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Dissociation equilibria of protonated hydroxybenzamides and alkoxybenzamides: water as a reactant

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Summary

In previous work, the Hammett acidity function, H_0, was used to describe the prototropic reactions of unsubstituted carboxamides. In that treatment, it was necessary to take into account the hydration requirements of the prototropic reactions of those carboxamides relative to the hydration requirements of the dissociations of the primary amines used as indicators to establish the H_0 scale.

In this work, the same approach was applied to the prototropic reactions of the hydroxybenzamides and their alkyl ethers in order to determine the influence of water, as a reactant, on these reactions.

It was found that the hydration requirements for the prototropic reactions of the hydroxybenzamides and their alkyl ethers were the same as the hydration requirements for the prototropic reactions of the unsubstituted carboxamides. Secondly, it was found that the differences between the basicities of the compounds studied here may be explained by the inductive and electromeric effects of the hydroxy group. Thirdly, it was found that the intramolecular hydrogen-bond in salicylamide is weak, does not occur in all salicylamide molecules and plays a much less dramatic role than does the intramolecular hydrogen-bond of salicylic acid in its chemistry.

Introduction

The acid-catalyzed hydrolyses of certain drugs, notably esters and amides, are important pathways of degradation (Garrett, 1967). Kinetic studies of such reactions

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have led to the postulation of mechanisms involving transition states or intermediates in which the ester or amide is protonated prior to hydrolytic decomposition (Yates, 1971). Such protonated species can be observed directly in concentrated mineral acids but their relationship to the hydrolytic reactions in dilute aqueous solutions is questionable because it is difficult to relate the reaction parameters measured in the concentrated acid to those determined from the kinetics of hydrolysis in aqueous solutions. In particular, it is nearly impossible to determine explicitly the proton activity in the concentrated electrolyte solutions represented by concentrated mineral acids.

Several empirical acidity scales, e.g. that of Hammett and Deyrup (Hammett and Deyrup, 1932), have been established in order to put acid-base chemistry in concentrated acid media on a quantitative footing. However, the universality of any given acidity scale is lacking as the prototropic behavior of even similarly charged compounds often cannot be quantitatively described by the same acidity scale (Boyd, 1969).

Recently, it was demonstrated that the prototropic dissociations of protonated arylamides and lactams (Lovell and Schulman, 1981; Schulman and Vogt, 1981), could be described in terms of the Hammett acidity scale established on the basis of the acid-base chemistry of primary arylamines, provided that water was taken into account as a reactant. This is not done in acid-base chemistry in dilute aqueous solutions because there, the activity of water is unity and therefore, always appears numerically as unity in the equilibrium constant regardless of how many water molecules may be involved in the acid-base reaction. It was shown that the acidity scale based upon the dissociation of protonated arylamines could be related to that based upon the dissociation of protonated arylamides in sulfuric acid solutions, up to about 8 M, if it was recognized that two fewer water molecules were involved in the dissociations of the latter class of acids than in the former.

In the present work it is desired to support the generality and accuracy of the hydration approach to acid-base chemistry in concentrated electrolytic media by examining the prototropic behavior of an arylamide, salicylamide, its isomeric hydroxybenzamides and their methyl or ethyl ethers. In particular, it is desired to learn whether their acid-base chemistry in moderately concentrated sulfuric acid will be accurately described by including water as a reactant in the same way that it was included in the previous study of protonated amide dissociation and whether, the presence of the hydroxy group in the amides affects the water requirements of the dissociation reactions. Finally, it is desired to determine whether the substituent effects on the dissociation constants can be rationalized in terms of molecular and electronic structures involved. The latter objective represents a way of assessing the credibility (or lack thereof) of the proposed reaction-model.

Materials and methods

Salicylamide and 2-ethoxybenzamide (Aldrich Chemicals, Milwaukee, WI) were recrystallized from 50% v/v aqueous ethanol. 3- and 4-hydroxybenzamides and their

methyl ethers were synthesized from the respective carboxylic acids by the following procedure. The hydroxy acids were acetylated by reacting them with acetic anhydride in pyridine overnight. Water was added to the mixture which was then filtered and dried. Thionyl chloride was added slowly to the acetylated benzoic acid or the methoxybenzoic acid dissolved in benzene and the mixture was treated with ammonia, heated with water, and then filtered. To cleave the acetyl group, the acetylated hydroxybenzamide was then heated with ammonia. The hydroxybenzamide was then extracted into ether. The compounds were checked for purity by I.R. and mass spectrometry.

