The Physical Organic Chemistry of Benzisoxazoles. III. The Mechanism and the Effects of Solvents on Rates of Decarboxylation of Benzisoxazole-3-carboxylic Acids

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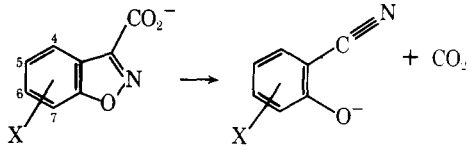
Abstract: The anions of 3-carboxybenzisoxazoles undergo a quantitative decarboxylation forming salicylonitriles. The reaction is assigned an intermediateless, concerted mechanism on the basis of substituent effects and the failure to detect 3-*H*-benzisoxazole as a product of reaction at pH 2 in the presence of tritiated water. Salt effect, pH rate profiles, and activation parameters are reported for aqueous reactions. Rate constants are reported for the tetramethylguanidine catalyzed decarboxylation of 3-carboxy-6-nitrobenzisoxazole in 24 solvents and 6 solvent mixtures and are found to vary over a range of 10^8. Hammett ρ values are reported for substituted benzisoxazoles for reaction in 14 solvents. Correlation of solvent rate data with solvent parameters of other workers is discussed.

In recent years, as a result of the investigations of several groups,[1-4] very large solvent effects on reaction rates have been recognized as features of a variety of organic reactions involving ions. These same effects have been postulated and cited as important contributors to the rate accelerations induced by enzymes.[5]

Earlier, we have reported[6] preliminary results of a study of the decarboxylation reactions of 3-carboxybenzisoxazoles (**1**) and have demonstrated that these reactions show exceedingly large rate accelerations as the solvent is changed from protic to polar aprotic. Since that report, other groups have applied this reaction to studies of micellar[7] and inclusion[8] catalysis.



1 **2**

Elsewhere,[9] we have described the detailed mechanistic features of the related base-catalyzed isomerization of 3-*H*-benzisoxazoles to salicylonitriles and established the reaction as an intermediateless, E_2 elimination which is exothermic by ca. 30 kcal/mol. The sensitivity of reaction rates to ring substitution, the separation of substituents from reacting bonds, the absence of significant conformations, and the mechanistic invariance led us to urge use of substituted benzisoxazoles as mechanistic probes,[9] and a first study of this kind applied the base catalyzed isomerism to the problem of curvature in selectivity–reactivity relationships.[10]

In this paper, we describe the detailed features of the decarboxylation reaction **1** → **2**, both in aqueous and nonaqueous solvents. In the following paper in this issue, we present the evidence and arguments which define the factors which contribute to large solvent rate accelerations for this reaction; in it we establish the reaction as involving true catalysis by selective transition state stabilization and define the nature of rate retardation effects in protic solvents.

Experimental Section

Elemental analyses were performed by Scandinavian Microanalytical Laboratories of Copenhagen. Melting points were taken with a Thomas-Hoover apparatus, uv spectra with Zeiss PMQ II or Cary 14 spectrometers, ir spectra with a Perkin-Elmer 237B spectrometer, and tritium measurements in dioxane-based counting solution with a Packard Model 3375 liquid scintillation spectrometer. Unless otherwise specified, reagents were reagent grade, and magnesium sulfate was used for drying of solutions.

Preparation of 3-Carboxybenzisoxazoles. The substances 6-nitro-3-carbomethoxybenzisoxazole, 6-nitro-3-carboxybenzisoxazole, 6-chloro-3-carbomethoxybenzisoxazole, and 6-chloro-3-carboxybenzisoxazole were prepared by literature procedures.[11-13]

6-Amino-3-carbomethoxybenzisoxazole and 6-Amino-3-carboxybenzisoxazole. A modification of Lindemann's[11] procedure was followed. 6-Nitro-3-carbomethoxybenzisoxazole, 25 g (0.11 mol), was mixed with an ice-cooled, stirred solution of 50 g of stannic chloride in 100 ml of 12 *M* HCl, and a solution of 75 g of stannous chloride in 50 ml of 12 *M* HCl was added dropwise over 30 min. After 4 hr, a white solid was collected, washed with ether, and added to a stirred mixture of ethyl acetate and saturated sodium bicarbonate solution. When solid had dissolved, the organic phase was separated, dried, and evaporated to yield a white solid, 15 g, 71%, which was recrystallized from benzene to give yellow needles, mp 205–208° (reported[11] 206°).

Hydrolysis of 5 g of a twice-recrystallized sample of this ester was carried out in 25 ml of 70% sulfuric acid at 80° for 5 hr, and amine salt was obtained by diluting with 25 ml of water and cooling. The salt was suspended in a stirred mixture of ethyl acetate and aqueous sodium acetate, and the pH was maintained at 3.5 by addition of sodium acetate. The organic phase was dried and evaporated to yield 4 g of amine which was recrystallized from ethanol–cyclohexane to yield pale brown crystals, mp 161–163° (reported[11] 160°).

Ethyl *o*-Nitrophenylglyoxylate Oxime, 3-Carboethoxybenzisoxazole, and 3-Carboxybenzisoxazole. To a solution of ethyl *o*-nitrophenylacetate,[14] 25 g (0.11 mol), and isoamyl nitrite, 15 g (0.13 mol), in 200 ml of ethanol was added a solution of sodium, 25 g (0.11 mol), in 50 ml of ethanol. The resulting orange solution was stirred at 50° for 2 hr, cooled, treated with 200 ml water to dissolve the precipitated salt, acidified, and extracted with ether. The extract was dried and evaporated to give 24 g (0.1 mol) of a brown solid which was recrystallized from benzene, mp 167–168°. Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.50; H, 4.24; N, 11.80. Found: C, 50.45; H, 4.42; N, 11.90.

A solution of 10 g (47 mmol) of dried oxime ester in 100 ml of diglyme, freshly distilled from calcium hydride and from sodium naphthalenide, was added dropwise to a vigorously stirred suspension of 1.2 g of pentane-washed sodium hydride dispersion in 100 ml of dry diglyme under nitrogen. The resulting thick solution was heated slowly to 150° and maintained at that temperature for 8 hr. The mixture was cooled, diluted with 200 ml of water, and extracted with ether. The extracts were dried and evaporated to an oil which was freed of diglyme by warming at 0.1 mm. Three recrystallizations from ligroin yielded 6 g of white solid, 66%, mp 102–

103°. Anal. Calcd for $C_{10}H_9NO_3$: C, 62.85; H, 4.75; N, 7.33. Found: C, 62.78; H, 4.79; N, 7.28. The yield for this reaction was reduced if scrupulously dry conditions were not maintained.

