The Formation of 1,8-Naphthalide, 3,3-Dimethylphthalide, and 3,3-Diphenylphthalide in Aqueous Solution. General Acid Catalysis of Esterification[1]

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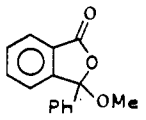
Abstract: In aqueous acid 8-hydroxymethyl-1-naphthoic acid cyclizes to the lactone, 1,8-naphthalide. The reaction is subject to catalysis by the acidic components of buffers of various structural types. In acetic acid buffer the catalytic rate constant, k_{HOAc}, is $3.35 \times 10^{-2}\ M^{-1}$ sec^{-1}, the solvent kinetic isotope effect, k_{HOAc}/k_{DOAc}, is 2.29, and the entropy of activation for the acetic acid catalysis is −38 eu. The formation of 3,3-dimethylphthalide and, on the basis of more limited data, the formation of 3,3-diphenylphthalide from their corresponding hydroxy acids behave similarly. These data are consistent with a rate-determining step involving proton transfer.

Our studies of the acid-catalyzed hydrolysis of methyl pseudo-2-benzoylbenzoate (**1**),[3] methyl pseudo-8-aroyl-1-naphthoates (**2**),[4] and related compounds[5] have uncovered some startling differences in the behavior of **1** and **2**. Thus, all the various empirical criteria which are used in mechanism studies in aqueous acid support an $A_{Al}1$ mechanism for the hydrolysis of **2**. On the other hand experiments of the same type lead to inconclusive results for the hydrolysis of **1** and related compounds. The vagaries exhibited by **1**, when compared with the straightforward behavior of **2**, led us to believe that a study of suitably substituted phthalides, **4**, and 1,8-naphthalides, **6**, would be useful in allowing us to observe the effect of a subtle change in structure on the overall hydrolytic behavior of these compounds.



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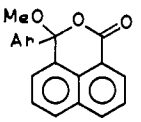

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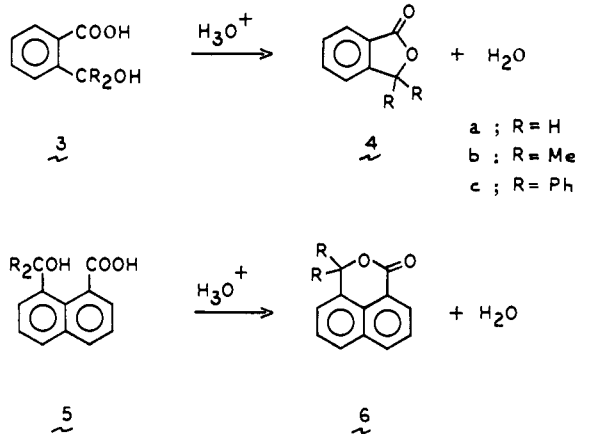
The phthalides and 1,8-naphthalides differ from the pseudo esters in one important respect. They are stable in aqueous acid. Therefore, we approached the mechanism of the lactone hydrolysis by studying the reverse reaction, *i.e.*, the lactonization of the corresponding *o*-hydroxymethylbenzoic acids, **3**, and 8-hydroxymethyl-1-naphthoic acids, **5**.



3 **4** **5** **6**

Experimental Section

Materials. The tendencies of all the hydroxy acids used in this study to lactonize was so strong that it was necessary to store them as the potassium salts. Therefore, the appropriate phthalide or naphthalide was prepared, purified, and then saponified by refluxing for 4 hr in methanol with an equivalent amount of potassium hydroxide. The solvent was evaporated and the salt stored under an inert atmosphere until it was used.

3,3-Dimethylphthalide (4b) was prepared by treating methylmagnesium iodide with diethyl phthalate:[6] mp 68–71° (lit.[6] mp 69–70°); ir (Nujol) 1750 cm^{-1}; nmr ($CDCl_3$) δ 7.35–8.0 (m, 4) and 1.68 ppm (s, 6).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.24; H, 6.10.

3,3-Diphenylphthalide (4c) was prepared by treating *o*-benzoylbenzoic acid with benzene and sulfuric acid: mp 114–117° (lit.[7] mp 112–113°); ir (Nujol) 1765 cm^{-1}.

Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.89; H, 4.93. Found: C, 83.63; H, 5.08.

1,8-Naphthalide (6a) was prepared from acenaphthene quinone by cleavage to 1,8-naphthaldehydic acid with KOH followed by a crossed Cannizzaro reaction with formaldehyde.[8] Acidification caused the 8-hydroxymethyl-1-naphthoic acid to lactonize to 1,8-naphthalide: mp 155–157° (lit.[8] mp 159–160°); ir ($CHCl_3$) 1725 cm^{-1}; nmr ($CDCl_3$) δ 7.14–8.40 (m, 6) and 5.72 ppm (s, 2).