Analytical grade sulfuric acid (Mallinckrodt Chemicals, St. Louis, MO) was diluted with distilled deionised water to prepare the solutions used to study the Hammett acidity region. Each solution was standardized against sodium hydroxide. The corrected Hammett acidity scale of Jorgenson and Hartter (Jorgenson and Hartter, 1963) was used to calibrate each sulfuric acid solution. The activity of water for each sulfuric acid solution was taken from the work of Giauque et al. (Giauque et al., 1960). 0.5 ml of a saturated aqueous solution of each carboxamide were injected into 10 ml volumetrics and made up to volume with the appropriate diluted sulfuric acid solution or distilled water. The concentrations of these acids were corrected for dilution by the carboxamide solution. The concentration of analyte ranged from approximately 10^{-4} M to 10^{-5} M.

Absorption spectra at 25°C were taken on a Cary 219 spectrophotometer. The appropriate sulfuric acid solution or distilled water was used as a blank.

For those spectra recorded in sulfuric acid, isosbestic points were observed at 270 nm for salicylamide, at 290 nm for 2-ethoxybenzamide, at 272 for 3-hydroxybenzamide, at 295 nm for 3-methoxybenzamide, at 250 nm for 4-hydroxybenzamide, and 228 nm for 4-methoxybenzamide. At values of H_0, just beyond where the HA^+ species were isolated, the spectra tend to red shift with less of isosbestic points, indicating either a general medium effect, or a specific change in the solvation of the cations. To determine pK_1, corresponding to the dissociation of the carboxamidium ion, analytical wavelengths were chosen at 315 nm for salicylamide, 310 nm for 2-ethoxybenzamide, 303 nm for 3-hydroxybenzamide, 305 nm for 3-methoxybenzamide, 280 nm for 4-hydroxybenzamide, and 285 nm for 4-methoxybenzamide. These analytical wavelengths correspond to the peak maxima for the carboxamidium ions.

To determine pK_2, corresponding to the dissociation of the hydroxy group of the hydroxybenzamides, aqueous solutions were prepared as described above. The pHs of these solutions were changed by using trace amounts of sodium hydroxide. A Markson Electromark pH meter equipped with a silver–silver chloride combination glass electrode was used to measure the pHs of the solutions. Analytical wavelengths were chosen at 291 nm for 4-hydroxybenzamide, 327 nm for 2-hydroxybenzamide, and 316 nm for 3-hydroxybenzamide. These wavelengths correspond to the peak maxima of the anions of the analytes.

Results and discussion

In work related to the hydrolysis of certain esters, Bunnett (1961) re-defined the Hammett acidity function h_0, to include water as a reactant as described by Eqn. 1:

$$h_0 = \frac{a_{H^+} f_B}{a_w^n f_{BH^+}} \tag{1}$$

where a_w is the activity of water in the aqueous mineral acid solution, n is the number of water molecules that enter into the reaction with BH^+ to form H^+ and B (n is the difference between the number of water molecules hydrating B and H^+ and the number hydrating BH^+) and f_B/f_{BH^+} is the activity coefficient ratio of the primary arylammonium ion indicators used to define h_0. Previously (Lovell and Schulman, 1981) it was shown that the dissociation constants of the primary arylcarboxamides would be given by:

$$K_1 = \frac{a_{H^+}}{a_w^r} \cdot \frac{f_A}{f_{HA^+}} \cdot \frac{[A]}{[HA^+]} \tag{2}$$

where r is the hydration requirement of the following reaction:

$$HA^+ + rH_2O \rightleftharpoons H^+ + A$$

Since A and B, and HA^+ and BH^+ are of the same charge types, it is reasonable to assume that the activity coefficient ratios f_B/f_{BH^+} of the arylamine indicators and f_A/f_{HA^+} of the primary arylcarboxamides are equivalent. Then, the dissociation constants of the arylcarboxamides would be given by:

$$K_1 = h_0 a_w^{n-r} \frac{[A]}{[HA^+]} \tag{3}$$

or in logarithmic form:

$$pK_1 = H_0 - \log\frac{[A]}{[HA^+]} - (n-r)\log a_w \tag{4}$$

which on rearrangement yields:

$$H_0 - \log\frac{[A]}{[HA^+]} = pK_1 + (n-r)\log a_w \tag{5}$$

A plot of $H_0 - \log[A]/[HA^+]$ vs $\log a_w$ should be linear with a slope of $(n-r)$ and intercept pK_1. For the unsubstituted carboxamides $(n-r)$ was found to be 2. Thus:

$$pK_1 = H_0 - \log\frac{[A]}{[HA^+]} - 2\log a_w \tag{6}$$

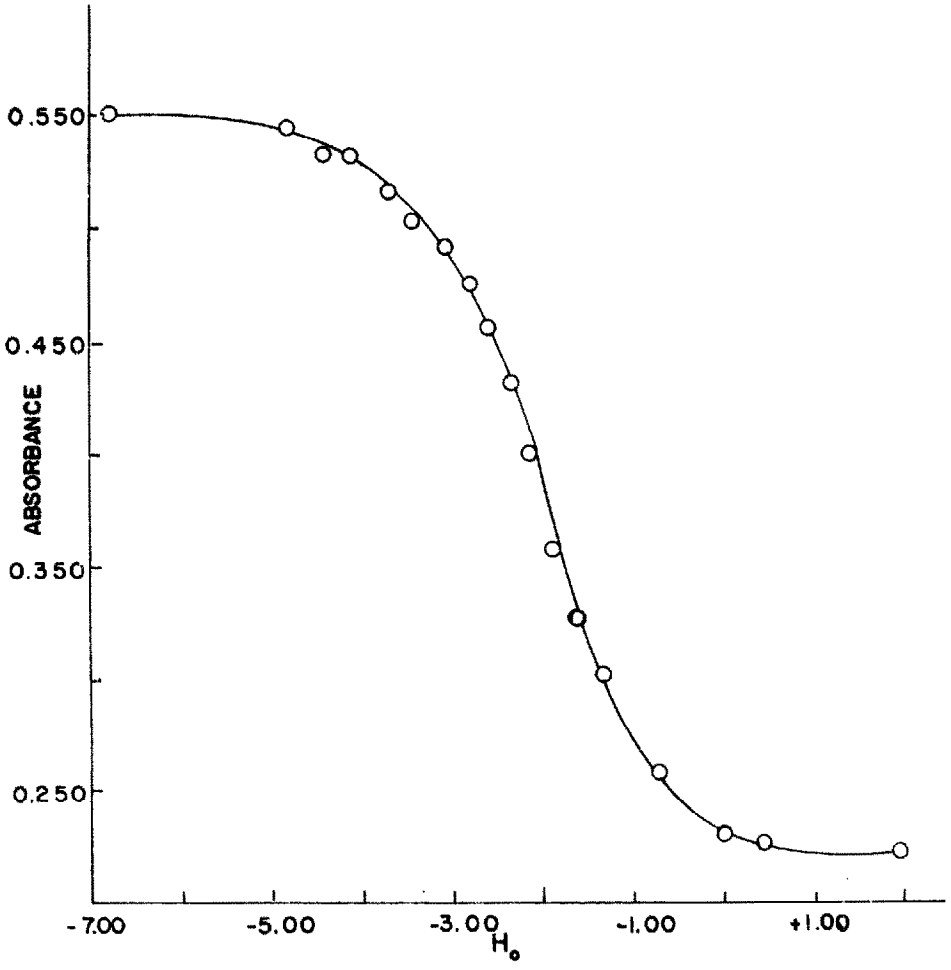

Fig. 1. Variation of the absorbance of 1.3×10^{-4} M salicylamide at 315 nm with the Hammett acidity function H_0 in aqueous sulfuric acid.

Fig. 1 shows a plot of absorbance at 315 nm vs H_0 for salicylamide. This titration curve is sigmoidal like those obtained in dilute aqueous solution except that the inflection region covers a wider range of acidity. From titration curves such as Fig. 1, values of $\log[A]/[HA^+]$ were calculated using the following equation:

$$\log\frac{[A]}{[HA^+]} = \log\frac{(a^0_{HA^+} - a)}{(a - a^0_A)} \tag{7}$$

where $a^0_{HA^+}$ and a^0_A correspond to the absorbances of the most concentrated and most dilute acid solutions, respectively. a is the absorbance at any intermediate acid concentration.