A solution of 5 g of ester in 100 ml of 70% sulfuric acid was heated at 80° for 4 hr, then poured onto ice, and extracted with ether. The extract was dried and evaporated, and the solid was recrystallized from benzene–hexane to give 4.0 g, 96%, of white needles, mp 145–148° (lit.[10] 145°).

6-Hydroxy-3-carboethoxybenzisoxazole, 6-Methoxy-3-carboethoxybenzisoxazole, and 6-Methoxy-3-carboxybenzisoxazole. Ethyl 2,4-dihydroxyphenylglyoxylate, 5.0 g (35 mmol), prepared from resorcinol and ethyl cyanoformate by the procedure of Hunsberger and Amstutz,[15] was added to a stirred solution of 4 g (35 mmol) of hydroxylamine *O*-sulfonate in 200 ml of water. After solution was complete, the mixture was added to equal volumes of vigorously stirred dichloromethane and saturated aqueous sodium bicarbonate. The organic phase was separated, dried, and evaporated to yield a solid which was recrystallized from benzene to give 4 g, 54%, of needles, mp 148–149°. Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.34; N, 6.76. Found: C, 57.92; H, 4.38; N, 6.80.

Methylation was carried out by addition of a solution of 5 g (23 mmol) of this ester in 30 ml of dimethoxyethane, dried by distillation from sodium naphthalenide, to a well stirred suspension of 0.6 g (25 mmol) sodium hydride in 20 ml of dimethoxyethane under nitrogen. Methyl iodide, 10 g (70 mmol), was added to the resulting light green solution which was stirred for 4 hr at 25°, then diluted with 50 ml of water, and extracted with ether. The extract was washed with 10% NaOH, dried, and evaporated to yield a solid which was recrystallized from octane to give 4.5 g (87%) of white needles, mp 77–78°.

Hydrolysis of 3 g of ester in 30 ml of 70% sulfuric acid was conducted at 80° for 5 hr; the solution was poured onto ice and extracted with ether. Drying and evaporation of the extract yielded, after recrystallization from benzene–hexane, 2.5 g (93%) of acid, mp 154–155°. Anal. Calcd for $C_9H_7NO_4$: C, 55.95; H, 3.79; N, 7.24. Found: C, 55.75; H, 3.93; N, 7.08.

5-Nitro-3-carboxybenzisoxazole. A solution of 3 g of 3-carboxybenzisoxazole in 20 ml of sulfuric acid was cooled at 0°, during the addition of 5 ml of nitric acid. After 3 hr at 25°, the solution was poured onto ice and the solid collected. Recrystallization from ethyl acetate–hexane gave 3.3 g of powder (89%), mp 165–168°. Anal. Calcd for $C_8H_4N_2O_5$: C, 46.15; H, 1.94; N, 13.46. Found: C, 46.11; H, 2.11; N, 13.33.

5,6-Dinitro-3-carbomethoxybenzisoxazole, 5,6-Dinitro-3-carboxybenzisoxazole, and 4,5-Dinitrosalicylonitrile. A solution of 5 g of 6-nitro-3-carbomethoxybenzisoxazole in 25 ml of sulfuric acid was maintained at or below 30° during the addition of 5 ml of nitric acid, whereupon the mixture was heated to 50° for 4 hr, cooled, and poured onto ice. Collection of the precipitate, drying, and recrystallization from benzene gave 5 g of product, 86%, mp 109–110°. Anal. Calcd for $C_9H_5N_3O_7$: C, 40.46; H, 1.89; N, 15.73. Found: C, 40.33; H, 1.98; N, 15.57.

A solution of 2 g of ester in 20 ml of 70% sulfuric acid was heated at 80° for 3 hr, cooled, and poured over ice. The precipitate was filtered and dried over phosphorus pentoxide to give 1.8 g of a white solid which decomposed to the corresponding salicylonitrile above 100°, upon attempted recrystallization, or upon storage. No nitrile band appeared in the ir spectrum of this substance; uv (H_2O, pH 1) 322 nm (3020).

Heating an aqueous solution of the acid at 30° for 1 hr gave, on chilling, 95% of nitrile which was recrystallized from methanol–water, mp 210°. Anal. Calcd for $C_7H_3N_2O_5$: C, 40.21; H, 1.45; N, 20.09. Found: C, 40.02; H, 1.20; N, 19.97.

Product Determinations Salicylonitriles were identified by uv spectroscopy and by direct isolation as the sole products observed from the decomposition of the above series of 3-carboxybenzisoxazoles in water and in acetonitrile. Spectroscopic identifications were made in other solvents. With the exception of the 6-amino derivative (65%), an average isolated yield of 92% was realized for the aqueous reactions, while an average of 93% was obtained in acetonitrile. Typical aqueous conditions were 50° for 80 hr.

Tritium Incorporation. A solution of 0.50 g of benzisoxazole (4.2 mmol), 1.0 g (6.1 mmol) of 3-carboxybenzisoxazole, 20 ml of ethanol, 2 ml of ^3H_2O (100 μCi/ml), and 50 ml of 2 *M* phosphoric acid was brought to pH 2, hydrion paper, with KOH and diluted to 100.0 ml. After 20 hr at 50° (1 half-life), the solution was extracted with 4 × 50 ml ether, and the extracts were washed with 1 *M* NaOH and brine, then dried and evaporated to yield 420 mg of benzisoxazole. Decomposition with sodium methoxide in methanol by the method previously described[9] and transfer of methanol collected by bulb-to-bulb distillation to a counting vial gave 28.8 cpm for the sample, background count 25.6 cpm. Had 1% of the 3-carboxybenzisoxazole been converted to benzisoxazole anion and trapped, a value of 860 cpm would have been observed.

