2-(hydroxymethyl)benzoic acid retarded acid-catalyzed lactonization to a phthalide derivative, whereas the same group in the 3- or 6-position accelerated cyclization. He considered the latter effect to represent steric acceleration, but did not further support or interpret this hypothesis. We find that fluorine in the 3- or 6-position retards lactonization, while 3- or 6-methyl accelerates it strongly. That the polar effect of 3- or 6-halogen is a decelerating one is shown by the influence of fluorine, whose bulk is small. The over-all rate-enhancing effect of the other halogens as 3- or 6-substituents is then understood as steric acceleration partially offset by polar deceleration. The steric accelerating effect of 3- or 6-methyl is not altered much by polar factors, and the over-all acceleration is therefore large. The steric acceleration is considered to arise from exclusion of certain low-energy initial state conformations. It is expressed in a diminished enthalpy of activation.

Under catalysis by dilute acid, 2-(hydroxymethyl)benzoic acids (I) lactonize to phthalides (II). The



condition of equilibrium in dilute aqueous solution favors the phthalide overwhelmingly.

Tirouflet⁴ determined rate coefficients for cyclization of several substituted 2-(hydroxymethyl)benzoic acids in water at 60°. He showed that three 5-substituents (Cl, Br, and NO₂) and six 4-substituents (Cl, Br, I, OCH₃, OC₂H₅, and NHCOCH₃) all retarded lactonization, and all to about the same extent. Rates were from 23 to 41% that for unsubstituted I.

Tirouflet's rate coefficients for lactonization of 3- and 6-substituted 2-(hydroxymethyl)benzoic acids, in which the substituent is *ortho* to -CH₂OH and to -COOH, respectively, are displayed in Table I. All *ortho* substituents accelerated the reaction. Tirouflet interpreted this as a steric effect,⁵ but he did not explain how or why 3- and 6-substituents augment reaction rate. His interpretation seemed plausible as far as it went, but we felt it desirable to provide further experimental evidence.

We reasoned that substituents which decelerate lactonization when in the 4- or 5-position of I should,

insofar as their polar or electronic effects were concerned, also decelerate when in the 3- or 6-position. Therefore a halogen too small to exert an appreciable steric effect ought to retard the reaction to about the

Table I. Tirouflet's Rate Coefficients for Lactonization of 3- and 6-Substituted 2-(Hydroxymethyl)benzoic Acids^a

Substituent	H	3-Cl	3-Br	3-I	3-OCH ₃	6-Cl
10 ³ k, M ⁻¹ sec. ⁻¹	7.2	28.2	47.5	53.3	38.4	(19) ^b
Relative rate	1.00	3.9	6.6	7.4	5.4	(2.6) ^b

^a Data of ref. 4, converted to second-order units. ^b Approximate value.

same extent in the 3- or 6-position as does a halogen in the 4- or 5-position. Also, if the effect of *o*-chlorine were primarily steric, a substituent of similar size and opposite polar effect should have a total kinetic influence similar to or greater than that of *o*-chlorine.

Accordingly we determined rates of lactonization of the 3-fluoro, 6-fluoro, 3-methyl, 6-methyl, and 3,6-dimethyl derivatives of I. The pK_a values of these acids were also determined.

Syntheses. Most of the 3- and 6-substituted 2-(hydroxymethyl)benzoic acids were so prone to cyclize that isolation of the hydroxy acids was impractical if not impossible. Therefore the corresponding phthalides (II) were prepared. These were saponified in dilute solution. Acidification then served to initiate a kinetic run.

Reduction of 3-nitrophthalic anhydride by means of zinc and hydrochloric acid in the presence of acetic anhydride, after Tirouflet,⁶ produced a separable mixture of 4- and 7-acetamidophthalides.⁷ The 4- and 7-aminophthalides from deacetylation were separately converted to diazonium fluoroborate salts which, on pyrolysis,⁸ afforded 4- and 7-fluorophthalides, respectively, in modest (*ca.* 35%) yields. 5-Fluorophthalide has been made by a similar procedure.⁹

4,7-Dimethylphthalide was obtained by reduction of 3,6-dimethylphthalic anhydride with lithium aluminum hydride, after Buchta and Loew,¹⁰ or with zinc and hydrochloric acid in acetic acid.

4-Methylphthalide, m.p. 68–69.5°, was prepared by photobromination of 2,3-dimethylbenzoyl chloride, treatment of the crude bromination product with aqueous sodium bicarbonate at reflux, and then acidification. The yield was 21%. This product was

(1) Research supported in part by the National Science Foundation.

(2) Presented to XIXth International Congress of Pure and Applied Chemistry, London, July 1963; Abstracts A, p. 92.

(3) This paper is based on the Ph.D. Thesis of C. F. Hauser, Brown University, 1962.

(4) J. Tirouflet, *Bull. soc. chim. France*, 799 (1954).

(5) We regret that the IUPAC meeting abstract² incorrectly describes Tirouflet's interpretation.

(6) J. Tirouflet, Thesis, University of Paris, 1952.

(7) It is regrettable that the official numbering systems for *o*-(hydroxymethyl)benzoic acid and phthalide give different numbers to corresponding positions, as shown in structures I and II.

(8) A. Roe, *Org. Reactions*, 5, 193 (1949).

(9) L. M. Yagupol'skii and R. V. Belinskaya, *Zh. Obshch. Khim.*, 33 (7), 2358 (1963); *Chem. Abstr.*, 59, 13909 (1963).