Anal. Calcd for $C_{12}H_8O_2$: C, 78.25; H, 4.38. Found: C, 78.14; H, 4.51.

All buffer solutions were prepared from reagent grade materials and doubly distilled water. Deuterated materials were obtained from Stohler Isotope Chemicals.

Rate Determinations. Solutions containing an appropriate amount of the potassium salt of the hydroxy acid in methanol were prepared for each day's rate determinations. A run was started by adding 0.01 ml of the solution to 3.0 ml of the reaction solution in a uv cell which had been equilibrated in the constant-temperature cell compartment of a Beckman DK-2 spectrophotometer equipped

(1) Presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Abstract No. ORGN 64.

(2) National Science Foundation Undergraduate Research Participant, 1967–1968. Taken from the Senior Honors Thesis submitted by X. C. to Seton Hall University, 1968.

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(8) R. C. Fuson and G. Munn, *J. Amer. Chem. Soc.*, 71, 1870 (1949).

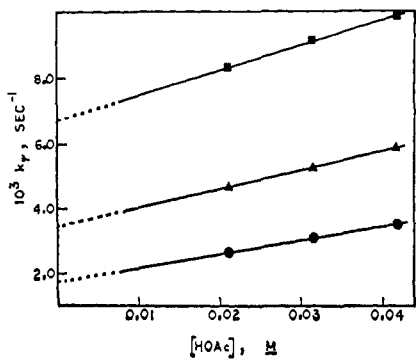


Figure 1. Formation of 1,8-naphthalide in acetic acid–sodium acetate buffers; plot of k_ψ against the concentration of acetic acid at 25.3° (●), 34.2° (▲), and 44.2° (■). The slopes, k_{HOAc}, are 3.9×10^{-2}, 5.4×10^{-2}, and 7.3×10^{-2} M^{-1} sec^{-1}, respectively.

with a time-drive attachment. Substrate concentrations were in the order of 5×10^{-5} M. Temperature control was ±0.05°.

The lactonizations of **3b**, **3c**, and **5a** were followed at 230, 285, and 245 mμ, respectively. All compounds obeyed Beer's law. A full spectrum of an hydrolysis run after ten half-lives was superimposable on a spectrum of the corresponding lactone at the same concentration. Pseudo-first-order rate constants were obtained from the slopes of plots of log $(A_\infty - A_t)$ against time which were linear over at least two half-lives. Correlation coefficients were 0.999 in all cases. Rate constants were independent of the initial concentration of the substrate.

Results

Rate constants for the formation of 1,8-naphthalide from 8-hydroxymethyl-1-naphthoic acid in acetic acid–sodium acetate buffers are shown in Tables I and II.

Table I. 1,8-Naphthalide Formation in Acetic Acid Buffers[a]

[HOAc], M	[NaOAc], M	[$NaClO_4$], M	$10^3 k_\psi$, sec^{-1}
[HOAc]/[NaOAc] = 1.0, pH 4.62, temp 25.5°			
0.10	0.10	0.00	4.21
0.08	0.08	0.02	3.46
0.06	0.06	0.04	2.79
0.04	0.04	0.06	2.23
[HOAc]/[NaOAc] = 2.0, pH 4.45, temp 25.7°			
0.20	0.10	0.00	8.71
0.16	0.08	0.02	7.50
0.12	0.06	0.04	6.24
0.08	0.04	0.06	4.74
0.04	0.02	0.08	3.50
0.02	0.01	0.09	2.57

[a] The slopes, k_{HOAc}, of plots of k_ψ against [HOAc] are 3.43×10^{-2} M^{-1} sec^{-1} at pH 4.45 and 3.30×10^{-2} M^{-1} sec^{-1} at pH 4.62.

Table II. 1,8-Naphthalide Formation in Acetic Acid Buffers

[HOAc], M	[NaOAc], M	[$NaClO_4$], M	Temp, °C	$10^3 k_\psi$, sec^{-1}
In Protioacetic Acid				
0.042	0.021	0.058	25.3	3.48
0.032	0.016	0.068	25.3	3.09
0.021	0.010	0.079	25.3	2.65
0.042	0.021	0.058	34.2	5.77
0.032	0.016	0.068	34.2	5.27
0.021	0.010	0.079	34.2	4.65
0.042	0.021	0.058	44.2	9.89
0.032	0.016	0.068	44.2	9.21
0.021	0.010	0.079	44.2	8.23
In Deuterioacetic Acid				
0.042	0.021	0.058	25.3	1.25
0.032	0.016	0.068	25.3	1.12
0.021	0.010	0.079	25.3	0.923