Table I. Uv Absorption Data for 3-Carboxybenzisoxazoles[a]

Substituent	pH 0–1	pH >4
H	255 (5670)	242 (7050)
	292 (5400)	288 (5070)
6-Methoxy	240 (4280)	258 (3970)
	275 (6850)	290 (6580)
6-Nitro	246 (6700)	275 (8500)
	275 (8500)	
6-Amino	228 (6700)	227 (16000)
	290 (4500)	266 (5750)
		305 (11000)
6-Chloro	260 (4850)	250 (5850)
	291 (4700)	288 (4630)
5-Nitro	240 (10500)	233 (12100)
	288 (5330)	280 (5330)
5,6-Dinitro	322 (3020)	

[a] In nm (H_2O).

pK_a Determination. Values for the pK_a's of the 3-carboxybenzisoxazoles were obtained for the H, 6-MeO, 6-NO_2, and 6-Cl derivatives by an uv method in buffer mixtures using eq 1.

$$pK_a = pH + \log [(A_{pH} - A_X)/(A_{HX} - A_{pH})] \quad (1)$$

Limiting values of A were measured after the addition of ca. ¼ pellet of KOH or a drop of sulfuric acid to the cuvette. Uv absorption maxima are given in Table I.

Kinetic Procedures. Purification of Reagents. Acetone, acetonitrile, benzene, hexamethylphosphoramide, benzonitrile, carbon tetrachloride, and chloroform were distilled from phosphorus pentoxide and used within a week; the latter two were used immediately. Methanol and ethanol were anhydrous reagents used without purification. Diethyl ether was stored over sodium; THF was distilled from $LiAlH_4$ immediately before use; diglyme was distilled from sodium naphthalenide at 30 mm. The following solvents were distilled through a 55-cm spinning-band column and stored over molecular sieves: DMF and DMAc (P_2O_5, 30 mm), Me_2SO (CaH_2, 10 mm), dioxane (CaH_2), tetramethylenesulfone (NaOH, 5 mm), *N*-methylpyrrolidone (P_2O_5, 10 mm). Formamide, *N*-methylformamide, and nitromethane were distilled through a 30-cm Vigreux column, stored over molecular sieves, and used within 2–7 days.

Inorganic salts were dried at 150° for 24 hr before use. Tetramethylguanidine (Eastman) was distilled twice from BaO and used within a week. Anhydrous *p*-toluene sulfonic acid was prepared by azeotropic distillation with benzene, recrystallized from benzene, and stored in a desiccator.

Phosphate, acetate, and phthalate buffers were prepared respectively from KH_2PO_4, KH phthalate, and NaOAc, and were standardized by titration with HCl using a pH meter.

Further experimental details are available in thesis form.[16]

pH Measurement. Acidities were measured with a Radiometer Model 4 pH meter equipped with G 202C and K401 electrodes and standardized with Fisher phthalate (pH 4.01) and phosphate (pH 6.98) buffers. The temperature was maintained at 30° by means of a small constant temperature bath.

Kinetic Measurements. Reactions with half-lives of over 5 hr were carried out in sealed tubes immersed in a cylindrical water bath equipped with stirrer, heaters, and thermoregulators. Absorbance measurements were carried out using Zeiss PMQ II or Beckman DU spectrometers. Reactions with half-lives between 10 sec and 5 hr were carried out in cuvettes contined in a cell block of the Zeiss, maintained at constant temperature (±0.05°) with a Haake Model F circulating bath. Reactions with half lives of less than 10 sec were observed by the stopped-flow method using a Durrum-Gibson stopped flow spectrometer. Oscilloscope traces were recorded on Polaroid film. Optical density measurements were carried out at the long wavelength absorption maximum of the products.

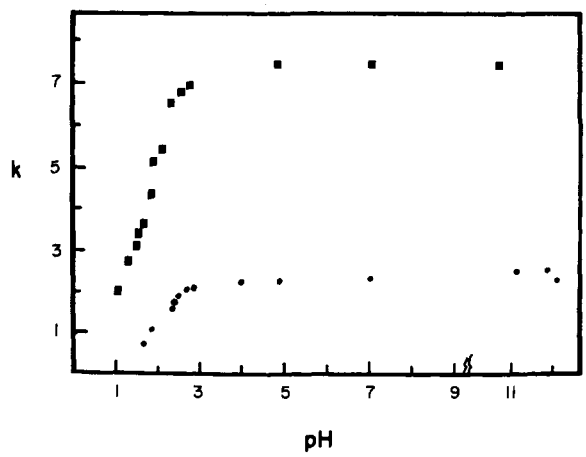


Figure 1. Rate constants for decarboxylation of 3-carboxybenzisoxazoles in aqueous buffers as a function of pH. T 30°, μ = 1.0 (KCl). k is in units of $sec^{-1} \times 10^6$. Circles are data points for **1** (X = 6-MeO); squares for **1** (X = 6-NO_2).

Aqueous reactions were conducted by adding 1 ml of an acetonitrile solution of 3-carboxybenzisoxazole to an aqueous solution of pH adjusted buffer containing KCl, diluting to 100.0 ml and filtering.[17] Runs at 50° were followed by quenching aliquots in an ice bath. For reactions run at pH values below the pK_a of the product, optical density readings were obtained by adding ¼ pellet KOH to the cuvette. Infinity points were obtained after 10 half-lives although, in the case of the substrates with electron-donating substituents at pH 13, a small amount of hydrolysis of nitrile to amide was noted during the long reaction times, and infinity points were approximated from the known product extinction coefficients. Aqueous reactions were conducted in phosphate, phthalate, acetate, formate, and bicarbonate buffers; reactions conducted at pH values below 2.2 used hydrochloric acid as the sole buffer species. No extrapolation of rate constant to zero buffer concentration was carried out since buffer species were shown not to affect the rates.

Nonaqueous reactions were carried out by dissolving the 3-carboxybenzisoxazole in a freshly prepared solution of *p*-toluenesulfonic acid in the desired solvent. This solution was introduced into one of the reservoir syringes of the stopped-flow apparatus and a freshly prepared solution of tetramethylguanidine was introduced into the other. The scale expansion, time scale, and noise settings were adjusted and the sample syringes were repeatedly refilled and discharged through the mixing chamber until reproducible oscilloscope traces were observed. When at least three runs in a series gave identical traces, the storage display was photographed. Added salts were often found to catalyze the decomposition of substrate in organic solvents, even in the presence of added acid; consequently, salts were dissolved in the solution of basic catalyst. Slower nonaqueous reactions were followed in the Zeiss thermostatted cell block and were initiated by adding a drop of tetramethylguanidine to the thermally equilibrated solution containing substrate and *p*-toluenesulfonic acid.