(10) E. Buchta and G. Loew, *Ann.*, 597, 123 (1955).

expected only from bromination of the 2-methyl group. Bromination of the 3-methyl group would presumably lead to 2-methyl-3-(hydroxymethyl)benzoic acid which would not esterify under the conditions of acidification.

7-Methylphthalide, m.p. 85–87°, was similarly prepared from 2,6-dimethylbenzoyl chloride, in 40% yield. Since the two methyl groups were symmetrically disposed, the only side chain monobromination product that could have been formed was the desired one.

We first sought to prepare the two monomethylphthalides by reduction of 3-methylphthalic anhydride with zinc and hydrochloric acid in acetic acid, or with sodium borohydride. Recrystallization of either reduction product from a carbon tetrachloride–petroleum ether (b.p. 60–70°) mixture furnished a white solid of m.p. 62.5–63.0°. This was at first taken to be one of the monomethylphthalides, but the properties of the authentic samples (above) showed this identification to be erroneous. A rough determination of the melting points of mixtures of 4- and 7-methylphthalides indicated that the solid of m.p. 62.5–63.0° is a mixture of about equal parts of the two isomers. A small amount of 4-methylphthalide, m.p. 69–70°, was isolated by methylene chloride extraction of the aqueous layer from the zinc reduction mixture.

Experimental

Phthalide, m.p. 71–73° (lit.¹¹ m.p. 72–73°), and 2-(hydroxymethyl)benzoic acid, m.p. 122–124° (lit.¹² m.p. 120.5–121.5°), were obtained by standard methods.

4-Fluorophthalide. 4-Aminophthalide, m.p. 157–159° (lit.⁶ m.p. 158°), was prepared from 3-nitrophthalic anhydride in 20% over-all yield by the procedure of Tiroufflet.⁶ A suspension of 7.6 g. of 4-aminophthalide in 18 ml. of 48% fluoroboric acid and 15 ml. of water was stirred for 20 min. while cooling to 0°. While the temperature was held at 0°, a solution of 3.59 g. of sodium nitrite in 7 ml. of water was added dropwise with stirring. Stirring was continued for 20 min. after completion of addition. The heavy precipitate which had formed was collected, washed twice with dry ether, and dried 1 day *in vacuo* over concentrated sulfuric acid; it then weighed 11.3 g.

The dry solid was powdered and placed in a retort fitted with a series of three water-cooled condensers and two ice-cooled traps. Initially a low flame and then a hot flame were used to decompose the diazonium fluoroborate and drive the solid product away from the tarry pot residue. Most of the solid collected in the neck of the retort. It was crystallized once from dilute ethanol, whereupon a nearly white material, m.p. 100–102°, wt. 2.7 g. (35%), was obtained.

Anal. Calcd. for C₈H₅FO₂: C, 63.16; H, 3.31. Found¹³: C, 63.29; H, 3.29.

7-Fluorophthalide. 7-Aminophthalide, m.p. 119–120.5° (lit.⁶ m.p. 121–123°), was prepared after Tiroufflet.⁶ It was transformed into 7-fluorophthalide, m.p. 169–170°, by the method described above in 32% yield.

Anal. Calcd. for C₈H₅FO₂: C, 63.16; H, 3.31. Found¹³: C, 63.19; H, 3.26.

(11) J. H. Gardner and C. A. Naylor, Jr., "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 526.
(12) H. Gilman, G. E. Brown, F. J. Webb, and S. M. Spatz, *J. Am. Chem. Soc.*, **62**, 977 (1940).

(13) Analysis by Micro-Tech Laboratories, Skokie, Ill.

2-(Hydroxymethyl)-3-fluorobenzoic Acid. 4-Fluorophthalide was heated at reflux with excess aqueous sodium hydroxide. The cooled solution was incompletely neutralized with hydrochloric acid. The solid which separated was crystallized four times from an ethyl acetate–carbon tetrachloride mixture, whereupon it melted at 113–114°. The mixture melting point with 4-fluorophthalide was strongly depressed.

Anal. Calcd. for C₈H₇FO₃: C, 56.48; H, 4.15. Found¹³: C, 56.47; H, 4.45.

An effort to obtain pure 2-(hydroxymethyl)-6-fluorobenzoic acid by analogous treatment of 7-fluorophthalide was unsuccessful.

4-Methylphthalide. 3-Bromo-1,2-xylene, prepared from commercial 2,3-dimethylaniline by Bigelow's¹⁴ *o*-bromotoluene procedure, was converted to 2,3-dimethylbenzoic acid, m.p. 142–144° (lit.¹⁵ m.p. 142–143°) *via* the Grignard reagent in 88% yield. Treatment with thionyl chloride afforded 2,3-dimethylbenzoyl chloride, b.p. 110–112° at 14 mm. (lit.¹⁶ b.p. 128° at 22 mm.). To 36.3 g. of 2,3-dimethylbenzoyl chloride in a 100-ml. flask provided with stirrer, calcium chloride protected condenser, and addition funnel, half-immersed in an oil bath at 165°, and illuminated by 500- and 150-w. incandescent bulbs, 34.5 g. of bromine was added during 75 min. After another 15 min. of heating, the entire pot contents was distilled under reduced pressure. The whole distillate was combined with an excess of a saturated aqueous solution of sodium bicarbonate and heated at reflux for 2 hr. The white precipitate which formed upon cooling and acidification with hydrochloric acid was collected and dissolved in ether. The ether solution was extracted with aqueous sodium bicarbonate, washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from a carbon tetrachloride–petroleum ether mixture. The yield of white 4-methylphthalide, m.p. 69–70°, was 6.6 g. (21%).