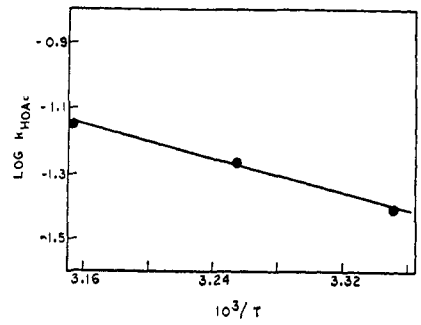


Figure 2. Formation of 1,8-naphthalide; plot of log k_{HOAc} against $1/T$. The Arrhenius energy, E_a, is 6.1 kcal mol^{-1} and the entropy of activation, ΔS^*, is -37.7 ± 3.0 eu.

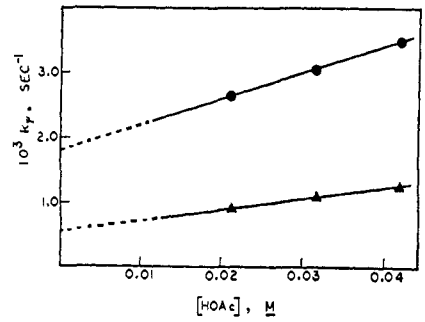


Figure 3. Formation of 1,8-naphthalide in acetic acid–sodium acetate buffers in H_2O (●), and acetic acid-d_1–sodium acetate buffers in D_2O (▲); plot of k_ψ against concentration of acetic acid.

Plotting the pseudo-first-order rate constants against the concentrations of acetic acid using the data in Table I gives straight lines for the two series of buffers having different ratios of concentration of acetic acid to concentration of sodium acetate. The slopes, k_{HOAc}, of these lines are essentially equal. These data show that we are dealing with a general acid catalyzed reaction, acetic acid being the catalytically active component of the buffer.

Figure 1 is a similar plot of the data in Table II. These data allow the calculation of k_{HOAc} at various temperatures. The linear relationship between the logarithm of k_{HOAc} and the reciprocal of the absolute temperature is shown in Figure 2. The entropy of activation is −37.7 eu. The appropriate data from Table II are plotted in Figure 3 so as to illustrate the solvent isotope effect, $k_{HOAc}/k_{DOAc} = 2.29$.

The observation of buffer catalysis in one buffer system is not sufficient to establish general catalysis since the possibility always remains that there is a specific catalysis by the buffer components. Indeed, the lactonization of *o*-hydroxymethylbenzoic acid (**3a**) is catalyzed by phosphoric acid buffers[9] but not by several carboxylic acid buffers.[10] The data presented in Tables III and IV show that buffer catalysis is observable by phosphate and ammonium acetate buffers as well as by acetic acid buffers. In each case there is a linear relationship between the observed rate constant and the buffer concentration.

(9) D. P. Weeks and J. F. Bunnett, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1964, ORGN 96.

(10) J. F. Bunnett, personal communication.

Table III. 1,8-Naphthalide Formation in Phosphate Buffers[a]

$[NaH_2PO_4]$, *M*	$[Na_2HPO_4]$, *M*	10^3k_ψ, sec^{-1}
0.15	0.075	1.32
0.10	0.05	0.999
0.08	0.04	0.921
0.05	0.025	0.729

[a] The temperature was 25.3°.

Table IV. 1,8-Naphthalide Formation in Ammonium Acetate Buffers[a]

$[NH_4OAc]$, *M*	[KCl], *M*	10^4k_ψ, sec^{-1}
0.10	0.00	5.00
0.05	0.05	4.29
0.02	0.08	4.13

[a] The temperature was 26.1°.

The data from the lactonization forming 3,3-dimethylphthalide from 2-(α-methyl-α-hydroxyethyl)benzoic acid are very similar to those from the formation of 1,8-naphthalide. Rate constants are listed in Table V.