Results

Typical pH–rate profiles for the decarboxylation reactions of 3-carboxybenzisoxazoles in water are shown in Figure 1, and data obtained from these reactions are reported in Table II. All observed pseudo-first-order rate constants observed at constant pH can be satisfactorily approximated by eq 2

$$k_{obsd} = \frac{(k_1 K_a)}{(H^+ + K_a)} \qquad (2)$$

and kinetic estimates of the pK_a values of the substrates were obtained as averages of the expression, pH + log $((k_1 - k)/k)$, in which k_1 is the limiting rate constant at high pH. For four of the six cases, pK_a values could be measured directly, using the difference of uv absorption for carboxylic acid and anion; the values are seen to be in good agreement.

Table II. pK_a Values and Rate Data for Decarboxylation of 3-Carboxybenzisoxazoles in Water

A. pH–Rate Behavior [μ = 1.0 (KCl), T 30°]

Substituent	$k \times 10^6$, sec^{-1}	pK_a(kinetic)	pK_a(spect)
H	1.06 (0.1)[a]	1.97 (0.08)[a]	1.92
6-Methoxy	2.45 (0.1)	2.03 (0.07)	2.02
6-Chloro	4.40 (0.1)	1.86 (0.08)	1.86
6-Nitro	7.35 (0.1)	1.57 (0.09)	1.55
5-Nitro	94.5 (1)	1.77 (0.07)	
5,6-Dinitro	1020 (100)	1.27 (0.05)	
6-Amino	2.00 (0.1)		

B. Effect of Buffer Species [μ = 1.0 (KCl), T 30°]

Substituent	Buffer acid (M)	pH	$k_{obsd} \times 10^6$, sec^{-1}
H	0.5 H_3PO_4	2.10	2.38
	0.05	2.14	2.50
	0.005	2.21	2.56
6-Chloro	0.5 HOAc	4.75	4.53
	0.05	4.75	4.52
	0.005	4.75	4.50
	0.5 H_3PO_4	2.10	2.78
	0.05	2.13	2.70
	0.005	2.20	3.00
6-Nitro	0.5 HOAc	4.75	7.40
	0.05	4.75	7.33
	0.005	4.75	7.37
	0.5 H_3PO_4	2.18	5.70
	0.05	2.35	6.20
	0.005	2.35	6.10

C. Effect of Ionic Strength. Solvent Isotope Effect (T 30°, salt, KCl)

Substituent	$k_1 \times 10^6$, sec^{-1} μ = 1.0	μ = 0.1	μ = 0.01
6-Chloro	4.48 (0.1)[a]	4.45 (0.1)[a]	4.40 (0.1)[a]
6-Nitro	7.32 (0.1)	7.40 (0.1)	7.30 (0.1)
5-Nitro	95.0 (1)	95.0 (1)	93.5 (1)
6-Nitro	$k_1(D_2O)/k_1(H_2O) = (5.80 \times 10^{-6})/(7.35 \times 10^{-6}) = 0.79$		
5-Nitro	$k_1(D_2O)/k_1(H_2O) = (8.60 \times 10^{-6})/(9.45 \times 10^{-6}) = 0.91$		

D. Activation Parameters [water, T 30–50°, μ = 1.0 (KCl)]

Substituent	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
6-Amino	+31.0[b]	+17.0[c]
H	32.0	18.9
6-Methoxy	32.0	20.8
6-Chloro	32.0	21.9
6-Nitro	32.0	22.9
5-Nitro	27.5	11.8
5,6-Dinitro	24.6	8.4

[a] Standard deviations are given in parentheses. [b] $\Delta H^\ddagger$ values have estimated errors of ±1 kcal/mol. [c] $\Delta S^\ddagger$ values have estimated errors of ±4 eu.

Also listed in the table in parts B and C are data which establish that there is no demonstrable catalytic effect of buffer acids on reaction rate and that the salt and solvent isotope effects are small. The activation parameters reported in part D are the result of measurements at three temperatures, 30, 40, and 50°; in all cases, excellent linearity was observed for Arrhenius plots.

In an attempt to trap an intermediate benzisoxazole-3-carbanion, the decarboxylation reaction was carried out in a tritiated aqueous ethanolic medium, in the presence of 0.5 M phosphoric acid and benzisoxazole as carrier. Isolation and purification of the latter substance gave no observable activity and, from the conditions of the experiment, it follows that less than 2×10^{-3}% of the substrate which decomposed can have been trapped as benzisoxazole.

Determination of simply interpretable rate constants for reactions of **1** in nonaqueous media rests on the availability of a strong, experimentally convenient base which quantitatively converts the substrate acid to its anion. Data of part

Table III. Effects of Bases and Salts on Rates of Decarboxylation of 3-Carboxy-6-nitrobenzisoxazole in Aprotic Solvents

A. Amine Effects (T 30°)

Solvent	Amine	[Amine] × 10^4, M	[TSA] × 10^4, M	[Substrate] × 10^4, M	k_{obsd}, sec^{-1} [a]
Me_2SO	TMG	23	10	2	10
		230	10	2	11
		2300	10	2	10
	Et_3N	50	10	2	10
		500	10	2	10
CH_3CN	TMG	32	14	2	2.8
		320	14	2	2.9
		3200	14	2	2.8
	Et_3N	100	14	2	1.3
		1000	14	2	1.1
Benzene	TMG	10	0	5	4.8×10^{-3}
		50	0	5	4.5×10^{-3}
		100	0	5	5.8×10^{-3}
		500	0	5	10×10^{-3}

B. Salt Effects (T 30°)

Solvent	Salt	[Salt], M	k_{obsd}, sec^{-1}
Me_2SO	$LiClO_4$	0.25	3.0
	$NaClO_4$	0.25	2.8
	$KClO_4$	0.25	3.9
	No salt	0.0	10
CH_3CN	$TMGH^+TSA^-$	0.0003	2.9
		0.03	2.5
	$Bu_4{}^+NBr^-$	0.0005	3.1
		0.05	2.7
		0.5	1.8
	$LiClO_4$	0.05	1×10^{-3}
	$NaClO_4$	0.01	1×10^{-2}

[a] Rate constants have a precision of ca. 10%.