Anal. Calcd. for C₉H₈O₂: C, 72.96; H, 5.44. Found¹³: C, 73.05; H, 5.57.

7-Methylphthalide. The synthesis started from commercial 2,6-dimethylaniline and was analogous to that above. The intermediate 2,6-dimethylbenzoic acid had m.p. 111–114° (lit.¹⁷ m.p. 116°). 7-Methylphthalide was obtained as a white crystalline solid, m.p. 85–87°.

Anal. Calcd. for C₉H₈O₂: C, 72.96; H, 5.44. Found¹³: C, 73.17; H, 5.46.

Reduction of 3-Methylphthalic Anhydride. 3-Methylphthalic anhydride, m.p. 116–117° (lit.¹⁸ m.p. 114–115°), was prepared essentially according to the method of Newman and Lord¹⁹ (for 3,6-dimethylphthalic anhydride) by sulfuric acid dehydration of the 2-methylfuran–maleic anhydride adduct.²⁰ A suspension of 97.2 g. of 3-methylphthalic anhydride in 250 ml. of glacial acetic acid and 215 ml. of concentrated hydrochloric acid was placed in a 2-l. flask equipped with

(14) L. A. Bigelow, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 135.

(15) W. R. Brasen and C. R. Hauser, *J. Org. Chem.*, **18**, 806 (1953).

(16) O. Brunner, H. Hofer, and R. Stein, *Monatsh.*, **63**, 93 (1933).

(17) R. Hufferd and W. Noyes, *J. Am. Chem. Soc.*, **43**, 929 (1921).

(18) V. Jurgens, *Ber.*, **40**, 4413 (1907).

(19) M. S. Newman and B. T. Lord, *J. Am. Chem. Soc.*, **66**, 733 (1944).

(20) K. Alder and K. Backendorf, *Ann.*, **535**, 101 (1938).

condenser, stirrer, and addition port. With stirring, 120 g. of zinc dust was added gradually during 20 min. The mixture was heated at reflux for 5 hr. and then filtered hot to remove excess zinc. The filtrate was poured into 1300 g. of ice and water and it was kept chilled overnight. The solid which separated was collected and washed twice with cold water; dried, it weighed 76.1 g. (86%) and melted at 58–61°. Repeated crystallization from carbon tetrachloride–petroleum ether raised the melting point to 62.5–63°.

Anal. Calcd. for $C_9H_8O_2$: C, 72.95; H, 5.44. Found¹³: C, 73.06; H, 5.53.

As told in the text, this product appears to be a mixture of 4- and 7-methylphthalides.

By extraction of the main aqueous filtrate with methylene chloride, 3.5 g. (4%) of 4-methylphthalide, m.p. 69–70°, was isolated. This was identical in infrared spectrum and by mixture melting point with an authentic sample (*vide supra*).

Reduction of 3-methylphthalic anhydride with sodium borohydride in bis(2-methoxyethyl) ether (reagents mixed at room temperature with spontaneous heating, then kept at 80° for 1 hr.) afforded a similar product, m.p. 62.5–63°, in 64% yield. Its infrared spectrum was identical with that of the zinc reduction product.

*pK_a Determinations.*²¹ Solutions of sodium salts of the several *o*-(hydroxymethyl)benzoic acids were prepared by heating the respective lactones with a small excess of a sodium hydroxide solution for a short time on the steam bath. The resulting solutions were mostly either 10^{-3} or 2.5×10^{-3} *M*. They were first titrated potentiometrically with 0.07 *M* hydrochloric acid solution to the point of neutralization of the excess sodium hydroxide and then titrated further to the vicinity of half-neutralization of the sodium *o*-(hydroxymethyl)benzoates, where the pH was measured at four or five points as a function of the volume of hydrochloric acid added. Measurements were made at room temperature, 25–30°. The *pK_a* value was reckoned from the equation, $pK_a = pH - \log \{([A^-]_{st} + [H^+])/([HA]_{st} - [H^+])\}$, where pH is the value read from the (previously calibrated) pH meter and $[H^+]$ is derived therefrom. Trial determinations on benzoic and acetic acids gave *pK_a* values in agreement with literature values.

Measurements were made in water and in 10% ethanol:90% water at the ionic strength provided by the method used (*ca.* 10^{-3}). Results are recorded in Table II. Measurements at higher ionic strengths (up to 0.1) indicated that the apparent *pK_a* was decreased by not more than 0.2 *pK* units.

Table II. *pK_a* Values of Substituted 2-(Hydroxymethyl)benzoic Acids^a

Substituent	<i>pK_a</i> (in H ₂ O)	<i>pK_a</i> (in 10% C ₂ H ₅ OH)
H	3.84	3.96
3-F	3.52	3.62
6-F	2.86	2.96
3-CH ₃	3.79	3.96
6-CH ₃	3.31	3.42
3,6-(CH ₃) ₂	3.36	3.62

^a The average deviation of *pK_a* determinations was mostly 0.02.

(21) The *pK_a* determinations were made by Mr. Claude Bernasconi, to whom we express our gratitude.

Kinetic Procedure. The solvent for all rate determinations was 9% ethanol:91% water (w./w.). Reactions were run in the cell of a Beckman DK-1 spectrophotometer, and absorbance at a selected wave length was recorded. Temperature control was precise to $\pm 0.2^\circ$. Concentrations of the substrate and of the hydrochloric acid catalyst were as indicated in Table III. Good pseudo-first-order kinetics were observed except in certain runs with 3,6-dimethyl-2-(hydroxymethyl)benzoic acid, which are discussed below.