Fig. 2 shows plots of $H_0 - \log[A]/[HA^+]$ vs $\log a_w$ for salicylamide and 2-ethoxybenzamide. The intercepts were, respectively, -1.65 ± 0.01 and -1.67 ± 0.04.

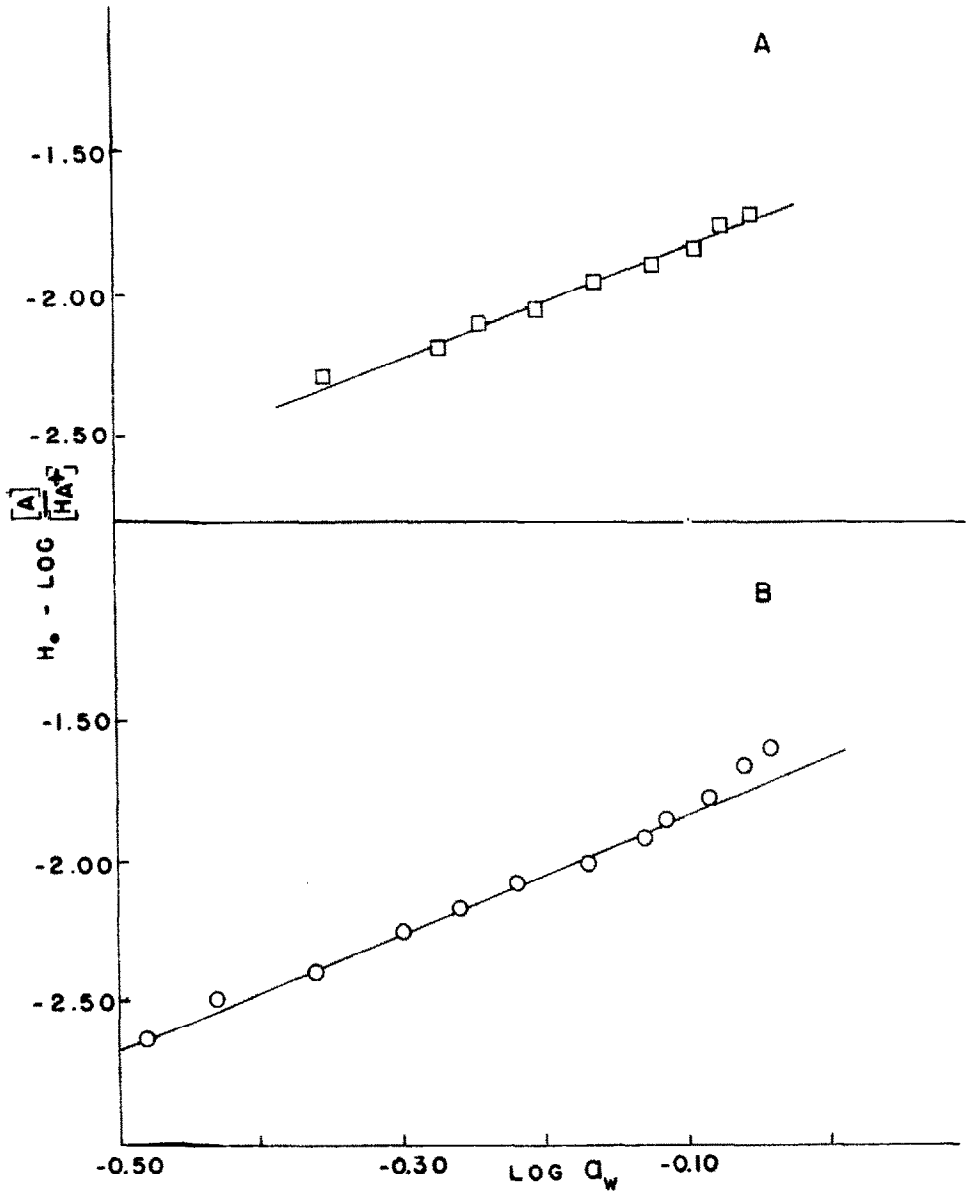

Fig. 2. Variation of $H_0 - \log[A]/[HA^+]$ (where A is an arylcarboxamide and HA^+ is its conjugate acid) with the logarithm of the activity of water (a_w) in aqueous sulfuric acid: (A) 2-ethoxybenzamide; (B) salicylamide.