A of Table III establish that the strong base, anhydrous tetramethylguanidine (TMG) appears to fulfill this condition, in that the observed rate constants are independent of amine concentration. Moreover, in all dipolar aprotic solvents studied, except acetone, nitromethane, acetonitrile, and benzonitrile, identical rate constants are observed with TMG and with the much weaker base, triethylamine. For the latter solvents, the usual observation is a constant rate up to at least a 100-fold excess of TMG over acidic species, with a small rate increase, which is probably a medium effect, at higher base concentrations. Triethylamine, in these solvents, usually resulted in rate constants which increased with base over a wide concentration range. In nonpolar aprotic solvents, small rate increases with TMG concentration were observed while, with triethylamine as base, complex behavior was observed.

A similar pattern is seen in the salt effects given in part B of the table. The absence of large salt effects in Me_2SO at salt concentrations up to 10^3 times that of substrate is consistent with the notion that substrate anion in this solvent is largely present in dissociated, solvated form and not in the form of intimate ion pairs. On the other hand, the large rate decreases observed in acetonitrile in the presence of lithium or sodium ions suggests that ion pairing must be significant in this solvent. These observations are fully supported by direct studies of ion association phenomena in these solvents.[2,18]

The combination of substrate and TMG was employed throughout the solvent studies which we now report. It is clear from the above considerations that the rate data so obtained should be simply interpretable for the cases of maximum interest—polar protic and polar aprotic solvents. For the data obtained in aprotic solvents of low to medium polarity, the observed rate constants are certainly not cation independent and may in some isolated cases not even reflect complete acid dissociation; they must, however, be lower bounds on the true rate constants for dissociated salt. To the degree that they are unexpectedly large or reveal wide variations among solvents of similar structural type, they must imply important fundamental phenomena even though they are the first crude observations of a possibly highly complex experimental situation.

In Table IVA are reported rate constants for the decarboxylation of the TMG salt of 3-carboxy-6-nitrobenzisoxazole in 24 solvents. The total rate range is 9.5×10^7 and, with the exception of the rate span between water and methanol, rate constant values within the total range appear to be uniformly represented.

Activation parameters for decarboxylation in three organic solvents are compared with those for water in Table V. Although the usual uncertainties apply to these parameters when measured over a narrow temperature range for a reaction involving major solvation changes, it is nonetheless very striking that the entirety of the effect of solvent change appears in the enthalpy term.

Data given in part B of Table IV provide evidence of the substituent sensitivity of the reaction for nearly all of the polar solvents studied. Although there appears to be a trend for the Hammett ρ value to increase for the solvents which induce the largest rate accelerations, there is considerable variation of ρ for solvents of similar accelerating tendency. Moreover, the least-squares error in ρ is ca. 0.15 for most of the values quoted, and it seems more appropriate to regard all but three solvents as characterized by a ρ of around 2.0—water, the most inhibitory solvent, as characterized by an anomalously low ρ value of 1.4, and the two highly accelerating solvents, HMPA and DMAc, as having a very high ρ of 2.4. Experimental limitations of the stopped-flow technique prevent measurement of most rate constants of the most reactive 5-nitro and 5,6-dinitro substrates. It may be noted, however, that these systems obey the Hammett relationship very satisfactorily in the four cases which could be studied. Assuming the relationship remains valid in HMPA, one estimates the total solvent rate range for the dinitro compound as 10^9 and its largest rate constant as 10^6 sec^{-1}.

Figure 2 illustrates the effects on rate constant of continuously varying the composition of a two-component solvent mixture. Although several of the graphs are a form which suggests approximation through a linear combination of rate constants observed in the pure solvents, two show clearly defined rate maxima for solvents of mixed composition. Although these maxima are not large enough to be of major practical importance, they do testify directly to the complexity of the phenomenon and pose serious difficulties for simple models.

Discussion

Mechanism of Decarboxylation in Aqueous Solution. As indicated by the results of Figure 1 and Table II, the available facts establish that the 3-carboxybenzisoxazoles undergo decarboxylative rearrangement to salicylonitriles only as their conjugate bases; the free acids appear to be completely nonlabile. Although rigorous kinetic measurements were not carried out at very low pH values, the conditions of the preparation of these substances from their ethyl esters involved hydrolysis at 80° for 3–4 hr in 70% sulfuric acid. Since the acids were almost invariably obtained in nearly quantitative yield, it can be concluded that no important specific acid catalyzed decomposition process is available to these systems. With the highly reactive 5,6-dinitro system, one can estimate that decomposition at 30° in 70% sulfuric acid must be at least 10^4 times slower than that observed at pH 2. Although the N-protonated conjugate acid of **1** and

Table IV. Rate Constants for Decarboxylation of 3-Carboxybenzisoxazoles in Nonaqueous Solvents (T 30°, Base = Tetramethylguanidine[a])

A. 3-Carboxy-6-nitrobenzisoxazole

Solvent	k, sec^{-1}	Log k
Water	7.4×10^{-6}	−5.13
Methanol	2.5×10^{-4}	−3.60
Formamide	7.4×10^{-4}	−3.13
Chloroform	8.0×10^{-4}	−3.09
Ethanol	1.0×10^{-3}	−3.00
Carbon tetrachloride	1.5×10^{-3}	−2.82
Benzene	4.8×10^{-3}	−2.32
N-Methylformamide	8.1×10^{-3}	−2.09
Dimethoxymethane	3.6×10^{-2}	−1.44
Dioxane	4.0×10^{-2}	−1.39
Dichloromethane	4.7×10^{-2}	−1.33
Diethyl ether	9.0×10^{-2}	−1.05
Nitromethane	5.8×10^{-1}	−0.24
Benzonitrile	2.5	0.40
Acetonitrile	2.9	0.46
Tetrahydrofuran	4.0	0.60
Diglyme	5.0	0.70
Dimethyl sulfoxide	1.0×10	1.00
Acetone	2.4×10	1.38
Dimethylformamide	3.7×10	1.56
Tetramethylenesulfone	6.4×10	1.81
Dimethylacetamide	1.6×10^2	2.20
N-Methylpyrrolidone	2.5×10^2	2.40
Hexamethylphosphoramide	$\sim 7.0 \times 10^2$	2.8