Table V. 3,3-Dimethylphthalide Formation in Acetic Acid Buffers

[HOAc], *M*	[NaOAc], *M*	$[NaClO_4]$, *M*	Temp, °C	10^4k_ψ, sec^{-1}
		In Protioacetic Acid		
0.20	0.10		23.7	17.1
0.20	0.10		35.0	36.5
0.20	0.10		44.2	64.2
0.10	0.10		25.7	9.05
0.08	0.08	0.02	25.8	7.48
0.06	0.06	0.04	25.8	6.60
0.042	0.021	0.058	25.3	9.67
0.032	0.016	0.068	25.3	9.13
0.021	0.010	0.079	25.3	8.63
		In Deuterioacetic Acid		
0.042	0.021	0.058	25.3	3.74
0.032	0.016	0.068	25.3	3.47
0.021	0.010	0.079	25.3	3.17

The similarity of the kinetics data from the two reactions is evident from the following observations. The lactonization of **3b** is catalyzed by acetic acid in an acetic acid–sodium acetate buffer, k_{HOAc} being 4.95×10^{-3} M^{-1} sec^{-1}. The catalytic rate constant in deuterated acetic acid buffers is 2.65×10^{-3} M^{-1} sec^{-1} giving a solvent isotope effect, k_{HOAc}/k_{DOAc}, of 1.87. The data in Table V are not sufficient to calculate activation parameters for the acetic acid catalyzed term but the activation parameters calculated from k_ψ for the lactonization of **3b** are comparable to those calculated from k_ψ for the lactonization of **5a** (Table VI).

Table VI. Activation Parameters Calculated from k_ψ for the Formation of 1,8-Naphthalide and 3,3-Dimethylphthalide

Reaction	E_a, kcal mol^{-1}	ΔS^*, eu
3b → **4b**	12.3	−31.8
5a → **6a**	10.6	−36.1

In the case only of the lactonization of **3b**, it was possible to follow the rate in 0.001 *M* aqueous perchloric acid. The rate constants for this reaction at various temperatures along with the activation parameters are given in Table VII.

Table VII. 3,3-Dimethylphthalide Formation in Aqueous Perchloric Acid[a]

$[HClO_4]$, *M*	Temp, °C	10^2k_ψ, sec^{-1}
0.001	22.7	4.19
0.001	27.5	5.39
0.001	33.9	8.37

[a] The activation energy, E_a, is 11.6 kcal mol^{-1} and the entropy of activation is −13.9 eu.

Our attempts to collect comparable rate data on the ring closure of 2-(α,α-diphenyl)hydroxymethylbenzoic acid (**3c**) were unsuccessful because the product, 3,3-diphenylphthalide (**4c**), was not sufficiently soluble in aqueous solution. However, we were able to investigate the rate of this reaction by using 75% aqueous dioxane. The data, listed in Table VIII, show that this reaction is subject to buffer catalysis also. In order to compare the rates of ring closure for the three compounds, we determined the observed rate constants for the lactonization of **3b** and **5a** under the same conditions.

Table VIII. 3,3-Diphenylphthalide Formation in Acetic Acid Buffers[a]

[HOAc], *M*	[NaOAc], *M*	$[NaClO_4]$, *M*	10^4k_ψ, sec^{-1}
0.20	0.10	0.00	3.66
0.15	0.075	0.025	2.89
0.10	0.05	0.05	2.36
0.05	0.025	0.075	1.67

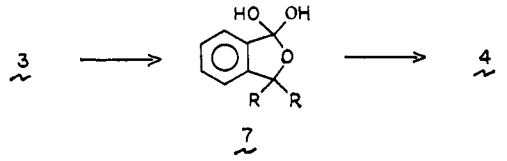
[a] The solvent was 75% aqueous dioxane. The temperature was 25.6°. Observed rate constants for **3b** → **4b** and **5a** → **6a** determined under conditions identical with line one were 10.7×10^{-4} and 64.2×10^{-4} sec^{-1}, respectively.

Discussion

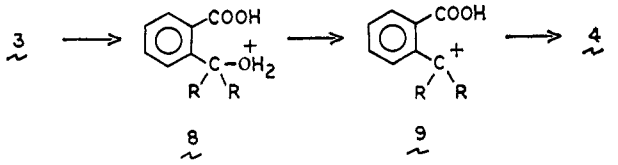
The data cited here for the formation of 1,8-naphthalide and 3,3-dimethylphthalide from their corresponding hydroxy acids indicate that both reactions proceed *via* similar pathways. What few data are available for the formation of 3,3-diphenylphthalide would put this reaction in the same category. Therefore, the present study will provide no fundamental insight into the reasons for the striking differences in the hydrolytic behavior of **1** and **2**.

The evidence from this study together with some previously published work is consistent with a pathway which is the reverse process of the $A_{Ac}2$ ester hydrolysis mechanism. The general outline of this mechanism is shown in Scheme A. The alternative, carbonium ion pathway which could compare with the mechanism of hydrolysis of **2**, and perhaps **1**, is shown in Scheme B. The pathways in Schemes A and B are written for the formation of the phthalides but the reasoning below can be applied to similar pathways for the 1,8-naphthalides.