	Slope	Intercept	Correlation coefficient
2-Ethoxybenzamide	1.92 ± 0.07	-1.67 ± 0.04	0.995
Salicylamide	2.06 ± 0.05	-1.64 ± 0.01	0.998

The slopes were 2.06 ± 0.05 and 1.92 ± 0.01. These values of the intercepts, slopes, and their standard errors were obtained by the method of least-squares.

Calculations of pK_i using Eq. 4 were done using trial values of $(n - r) = 0, 1, 2, 3$.

TABLE 1

VARIATION $H_0 - \log[A]/[HA^+] - (n-r)\log a_w$ WITH $(n-r)=0, 1, 2, 3$ FOR SALICYLAMIDE AT 25°C

H_0	$H_0 - \log\frac{[A]}{[HA^+]}$	$H_0 - \log\frac{[A]}{[HA^+]} - \log a_w$	$H_0 - \log\frac{[A]}{[HA^+]} - 2\log a_w$	$H_0 - \log\frac{[A]}{[HA^+]} - 3\log a_w$
−3.50	−2.64	−2.16	−1.68	−1.20
−3.30	−2.50	−2.07	−1.64	−1.21
−3.00	−2.40	−2.04	−1.68	−1.32
−2.70	−2.26	−1.96	−1.66	−1.36
−2.50	−2.17	−1.91	−1.65	−1.39
−2.30	−2.09	−1.87	−1.65	−1.43
−2.00	−2.02	−1.85	−1.68	−1.51
−1.70	−1.92	−1.79	−1.66	−1.53
−1.50	−1.86	−1.76	−1.65	−1.55
−1.30	−1.80	−1.72	−1.63	−1.55

A sample of these calculations for salicylamide is given in Table 1 which shows that the most reproducible values of pK_1 were obtained for $(n-r)=2$. This is in agreement with the slopes obtained for the plots in Fig. 1. Moreover, the values calculated for $(n-r)\neq 2$ approach the value of pK_1, for $(n-r)=2$, in the most dilute solutions where $a_w \rightarrow 1$. Calculations for other carboxamides studied here also show the same trend. This suggests that the values of pK_1 for salicylamide and other hydroxybenzamides studied here correspond to infinite dilution in water where $a_w \rightarrow 1$.

The fact that $(n-r)$ is 2 and pK_1 is -1.65 for salicylamide suggests that any hydrogen-bond that may exist in salicylamide is weak and does not exert a dominant effect on the acidity of the carboxamido group because a strong hydrogen-bond should make pK_1 for salicylamide more acidic than that for the other two isomers and conceivably change the hydration requirement for the dissociation of the salicylamidium ion. Values of pK_1 for the hydroxybenzamides and their alkyl ethers are shown in Table 2. The order of the pK_1s can be explained by resonance and inductive effects. The resonant effect of the hydroxy group would be the same in both the ortho and para isomers and make these isomers less acidic than the meta isomer. However, because of the proximity of the electronegative hydroxy group to the carboxamide group in salicylamide, this isomer should be less acidic than the para isomer. The alkyl ethers would be expected to follow the same order but be slightly more acidic than the hydroxy compounds. This is indeed the case as shown in Table 2.

The conclusion that the intramolecular hydrogen-bond in salicylamide is weak is further supported by a comparison of pK_2 for the hydroxybenzoate mono-anions and the hydroxybenzamides. In Table 3 which shows pK_2 for the hydroxybenzoates, salicylate is considerably less acidic than the other two isomers because the intramolecular hydrogen-bond in the former is stabilized by the negatively charged carboxylate group. This makes it more difficult to remove the hydroxylic proton. Singly charged 3-hydroxybenzoate is less acidic than 4-hydroxybenzoate because the acid strengthening electromeric effect of the carboxylate group is smaller at the meta position than at the para position.