B. Substituted 3-Carboxybenzisoxazoles (T 30°, Base = Tetramethylguanidine)

	Log k							
	6-NH_2	H	6-MeO	6-Cl	6-NO_2	5-NO_2	5,6-$(NO_2)_2$	ρ (CC)[b]
H_2O	−5.700	−5.975	−5.611	−5.357	−5.134	−4.025	−2.991	1.37 (0.983)
MeOH	−4.959	−4.770	−4.553	−4.000	−3.602	−2.410	−1.000	1.86 (0.998)
EtOH	−4.602	−4.398	−4.102	−3.509	−3.000	−1.796	−0.456	1.96 (0.998)
Formamide	−4.377	−4.097	−3.959	−3.456	−3.131	−1.796		1.75 (0.992)
N-Methylformamide	−3.745	−3.456	−3.149	−2.553	−2.092	−0.770		2.05 (0.998)
Nitromethane	−1.854	−1.509	−1.252	−0.620	−0.237	1.00	2.699	2.08 (0.997)
Acetonitrile	−1.071	−0.921	−0.638	0.079	0.462	1.800		2.02 (0.994)
Dimethyl sulfoxide	−0.700	−0.398	0.000	0.612	1.000			2.02 (0.984)
Acetone	−0.398	−0.155	0.255	0.944	1.380			2.15 (0.986)
Dimethylformamide	−0.091	0.176	0.672	1.255	1.568			1.99 (0.972)
Tetramethylene sulfone	0.079	0.477	0.653	1.431	1.806			2.05 (0.985)
Dimethylacetamide	0.279	0.544	0.903	1.845	2.204			2.39 (0.977)
N-Methylpyrrolidone	0.602	1.041	1.255	2.000	2.398			2.10 (0.986)
Hexamethylphosphoramide	0.820	1.255	1.447	2.342	2.845			2.40 (0.989)

[a] [Substrate] = $2-3 \times 10^{-4}$ *M*; [TMG] = ca. 3×10^{-3} *M*. [b] CC = Correlation coefficient.

its zwitterion would be expected to be highly reactive species by analogy with related systems,[19] the exceptionally low basicity of the benzisoxazole nitrogen[9] effectively excludes these species from mechanistic participation. As a further consequence of the highly electron-withdrawing character of the isoxazole function, we call attention to the high acidity of the 3-carboxybenzisoxazoles, whose pK_a values are similar to those of *o*-nitrobenzoic acids. As a result of this acidity, these substances decompose at constant rate over nearly the entire aqueous pH span, and conjugate bases can be present at high relative concentrations, even in poorly ionizing solvents.

The variation of pK_a with 5- or 6-substituent deserves brief comment. The pK_a data of Table I can be correlated by means of the Hammett equation, with σ^-_{para} values for the 6-substituents, σ_{meta} values for the 5-substituents, and $\sigma^-_{para} + \sigma_{meta}$ for the 5,6-dinitro derivative. A ρ value of 0.32 with a correlation coefficient (CC) of 0.993 is observed. On the other hand, a very poor correlation with the pK_a values of 6- and 7-substituted 1-naphthoic acids[20] is observed, slope 0.35, CC 0.81. The poor correlation arises from the values observed for the mononitro derivatives; in the naphthoic cases, the 7-nitro acid is stronger than the 6, as expected for a substituent effect which can be rationalized by a field model. Although the substituent effect is considerably smaller for the benzisoxazoles, the 5-nitro induces less of an acidity change than the 6, and the latter is best correlated with a σ^- value; both facts appear to be in-

Table V. Activation Parameters for the Decarboxylation Reaction of 3-Carboxybenzisoxazole (T 30–50°)

Solvent	$\Delta H^{\ddagger}$, kcal/mol[a]	$\Delta S^{\ddagger}$, eu[a]
CH_3CN	25	20
Me_2SO	24	18
HMPA	23	18
Water	32	19

[a] The $\Delta H^{\ddagger}$ values have estimated errors of ca. 1 kcal/mol; the $\Delta S^{\ddagger}$ values, 4 eu.

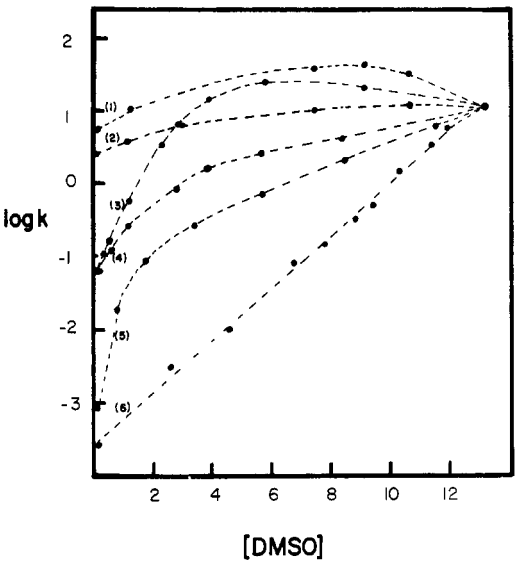
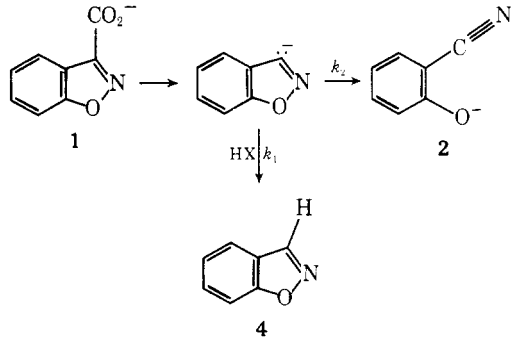


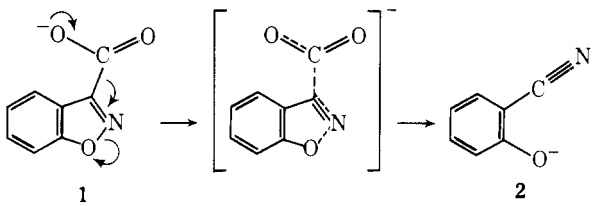
Figure 2. Logarithms of rate constants for the decarboxylation of 3-carboxy-6-nitrobenzisoxazole in solvent mixtures containing Me_2SO as functions of Me_2SO concentration: curve 1, diglyme; curve 2, acetonitrile; curve 3, benzene; curve 4, dichloromethane; curve 5, chloroform; curve 6, methanol. T 30°, three- to fivefold excess of TMG.

consistent with a simple through-space interaction model[20] and to argue for an effect based significantly on resonance. Since electrophilic substitution on benzisoxazoles occurs preferentially in the 5-position, the effect appears to involve a mutual interaction between the carboxy and nitro functions.