Absorbance due either to hydroxy acid reactant or lactone product was measured. Decrease in hydroxy acid absorbance was measured for 3-fluoro- and 6-fluoro-2-hydroxymethylbenzoic acids at 252 and 251 *mμ*, respectively. Increase in lactone absorbance was measured for 3,6-dimethyl-, 6-methyl-, and 3-methyl-2-hydroxymethylbenzoic acids at 254, 285, and 286 (or 292) *mμ*, respectively. Runs with unsubstituted I were performed both ways, decreasing hydroxy acid absorbance being measured at 254 *mμ* and increasing lactone absorbance at 276 *mμ*.

In general pseudo-first-order rate coefficients (*k_v*) were reckoned by the Guggenheim method.²² In several cases they were also calculated from plots of $\log (A_\infty - A_t)$ vs. time. Agreement between the two methods was good.

Standard solutions of the sodium salts of the hydroxy acids were prepared by careful saponification of the corresponding phthalides. Runs were then initiated by addition of a measured excess of standard hydrochloric acid solution.⁴ The following procedure is illustrative. 4-Methylphthalide (0.2963 g.) was mixed with 10.47 ml. of 0.482 *M* sodium hydroxide solution and 20 ml. of distilled water in a 100-ml. flask fitted with reflux condenser. The mixture was heated for 1 hr. at reflux, and allowed to cool. It was transferred quantitatively to a 250-ml. volumetric flask which was then diluted to the mark with distilled water and inverted several times to ensure thorough mixing. The stock solution so obtained was 8.0×10^{-3} *M* in sodium 2-hydroxymethyl-3-methylbenzoate, and the total base concentration (sodium salt and sodium hydroxide) was 2.02×10^{-2} *M*.

Five milliliters of this solution was placed in a 100-ml. volumetric flask, to which 12.0 ml. of 95% ethanol and about 70 ml. of distilled water were added. After the mixture had come to thermal equilibrium in the thermostat, 10.0 ml. of a thermostated standard solution of hydrochloric acid was added and then thermostated water was added to the mark. The flask was shaken to effect mixing and restored to the thermostat. The spectrophotometer cell was filled with this reaction solution and absorbance was recorded continuously.

The free hydrochloric acid concentration in each reaction solution was reckoned by subtracting the amount required to neutralize the sodium hydroxide and sodium benzoate derivative supplied. A second-order rate coefficient for each run was obtained by dividing the pseudo-first-order coefficient by the hydrochloric acid concentration.

Rates of lactonization of unsubstituted I were also

(22) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 49.

Table III. Rate Coefficients for the HCl-Catalyzed Lactonization of Substituted 2-(Hydroxymethyl)benzoic Acids in 9% Ethanol: 91% Water

Substituent	Temp., °C.	[HCl], ^a M	10 ² k _ψ , min. ⁻¹	k ₂ , ^b M ⁻¹ min. ⁻¹	Substituent	Temp., °C.	[HCl], ^a M	10 ² k _ψ , min. ⁻¹	k ₂ , ^b M ⁻¹ min. ⁻¹
H ^c	30.0	1.73 × 10 ⁻¹	7.39	0.427	3-F ^c	45.0	9.8 × 10 ⁻²	5.54	0.566
		2.48 × 10 ⁻¹	10.7	0.432			1.48 × 10 ⁻¹	8.49	0.574
	45.0	7.80 × 10 ⁻²	10.5	1.35		1.98 × 10 ⁻¹	11.3	0.573	
		8.80 × 10 ⁻²	11.9	1.35		2.48 × 10 ⁻¹	14.7	0.593	
	60.0	9.80 × 10 ⁻²	13.1	1.34		2.0 × 10 ⁻²	3.58	1.96	
		6.4 × 10 ⁻³	2.80	4.38		3.0 × 10 ⁻²	5.47	1.97	
3-CH ₃ ^d	20.0	1.34 × 10 ⁻²	5.39	4.02	4.0 × 10 ⁻²	7.50	1.93		
		1.84 × 10 ⁻²	7.45	4.05	5.0 × 10 ⁻²	9.48	1.99		
		4.0 × 10 ⁻³	4.89	12.4	2.48 × 10 ⁻¹	9.03	0.364		
		7.0 × 10 ⁻³	8.51	12.2	3.48 × 10 ⁻¹	13.1	0.376		
		8.0 × 10 ⁻³	9.91	12.4	9.84 × 10 ⁻²	11.5	1.17		
		9.0 × 10 ⁻³	11.2	12.4	1.38 × 10 ⁻¹	15.0	1.09		
	35.0	1.10 × 10 ⁻²	13.2	12.0	60.0	8.4 × 10 ⁻³	3.04	3.62	
		1.30 × 10 ⁻²	15.3	11.8	1.34 × 10 ⁻²	5.00	3.73		
		1.60 × 10 ⁻²	21.5	13.3	1.84 × 10 ⁻²	6.82	3.71		
		4.0 × 10 ⁻³	15.9	39.8	2.34 × 10 ⁻²	8.82	3.77		
		6.0 × 10 ⁻³	24.2	40.3	3,6-(CH ₃) ₂ ^e	20.0	1.09 × 10 ⁻³	8.67	(79.5) ^f
		8.0 × 10 ⁻³	30.5	38.1	1.39 × 10 ⁻³	11.7	(84.1) ^f		
50.0	1.0 × 10 ⁻³	9.80	97.6	1.69 × 10 ⁻³	15.0	(88.7) ^f			
	1.4 × 10 ⁻³	13.7	97.9	1.89 × 10 ⁻³	16.6	(87.8) ^f			
	2.0 × 10 ⁻³	19.2	96.0	2.09 × 10 ⁻³	19.5	(93.3) ^f			
	2.5 × 10 ⁻³	23.0	92.0	2.39 × 10 ⁻³	23.0	(96.2) ^f			
	3.0 × 10 ⁻³	26.0	86.7	2.89 × 10 ⁻³	28.2	(97.6) ^f			
	20.0	1.10 × 10 ⁻²	3.54	3.22	3.39 × 10 ⁻³	32.0	(97.3) ^f		
	35.0	1.30 × 10 ⁻²	4.27	3.28	4.39 × 10 ⁻³	44.2	(101) ^f		
		1.60 × 10 ⁻²	5.30	3.31	5.39 × 10 ⁻³	57.0	(106) ^f		
		2.20 × 10 ⁻²	7.45	3.25	6.39 × 10 ⁻³	67.8	(106) ^f		
		9.0 × 10 ⁻³	9.06	10.1	7.39 × 10 ⁻³	80.6	(109) ^f		
		1.10 × 10 ⁻²	11.3	10.3	8.39 × 10 ⁻³	89.1	(106) ^f		
		1.30 × 10 ⁻²	13.3	10.3	35.0	7.85 × 10 ⁻⁴	15.7	(200) ^f	
50.0	2.0 × 10 ⁻³	5.79	29.0	1.09 × 10 ⁻³	22.8	(209) ^f			
	2.5 × 10 ⁻³	7.25	29.0	1.39 × 10 ⁻³	30.3	(218) ^f			
	3.0 × 10 ⁻³	8.87	29.6	1.89 × 10 ⁻³	43.0	(228) ^f			
	3.5 × 10 ⁻³	10.1	29.0	2.89 × 10 ⁻³	68.5	(237) ^f			
	4.0 × 10 ⁻³	11.8	29.5	50.0	4.70 × 10 ⁻⁴	11.0	(230) ^{f,o}		
	5.0 × 10 ⁻³	14.8	29.6	5.20 × 10 ⁻⁴	11.8	(230) ^{f,o}			
30.0	3.98 × 10 ⁻¹	6.85	0.172	5.70 × 10 ⁻⁴	15.1	(260) ^{f,o}			
	5.98 × 10 ⁻¹	10.9	0.182	6.20 × 10 ⁻⁴	16.0	(260) ^{f,o}			
				7.20 × 10 ⁻⁴	16.9	(240) ^{f,o}			
				8.20 × 10 ⁻⁴	22.1	(269) ^f			
				9.70 × 10 ⁻⁴	29.4	(303) ^f			