TABLE 2

pK_as OF THE HYDROXYBENZAMIDES AND THEIR ALKYL ETHERS

	pK_1	pK_1' [a]	pK_2
		(mean ± S.D.)	
Salicylamide	−1.64 ± 0.01	−1.96 ± 0.23	8.14 ± 0.01
3-Hydroxybenzamide	−1.73 ± 0.01	−2.06 ± 0.14	9.30 ± 0.00
4-Hydroxybenzamide	−1.43 ± 0.04	−1.88 ± 0.36	8.55 ± 0.01
2-Ethoxybenzamide	−1.60 ± 0.01	−1.98 ± 0.15	
3-Methoxybenzamide	−1.80 ± 0.04	−2.19 ± 0.18	
4-Methoxybenzamide	−1.51 ± 0.02	−1.85 ± 0.21	

[a] pK_1' calculated using the H_0 scale but excluding water as a reactant.

TABLE 3

pK_2 OF HYDROXYBENZOIC ACIDS

	pK_2 [a]
Salicylic acid	13.40
3-Hydroxybenzoic acid	10.00
4-Hydroxybenzoic acid	9.13

[a] Dissociation constants of organic acids in aqueous solution from Kortum, G., Vogel, W. and Andrussow, D. (Eds.), Butterworths, London, 1961.

In the case of the hydroxybenzamides the order of pK_2 is different from that in the hydroxybenzoates as shown in Table 2. For salicylamide pK_2 is smaller than that of 4-hydroxybenzamide which in turn is smaller than that of 3-hydroxybenzamide. This confirms that even though salicylamide has been shown to exist as intramolecularly and non-intramolecularly hydrogen-bonded conformers (Schulman and Underberg, 1979) in water, this hydrogen-bond is weak and does not exert a dominant effect on the acidity of the hydroxy group. Again, the resonant effect of the carboxamido group should be the same in the para and ortho positions but the inductive effect should make the ortho isomer more acidic than the para isomer. This adequately explains the order of the pK_2s in Table 2.

Conclusion

The values of pK_1 shown in Table 2 confirm that as in the dissociations of the simple carboxamides studied previously, the dissociation of the protonated hydroxy- and alkoxybenzamides could be described by the H_0 scale if the activity of water in the sulfuric acid medium is taken into account. When water is not taken into account as a reactant, (i.e. when $n - r = 0$ in Eqn. 4), the scatter in the values obtained for pK_1 (Table 2) is inferior. It is clear that the order of the values established here for pK_1 can be adequately explained by the same substituent effects used to rationalize the well established chemistry reflected in the order of the values of pK_2 of the hydroxybenzamides. This fact tends to validate the approach used here.

References

Boyd, R.H., Acidity functions. In Coetzee, F.F. and Ritchie, C.D. (Eds.) Solute–Solvent Interactions, Dekker, New York, 1969, pp. 97–218.

Garrett, E.R., In H.S. Bean, A.H. Beckett and J.E. Carless (Eds.), Advances in Pharmaceutical Sciences, Vol. 2, Academic Press, New York, 1967, pp. 1–94 and refs. contained therein.

Giauque, W.F., Hornung, E.W. Kunzler, J.E. and Rubin, T.R., The thermodynamic properties of aqueous sulfuric acid solutions and hydrates from 15 to 300°K. J. Am. Chem. Soc., 82 (1960) 62.

Hammett, L.P. and Deyrup, A.J., Basic indicators (1). Acidity functions of mixtures of H_2SO_4 and with H_2O. J. Am. Chem. Soc., 54 (1932) 2721.

Jorgenson, M.J. and Hartter, D.R., A critical re-evaluation of the Hammett acidity function at moderate and high acid concentrations of sulfuric acid. New H_0 values based solely on a set of primary aniline indicators. J. Am. Chem. Soc., 85 (1963) 878.

Lovell, M.W. and Schulman, S.G., A simple relationship between the Hammett acidity function, H_0, and the thermodynamic pK_a values of unsubstituted aromatic carboxamides. Anal. Chim. Acta, 127 (1981) 203.

Schulman, S.G. and Vogt, B.S., Proton-transfer kinetics of 2- and 4-quinolone in the lowest excited singlet state in moderately concentrated perchloric acid. J. Phys. Chem., 85 (1981) 2074.

Schulman, S.G. and Underberg, W.J.M., Excitation wavelength dependence of salicylamide in the lowest excited singlet state. Photochem. Photobiol., 29 (1979) 937.

Yates, K., Kinetics of ester hydrolysis in concentrated acid. Acc. Chem. Res., 4 (1971) 136.