Of the two viable mechanisms for the conversion of **1** to **2**, the stepwise mechanism can be excluded and the intermediateless concerted mechanism established by consideration of the failure to trap an intermediate carbanion by protonation. When the decomposition of 3-carboxybenzisoxazole is run in tritiated water at pH 2 in the presence of 0.5 M phosphoric acid, no tritiated benzisoxazole (**4**) could be detected. Even allowing a factor of 10–20 for a possible isotope effect on the formation of **4**, the experimental results establish that k_2 must be larger than 10^4 k_1. Since the rates of protonation of a benzisoxazole-3-carbanion must lie at the diffusion limit for both H_3O^+ and phosphoric acid,



k_2 is therefore calculated to exceed 10^{12}–10^{14} sec^{-1},[21] and a discrete carbanion is therefore excluded as a significant reactive intermediate. The remaining possibility is a concerted process. Exactly similar conclusions have been reached on the basis of substituent effects and negative exchange results for the deprotonation reactions of benzisoxazoles bearing a 3-hydrogen.[9]



Although calorimetric measurements have not been carried out for the conversion **1** → **2**, the $\Delta H°$ values for the conversion of RCO_2H to RH + CO_2, in solution or in the gas phase, are in nearly all cases negative by a few kcal/mol.[24] This fact, together with the observed $\Delta H°$ value for the isomerization of benzisoxazole to salicylonitrile[9] allows one to estimate that the conversion of a 3-carboxybenzisoxazole to carbon dioxide and a salicylonitrile must be exothermic by slightly more than 30 kcal/mol, a value which will be reduced by a few kcal/mol for the related reaction involving the conjugate bases of starting material and product. From Table IID, one can conclude that the transition state for the latter reaction is separated in energy from starting material by 30 kcal/mol and from product by nearly 60 kcal/mol.

Both entropies of activation and salt effects are in accord with a unimolecular reaction in which charge is conserved. The absence of general acid catalysis is more striking. In the case of 3-carboxybenzisoxazole, for which the pK_a of the product is 6.9, a reaction run at pH 2 in the presence of 0.5 M phosphoric acid generates salicylonitrile anion under conditions in which it is unstable with respect to its conjugate acid by a factor of nearly 10^5. Moreover, a significant fraction of the substrate molecules are likely to be in immediate proximity to potential catalyst molecules. Yet no catalysis can be demonstrated. It is simple to show that only in cases in which proton transfer for the catalytic step occurs in a thermodynamically favorable direction can general catalysis lead to rate accelerations.[25] The case at hand points up the fact that the rule provides a necessary but by no means sufficient condition for general catalysis. All of the aqueous rate data provide a consistent picture of a reaction which is apparently self contained in the sense that its rates are not changed by catalysts, salts, and to a large degree, pH. The behavior of the system in nonaqueous solvents reveals the water results to be a simple facade which falsely represents a system of extreme perturbability.

The most striking feature of the reaction **1** → **2** is the rate increase observed in dipolar aprotic solvents, relative to water. Both the magnitude and the pattern of solvent effects on rate are similar to those reported by Parker as characteristic of solvent effects on rates of a variety of substitution reactions which involve anions as reactants. That the decarboxylation reactions of 3-carboxybenzisoxazoles display similar solvent sensitivites to Parker's systems is illustrated by a correlation coefficient of 0.985 and a slope of 0.9 for a linear correlation of rates of decarboxylation of **1** (X = 6-NO_2) with rates of reaction of azide ion with 4-nitrofluorobenzene in nine solvents.

Parker's studies have been confined almost entirely to polar solvents, and as a result, it is not possible to compare his results with rate constants observed in this study for the reaction **1** → **2** conducted in ethers, halocarbons, and aro-

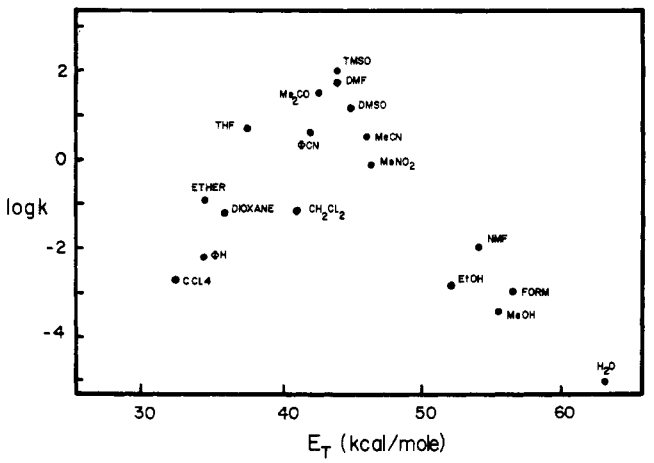


Figure 3. Plot of log k values for the decarboxylation of 3-carboxy-6-nitrobenzisoxazole (Table IIIA) as functions of the Dimroth E_T parameter.

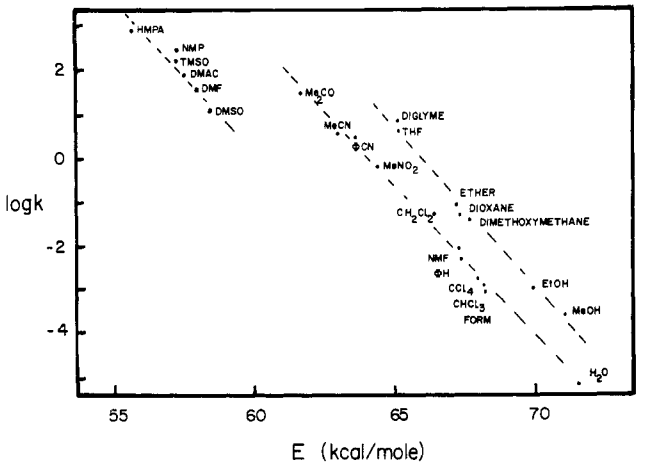


Figure 4. Plot of log k values for the decarboxylation of 3-carboxy-6-nitrobenzisoxazole (Table IIIA) as functions of the molar transition energy of the long wavelength electronic absorption maximum of the TMG salt of 2-cyano-5-nitrophenol.

matic hydrocarbons. Although, as noted previously, the TMG-carboxylic acid combination is unlikely to yield dissociated ions in these solvents, and, as a result, rate constants must be interpreted as lower bounds, the striking features of these processes are their rapidity and range. Within the series of ethers, there is suggestion of a correlation with basicity, the rate range is nearly 140-fold, and the most catalytic ethers are THF and diglyme, which, it may be noted, are comparable with the dipolar aprotic solvents acetonitrile and Me_2SO in accelerating tendency. These ethers are well known for their cation-solvating tendencies and Lewis basicity. Since it is most unlikely that these roles can be invoked for reactions involving guanidinium ions, their accelerating capacity for the reaction at hand must be attributed to another feature of these substances, most likely associated with dispersion effects. Whatever the explanation, the demonstrated capacity of these solvents for facilitating an anionic isomerization reaction raises the question whether similar facilitating features may not contribute to the effects these solvents have on rates of many organometallic reactions for which cation stabilizing effects are also important.