^a Concentration of free hydrochloric acid. ^b k₂ is k_ψ/[HCl]. ^c Substrate concentration 8.0 × 10⁻⁴ M. ^d Substrate concentration 4.0 × 10⁻⁴ M. ^e Substrate concentration 6.4 × 10⁻⁴ M. ^f Apparent k₂; see text. ^o The first-order plot was obviously curved; k_ψ based on first half-life.

determined with reaction solutions prepared directly from the isolated hydroxy acid. Within experimental error, these were the same as from runs in which solutions of sodium 2-(hydroxymethyl)benzoate were acidified.

In the case of 3,6-dimethyl-2-(hydroxymethyl)benzoic acid, which lactonizes very rapidly, comparatively low hydrochloric acid concentrations were employed in order to obtain conveniently measurable rates. At the lower of these concentrations, an appreciable fraction of the hydroxy acid was dissociated, and in some cases the oxonium ion concentration from this source considerably augmented that from the hydrochloric acid. As the hydroxy acid reacted, the oxonium ion concentration fell and with it the instantaneous first-order rate coefficient. The first-order plot showed curvature. In other cases, the oxonium ion concentration did not change much during a run and the first-order plot was straight, but the fraction of hydroxy acid dissociated and therefore the quotient, k_ψ/[H⁺], was strongly dependent on hydrochloric acid concentration (see Table III).

The true second-order rate coefficient for 3,6-di-

methyl-2-(hydroxymethyl)benzoic acid lactonization could be estimated in various ways. The most direct method (A) involved making a small correction, based on the measured pK_a value, to the apparent second-order rate coefficients (as listed in Table III) at the highest hydrochloric acid concentrations studied. This could be applied with confidence to the 20 and 35°, but not to the 50°, data. A second method (B) utilized the easily derived expression

$$\frac{[H^+]}{k_\psi} = \frac{K_a}{k_2} \frac{1}{[H^+]} + \frac{1}{k_2}$$

which takes accurate account of the decrease in concentration of undissociated acid but not of the increase in oxonium ion concentration. It is therefore most valid at higher hydrochloric acid concentrations. The intercept of a plot of [H⁺]/k_ψ against 1/[H⁺] is taken to be the reciprocal of the true second-order rate coefficient, k₂. A third method (C) used the expression

$$k_2 = \frac{k_\psi[HA]_{st}}{([HA]_{st} - x)([HCl] + x)}$$

in which $[HA]_{st}$ is the stoichiometric hydroxy acid concentration and x the concentration of the anion derived from it, estimated by means of the pK_a value. This computation used the average k_{ψ} value for the first half-life and values for $[HA]_{st}$ and x reckoned after 25% lactonization. At 20°, methods A, B, and C gave k_2 values of 108, 113, and 108 l. mole⁻¹ min.⁻¹, respectively; 109 l. mole⁻¹ min.⁻¹ was taken as the best value. At 35°, the k_2 values reckoned were 251, 254, and 254, respectively, and the best value was taken as 253 l. mole⁻¹ min.⁻¹. The three methods of correction gave discordant k_2 values at 50°, all widely variant from that extrapolated from lower temperatures by the Arrhenius equation. The 50° data were therefore ignored in reckoning activation parameters and extrapolated rate coefficients.