SCHEME A



SCHEME B

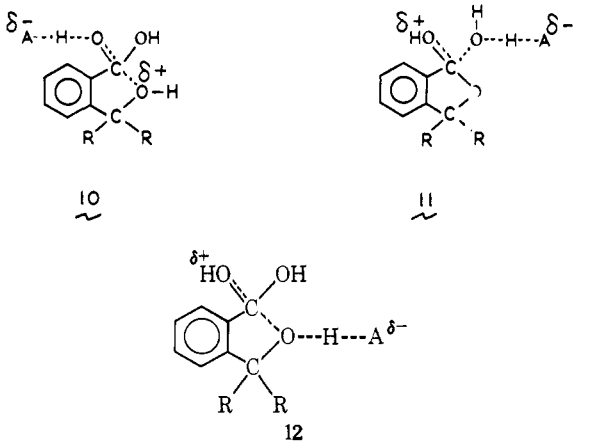


Some elegant O^{18} tracer work by Martin and Koenig[11] on the saponification and subsequent relactonization of 3-benzhydrylphthalide proved that the alkyl oxygen of the lactone comes from the alcohol oxygen of the hydroxy acid. Bunnett and Hauser[12] have shown that phthalide formation is accelerated by bulky groups in the 3 and 6 positions of the phenyl ring and that the reaction has a negative entropy of activation. These observations cannot be accommodated easily with the process in Scheme B.

The acidity of the solution needed to bring about the lactonization in this work is much lower than that needed to promote hydrolysis of **1** and **2** and also lower than the acidity associated with alcohol dehydration. Finally, the mechanism proceeding *via* the benzyl cation, **9**, would not be expected to show buffer catalysis, a negative entropy of activation, or a k_H/k_D greater than 1.0. Neither would it be expected to show the relative rate order **5a** > **3b** > **3c** since the least stable cation would arise from **5a**, the compound with the fastest rate of reaction.

The kinetics data presented in this work establish that proton transfer from an un-ionized acid is occurring in the transition state of the rate-determining step. The observed solvent isotope effects, k_H/k_D, in the vicinity of two cannot be accounted for by secondary isotope effects[13] and, therefore, support the observation of buffer catalysis. The large, negative entropies of activation arise from the association of the un-ionized acid with the substrate in the rate-determining step along with the loss of rotational freedom concomitant with the formation of the ring.

There are several ways in which rate-determining proton transfer might be incorporated into Scheme A. Transition states involving general acid catalysis during formation and during decomposition of the intermediate, **7**, are shown as **10** and **11**, respectively. In addition, kinetically indistinguishable specific acid–general base catalysis, represented by **12**, is a possibility providing that the hydroxyl hydrogens of the substrate are exchanged rapidly in the deuterated media used in this work.



The experimental observations in this study do not allow a choice among these possibilities and speculation on their relative merits is always inconclusive. For example, there are several acid-catalyzed hydrolysis reactions which require rate-determining protonation on oxygen. Two of these are oxazolidine hydrolysis[14] and ortho ester hydrolysis.[15] These cases are thought to be due to the reduced basicity of the oxygen atom relative to the oxygen atoms of their counterparts, 1,3-dioxolanes and acetals, which do not show buffer catalysis. The intermediate, **7**, resembles an ortho ester and might be expected to require rate-determining protonation for its decomposition. However, this line of reasoning is based on the assumption that the transition state **11** resembles **7** for which there is no justification. Hence, the basis for speculation becomes quite arbitrary.

A recent communication[16] describes the lactonization of a phenolic acid, some repetition of our work on **3b**, and some experiments on **3a**.[9] The authors found evidence for catalysis of the lactonization of **3b** not only by the acid component of the buffer but also by the basic component. Our data do not support this second conclusion although, in fairness, they are sufficient to calculate only two points for the appropriate plot of k_{cat} against the fraction of acid in the buffer. The authors found catalysis of the lactonization of **3a** by acetate and formate buffers but others[10] have not detected catalysis of this reaction by cyanoacetic acid–cyanoacetate or chloroacetic acid–chloroacetate buffers.

(11) J. C. Martin and T. W. Koenig, *J. Amer. Chem. Soc.*, **86**, 1771 (1964).
(12) J. F. Bunnett and C. F. Hauser, *ibid.*, **87**, 2214 (1965).
(13) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 42, 3207, 3214 (1961).
(14) T. H. Fife and L. Hagopian, *ibid.*, **90**, 1007 (1968).
(15) C. A. Bunton and R. H. DeWolfe, *J. Org. Chem.*, **30**, 1371 (1965).
(16) S. Milstein and L. A. Cohen, *J. Amer. Chem. Soc.*, **91**, 4585 (1969).