Among the ethers, halocarbons, and aromatics, the overall rate range is 6×10^3, which is 40% of the total rate range observed for all solvents; there appears to be little or no correlation with solvent polarity, although the slow rate observed in chloroform may reflect the hydrogen-bonding tendencies of this solvent.

Among the various tools for assessing solvent polarity,[26] probably the most general and useful are those based upon solvent effects on an electronic transition; the Dimroth E_T[27] and the Kosower Z values[28] are examples. As typified by Figure 3, a poor correlation was observed between our data and either of these parameters.

Using an electronic transition of the reaction product as solvent parameter, the more orderly correlation of Figure 4 is observed, which groups solvents into three classes. The argument for the cogency of this correlation must rest on an analogy between the solvation requirements of transition state and product electronic excited state; its weakness is a failure to allow for changes of solvation state of starting material.

Although deviations exist for the slowest and two of the fastest solvents, the Hammett coefficients for the remaining cases of Table IVB are remarkably similar. Parker has argued that transition states can be expected to change markedly in structure as solvation is varied. The above fact, together with the constancy of $\Delta S^{\ddagger}$ terms for this reaction, which involves a unimolecular fragmentation, can be taken to suggest that little change in transition state structure occurs. It is interesting to note that to the extent that a systematic change occurs in Hammett coefficient, it is in the direction of increased sensitivity to solvation as reactivity is increased.

Studies of rates of reactions of anions in mixtures of protic and dipolar aprotic solvents have revealed a monotonic variation of rate constant with solvent composition.[1] Six of our 11 studies of solvent mixtures are presented in Figure 2. Taking the region in which dipolar solvent concentration is high as the easiest to rationalize, we find three patterns of rate behavior. In MeOH–Me_2SO or water–DMF, a plot of log k vs. concentration of dipolar aprotic solvent shows a steep rate decrease with protic solvent. A similar effect is seen with mixtures of the weakly hydrogen bonding solvents, chloroform and dichloromethane, with DMF or Me_2SO, although the decrease is much less steep (curve 5, Figure 2). A mixture of Me_2SO and acetonitrile shows a concentration dependent linear combination of rate constants. Rate maxima are observed for mixtures of ether, diglyme, or benzene with DMF, Me_2SO, or HMPA (curves 1 and 2, Figure 2). These are to our knowledge unprecedented for solvent mixtures of this kind and carry the implication that the pure dipolar aprotic solvents are not quite optimal for rate acceleration. More information is needed before the phenomenon can be established as a transition state effect and not a ground state interaction of a sort which has complicated studies of solvolysis processes in solvent mixtures.

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The Physical Organic Chemistry of Benzisoxazoles. IV. The Origins and Catalytic Nature of the Solvent Rate Acceleration for the Decarboxylation of 3-Carboxybenzisoxazoles

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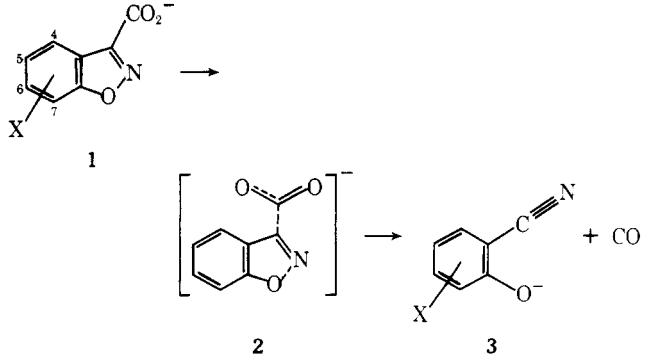
Abstract: Benzisoxazoles bearing 3-hydrogens isomerize to salicylonitriles in the presence of tetrabutylammonium acetate in dipolar aprotic solvents at rates which are up to 10^7 times larger than those observed in water. The decarboxylation of salts of 3-carboxy-6-nitrobenzisoxazole in water is accelerated by as much as 10^4 by the addition of a benzonitrile phase. In striking contrast to the behavior of other 3-carboxybenzisoxazoles, the decarboxylation of 3-carboxy-4-hydroxybenzisoxazole occurs at rates which are nearly solvent independent. From these observations, it is concluded that the factors which influence the rates of decarboxylation are carboxylate ion hydrogen bond formation in protic solvents which inhibits the reaction by selectively stabilizing the starting material, and transition state stabilization in dipolar aprotic solvents which accelerates the reaction. Indirect evidence requires that carboxylate anions exist to a significant extent as nonhydrogen bonded species in benzonitrile saturated with water. The latter two factors are argued to be the essential preconditions for the construction of practical enzyme-like catalysts for this reaction.

The data presented in the previous paper[1] establish the decarboxylation of 3-carboxybenzisoxazoles as proceeding by way of the intermediateless mechanism, **1** → **2** → **3** and further establish that very large rate accelerations result if the solvent water is replaced by dipolar aprotic solvents.



In this paper we explore the problem of catalysis of this reaction by solvent extraction from water. The existence of large solvent rate accelerations need not imply that realizable catalysis can be derived from equilibrated solvent partitionings of substrate. Following an introduction in which we develop the possible relationships between rate acceleration and catalysis, we present experiments which in fact demonstrate marked catalysis of the reaction **1** → **3** through partitioning between water and benzonitrile. A further experiment involving the intramolecularly hydrogen bonded substrate, 4-hydroxy-3-carboxybenzisoxazole, is used to assess the key role of hydrogen bonding in the solvent catalysis of these reactions. Finally, the generality of these reactions is considered by a study of solvent catalysis of base decomposition of benzisoxazoles with hydrogens in the 3-position.

Large solvent effects on rates of reactions involving anions have received much attention in several laboratories[2-5] and have been implicated in enzymatic mechanisms.[6] In a discussion section, we propose a model for solvent induced