The measured pseudo-first-order rate coefficients (k_{ψ}) and the second-order coefficients, computed as $k_{\psi}/[H^+]$, for all substrates are set forth in Table III; in the case of 3,6-dimethyl-2-(hydroxymethyl)benzoic acid, the latter are apparent.

Enthalpies and entropies of activation were reckoned for all reactions by means of standard expressions. They are given in Table IV together with rate coefficients at 45°.

Table IV. Summary of Kinetic Data^a

Substituent	k_2 at 45°, $M^{-1} \text{ sec.}^{-1}$	Relative rate, 45°	ΔH^* , kcal./ mole	ΔS^* , e.u.
H	2.25×10^{-2}	1.00	14.6	-20.6
3-F	9.60×10^{-3}	0.43	15.5	-19.3
6-F	1.88×10^{-2}	0.84	14.8	-20.2
3-CH ₃	1.19 ^b	53	12.2	-20.2
6-CH ₃	3.49×10^{-1b}	15.5	13.2	-19.4
3,6-(CH ₃) ₂	7.08 ^b	315	9.5	-25

^a Based on data in Tables II and III. ^b Interpolated or extrapolated value.

Discussion

pK_a Values. Tirouflet⁴ measured pK_a values for several derivatives of 2-(hydroxymethyl)benzoic acid (I). A feature of interest was that the acid-strengthening effect of a halogen substituent depended on its site, the order being 6 >> 3 > 5 > 4.

Our determinations, reported in Table II show some of the same features. Our value for unsubstituted I in water (3.84) is the same as reported by Tirouflet. We found the 3-methyl substituent to have, within experimental error, no effect on pK_a . 6-Methyl, however, has a pronounced acid-strengthening effect.

Substituents *ortho* to the carboxyl group characteristically raise the acid dissociation constant of benzoic acid. The effect is considered to be steric.²³ An *ortho* substituent tends to turn the carboxyl or carboxylate group out of coplanarity with the benzene ring, and thereby to interfere with mesomeric interaction which stabilizes the undissociated acid more than the anion.

Introduction of a 3-methyl group into 6-methyl-2-(hydroxymethyl)benzoic acid again has little effect on

(23) Cf. G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 428; H. A. Staab, "Einführung in die Theoretische Organische Chemie," Verlag Chemie, Weinheim/Bergstr., Germany, 1960, p. 623.

pK_a . Tirouflet proposed that 3-substituents may augment the acid strength of I by a steric (buttressing) effect. If one were to argue that a 3-methyl group should diminish the acid strength of I for its polar influence, he could construe our observation of almost no over-all effect as evidence for a favorable steric effect which almost exactly counteracts the unfavorable polar influence.

As would be expected of an electron-attracting substituent, fluorine in either the 3- or the 6-position is acid strengthening. However, the effect is much greater in the 6-position. The margin by which the 6-fluoro is stronger than the 3-fluoro acid is about the same as that by which *o*-fluoro- is stronger than *m*-fluorobenzoic acid. Presumably the over-all effect of *o*-fluorine represents the sum of a small steric and a large polar contribution.

Rates of Lactonization. Our data are summarized in Table IV. Our rate coefficient for the acid-catalyzed lactonization of unsubstituted I in 9% ethanol:91% water at 60° (4.15 l. mole⁻¹ min.⁻¹) is in good agreement with Tirouflet's coefficient, 4.30 l. mole⁻¹ min.⁻¹, for the same reaction and temperature in water.

Whereas chlorine, bromine, or iodine in the 3- or 6-position accelerates lactonization (Table I), 3- or 6-fluorine retards it (Table IV). The decelerating influence of 3- or 6-fluorine is reasonably attributed to a polar effect, similar to that of halogens in the 4- or 5-position.²⁴ It is not complicated to any large extent by steric effects because of the small size of fluorine. The accelerating influence of the other halogens in the 3- or 6-position is then understood as steric acceleration partially offset by polar deceleration. This interpretation is further strengthened by the fact that the order of acceleration by 3-halogens is the order of increasing size (Table I).

The accelerating effect of 3- or 6-methyl (Table IV) is greater than that of 3- or 6-halogens (Table I). Since the size of methyl is similar to that of chlorine or bromine,²⁶ steric acceleration of similar magnitude is anticipated. The over-all effect of 3- or 6-methyl is probably greater because its polar effect enhances reaction rate and adds to the acceleration of steric origin.²⁷

Since 3- and 6-methyl separately accelerate lactonization, it is consistent that they cooperate to cause an especially high rate of cyclization for the 3,6-dimethyl acid.

Identification of the accelerating effects of methyl and halogen substituents in the 3- and 6-positions as primarily steric in origin is strengthened by the difficulty of accounting for them in other terms. Short-range nonbonding attractive forces, especially London

(24) The polar effect of *o*- or *m*-fluorine, as judged by Hammett σ or Taft σ^* parameters,²⁵ is similar to that of the other halogens.

(25) J. F. Bunnett in "Investigation of Rates and Mechanisms of Reactions," S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Part I, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1961, pp. 215, 227.

(26) R. L. Shriner and R. Adams in "Organic Chemistry," Vol. I, H. Gilman, Ed., 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 362; R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 598.

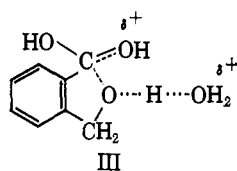
(27) However, since both the electron-releasing ethoxy and acetamido groups and the electron-attracting halogen atoms, as 4-substituents, decelerate lactonization,⁴ one cannot be certain that the polar influence of 3- or 6-methyl would increase lactonization rate.

forces, between *ortho* substituents and nucleophiles of high polarizability appear to accelerate certain nucleophilic substitutions.²⁸ But in this lactonization reaction, the particles acquired in forming the transition state are a proton and (probably) some water molecules. The water molecules have low polarizability, and the proton because of its charge should decrease the polarizability of the collection of atoms around the reacting center in the transition state. London force effects on rate should therefore be small, too small to account for the accelerations displayed in Tables I and IV.

It is also unreasonable that the *ortho* methyl and halogen substituents stabilize the transition state by acting as acceptor (basic) termini for hydrogen bridges from rather acidic O-H bonds.

The activation parameters (Table IV) show that the decelerating effects of 3- and 6-fluorine and the accelerating effects of 3- and 6-methyl have their origin in the enthalpy of activation. Except for 3,6-dimethyl-2-(hydroxymethyl)benzoic acid, the entropy of activation is substantially constant. ΔS^* for lactonization of the 3,6-dimethyl acid is lower by about 5 e.u., equivalent to a 12-fold deceleration; were it not for the entropy effect, the degree of acceleration by 3,6-dimethyl substitution would be even greater than observed.²⁹

Interpretation of Steric Effects. The probable mechanism of lactonization is the usual one for acid-catalyzed esterification, in which a chain of events is started by attack of the alcoholic hydroxy group on the protonated carboxy group. In unpublished work, Dr. Daniel P. Weeks has shown that lactonization of 2-(hydroxymethyl)benzoic acid is general acid catalyzed in H_3PO_4 - $H_2PO_4^-$ buffers. In the oxonium ion catalyzed reaction, the conjugate base of the catalyzing acid is water, and its function is possibly to detach the proton from the OH group as it attacks the $C(OH)_2^+$ group. Structure III is a possible formulation of the transition state.



Mechanisms incompatible with the evidence require comment. A-1 mechanisms involving acylium ion or benzyl carbonium ion type intermediates are unlikely in view of the large negative entropy of activation.³⁰ An intramolecular displacement mechanism within a tautomer of I, in which the carboxylate (COO^-) group attacked and displaced water from the protonated alcoholic function, would not account for the observed acid catalysis.

Transition state III and other possibilities closely related to it have certain geometrical requirements.

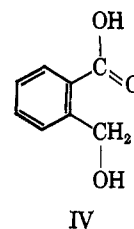
(28) J. D. Reinheimer and J. F. Bunnett, *J. Am. Chem. Soc.*, **81**, 315 (1959); J. F. Bunnett and J. D. Reinheimer, *ibid.*, **84**, 3284 (1962); D. L. Dalrymple, J. D. Reinheimer, D. Barnes, and R. Baker, *J. Org. Chem.*, **29**, 2647 (1964).

(29) It should be noted, however, that the experimental basis of the activation parameters for the 3,6-dimethyl acid is less substantial than in the other cases.

(30) L. S. Schaleger and F. A. Long in "Advances in Physical Organic Chemistry," Vol. 1, V. Gold, Ed., Academic Press Inc., New York, N. Y., p. 23.

The protonated carboxyl group must be rotated so that the plane defined by the carbon and two oxygens is nearly perpendicular to that of the benzene ring. This is necessary in order that an orbital be properly disposed for formation of a bond to the alcoholic oxygen atom. And obviously the hydroxymethyl group must be arranged so that its oxygen approaches the carboxyl carbon.

However, the preferred conformation for 2-(hydroxymethyl)benzoic acid in water solution probably approximates structure IV, in which the carboxyl group is coplanar with the benzene ring and the hy-



droxymethyl group is rotated so that the hydroxy group is remote from the carboxyl. This conformation would maximize delocalization of electrons between the carboxyl group and the ring, and it would tend to minimize repulsive interactions between the substituents.

Formation of III from IV would require that the carboxyl group be rotated out of coplanarity with the ring and that the oxygen of the hydroxymethyl group be forced against the carboxyl group. Both types of rotation require energy, and the energy required contributes to the activation energy.

If the 3-position is occupied by a substituent as large as chlorine or methyl, the conformation in which the hydroxymethyl oxygen is farthest removed from carboxyl carbon is no longer favored because of repulsive interaction with the 3-substituent. The hydroxymethyl group is pushed around to conformations more nearly resembling the transition state geometry. Less energy is then required to form the transition state.

If the 6-position is occupied by a substituent of substantial size, strain is imposed on the conformation in which carboxyl is coplanar with the ring, or the carboxyl is rotated out of coplanarity with loss of resonance stabilization. In either case less energy is required to orient the carboxyl as required for the transition state.

Thus substitution in either the 3- or the 6-position raises the energy of the initial state. However, neither type of substitution should much affect the energy of the transition state, apart from direct crowding interactions which are unavoidable in either initial or transition state. Consequently, the effect of 3- or 6-substitution by chlorine or larger groups is to decrease the activation energy and to accelerate the reaction.³¹

The observed steric acceleration is thus judged to have its origin in steric regulation of initial state conforma-

(31) This discussion is offered in terms of unprotonated hydroxy acids because the unprotonated hydroxy acid is the predominant form of the substrate in the reaction medium. In transition state theory, the activation process is considered as though an equilibrium between initial and transition states. The protonated hydroxy acid is a key intermediate, but it does not need to be taken into account in a thermodynamic discussion.

tion. It is noteworthy that this factor is expressed entirely in the enthalpy of activation; see Table IV.³²

(32) It is not clear why the entropy of activation for 3,6-dimethyl-2-(hydroxymethyl)benzoic acid lactonization is about 5 e.u. lower than for the other hydroxy acids studied.²⁹ Restriction of initial state freedom of rotation should tend to increase, not decrease, ΔS^\ddagger . A possibility is that solvation of the initial state but not of the transition state is diminished by 3,6-disubstitution, either by direct steric interference with solvation or by obliging the hydroxy and carboxy groups to hydrogen bond with each other with consequent reduction of opportunity to form hydrogen bonds to water molecules.

Bunnett and Okamoto³³ observed huge steric acceleration of the Smiles rearrangement of 2-hydroxy-2'-nitrodiphenyl sulfones by 6-substituents. It also was judged to stem from steric regulation of initial state conformation, and it also appeared to be expressed entirely in a decreased enthalpy of activation.

(33) J. F. Bunnett and T. Okamoto, *J. Am. Chem. Soc.*, **78**, 5363 (1956).

The Relative Signs of the Nuclear Magnetic Resonance Proton-Proton Coupling Constants in Styrene Sulfide and Styrenimine¹

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Contribution from the Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California, and Esso Research and Engineering Company, Linden, New Jersey. Received December 28, 1964

From n.m.r. double resonance experiments in which a weak perturbing radiofrequency field was applied to certain spectral lines, it was found that the 1.37-c.p.s. geminal proton-proton coupling in styrene sulfide (III) is a different sign (presumably negative) than the two vicinal couplings of 5.55 and 6.60 c.p.s. between protons in the thiirane ring. Similar experiments on styrenimine (II) showed that the 0.87-c.p.s. geminal coupling in this molecule is the same sign as the 3.29- and 6.12-c.p.s. vicinal couplings in the aziridine ring. These results are discussed in relation to the magnitudes and relative signs of other geminal and vicinal proton-proton coupling constants and their correlation with substituent electronegativities. It is concluded that the linear correlations of geminal and vicinal couplings with substituent electronegativities may be better than previously expected, provided the substituents involved do not possess electronic effects which contribute to the coupling and which are not measured by thermochemical data.

Introduction

Recently it has been conclusively demonstrated by high-resolution analyses,⁴ double resonance experiments,⁵ and double quantum transition spectra⁶ that

(1) This paper represents the results of one phase of research carried out at the Jet Propulsion Laboratory, California Institute of Technology, under Contract No. NAS 7-100, sponsored by the National Aeronautics and Space Administration.

(2) Jet Propulsion Laboratory, California Institute of Technology, Pasadena, Calif.

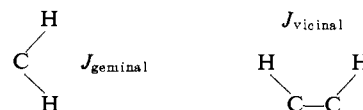
(3) Esso Research and Engineering Co., Linden, N. J.

(4) (a) R. R. Fraser, R. V. Lemieux, and J. D. Stevens, *J. Am. Chem. Soc.*, **83**, 3901 (1961); (b) F. Kaplan and J. D. Roberts, *ibid.*, **83**, 4474 (1961); C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **35**, 1522 (1961); H. Finegold, *Proc. Chem. Soc.*, 213 (1962).

(5) (a) R. Freeman, K. A. McLaughlan, J. I. Musher, and K. G. R. Pachler, *Mol. Phys.*, **5**, 321 (1962); (b) R. Freeman and W. A. Anderson, *J. Chem. Phys.*, **37**, 2053 (1963); (c) R. Freeman and N. S. Bhacca, *ibid.*, **38**, 1088 (1963).

(6) K. A. McLaughlan and D. H. Whiffen, *Proc. Chem. Soc.*, 144 (1962).

the relative sign of the geminal proton-proton n.m.r. coupling constant is different from the relative sign of the vicinal proton-proton coupling constant in saturated



organic molecules where the carbon hybridization is close to sp^3 . Recently we found by double resonance studies that the relative signs of the coupling constants between the three protons of the oxirane ring of styrene oxide (I) are all the same.⁷ This rather striking contrast in the relative signs of geminal coupling constants between those in nearly sp^3 -hybridized systems and that in I which contains a three-membered ring suggested to us that a study of the proton n.m.r. spectra of the nitrogen and sulfur analogs of I should provide some additional information relative to the factors dictating the signs and magnitudes of geminal proton-proton coupling constants. This study is herein described.

Experimental

The styrenimine (II) was prepared as described elsewhere.⁸ The styrene sulfide (III) was prepared by the reaction of styrene oxide and potassium thiocyanate in an aqueous ethanol solution similar to the procedures described by Snyder, Stewart, and Ziegler.⁹

The spectra were obtained with Varian HR-56.4-60 and A-60 spectrometers. The HR spectrometer had a field-frequency lock system similar to that described by Anderson and Freeman.^{5b,10} Spectra were recorded by sweeping the frequency of a second audio oscillator with a synchronous motor. In the double resonance experiments a third modulation of an index sufficiently

(7) D. D. Elleman and S. L. Manatt, *J. Mol. Spectry.*, **9**, 477 (1962).

(8) S. J. Brois, *J. Org. Chem.*, **27**, 3532 (1962).

(9) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Am. Chem. Soc.*, **69**, 2674 (1947).

(10) W. A. Anderson and R. Freeman, *J. Chem. Phys.*, **38**, 85 (1962).