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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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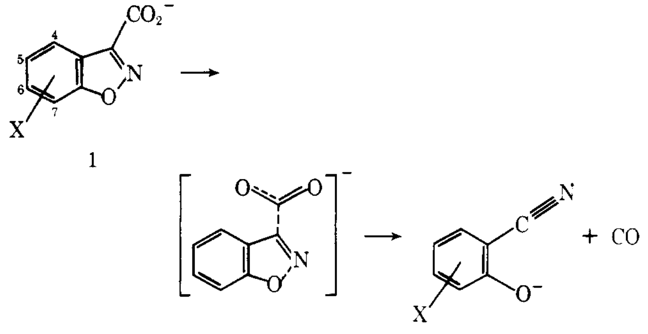
Abstract: Benzisoxazoles bearing 3-hydrogens isomerize to salicylonitriles in the presence of tetrabutylammonium acetate in dipolar aprotic solvents at rates which are up to 10^7 times larger than those observed in water. The decarboxylation of salts of 3-carboxy-6-nitrobenzisoxazole in water is accelerated 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.



1

2

3

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 catalysis of the reaction **1** → **3** which we believe applies more generally to reactions of other anions.

Experimental Section

Elemental microanalyses were performed by Midwest Microlab, Ltd, Indianapolis, Ind. Instrumental measurements and rate determinations, benzisoxazole preparations, and reagent or solvent purifications were carried out as described previously.[1]

Tetrabutylammonium Acetate. This substance was prepared from silver acetate and tetrabutylammonium bromide, following the procedure of Parker.[7] After treatment in benzene with basic alumina and evaporation of solvent, 15 mmol of salt was recrystallized in a Dewar jacket fritted glass funnel from 5 ml of benzene, 2 ml of ethyl acetate, and 4 ml of pentane by cooling to −25°. Filtration and drying (N_2) were followed by immediate solution in the desired solvent. Concentrations were determined by titration with HCl in acetone–water to a bromphenol blue endpoint.

Methyl 2,6-Dinitrophenyloximinoacetate. Into a dry flask equipped with dry ice condenser, gas inlet tube, serum stopper, and stirring bar were introduced 0.50 g (22 mmol) of clean sodium metal, 5 ml of anhydrous methanol, and 25 ml of anhydrous dimethoxyethane. The solution was cooled to −78°, and dry methyl nitrite (ca. 100 mmol) was introduced via a cannula over 30 min. (The methyl nitrite was generated from 8 g of sodium nitrite, 42 g of methanol, and 30 ml of water to which 20 ml of 50% sulfuric acid was added slowly, and the mixture was dried by passage through 18 cm of indicating Drierite and condensed over calcium chloride.) A solution of 2.5 g (10.4 mmol) of methyl 2,6-dinitrophenylacetate[8] in 25 ml of dry dimethoxyethane was then added slowly, and the solution was allowed to warm to 0° and was stirred for 1.5 hr. A cold solution of 5 ml of sulfuric acid in 5 ml of methanol was added, followed by 200 ml of dichloromethane. The organic solution was washed with water, dried, and evaporated to yield pale orange needles, 2.7 g; recrystallization from chloroform yielded a total of 2.05 g (73%) of nearly colorless needles, mp 188–190° dec. Anal. Calcd for $C_9H_7N_3O_7$: C, 39.99; H, 2.71; N, 15.67. Found: C, 40.16; H, 2.62; N, 15.61. The excess methyl nitrite used appears to act as a scavenger for traces of water; without it, appreciable amounts of 2,6-dinitrophenylacetic acid are isolated; isoamyl nitrite gives unsatisfactory yields.

3-Carbomethoxy-4-nitrobenzisoxazole. Into a flask equipped with condenser, stirring bar, serum stopper, and nitrogen inlet were introduced 9 mmol of pentane-washed sodium hydride dispersion and 30 ml of anhydrous dimethoxyethane. To this suspension was added slowly a solution in dry dimethoxyethane of 2.0 g (7.5 mmol) of methyl 2,6-dinitrophenyloximinoacetate. The resulting brown solution was warmed slowly to reflux, maintained for 10 min, and cooled. Water (100 ml) and ether (200 ml) were added, and the organic phase was extracted with NaOH solution and water, dried, and evaporated to yield 1.5 g solid which was recrystallized from ethyl acetate-cyclohexane to yield 1.3 g (78%) of pale yellow needles, mp 89–91°. Anal. Calcd for $C_9H_6N_2O_5$: C, 48.67; H, 2.72; N, 12.61. Found: C, 48.56; H, 2.89; N, 12.45.

3-Carboxy-4-hydroxybenzisoxazole. A stirred suspension of 1.25 g (5.6 mmol) of 3-carbomethoxy-4-nitrobenzisoxazole in 7.5 ml of 12 *M* HCl is stirred at 0° and treated dropwise with 3.8 g (16 mmol) of stannous chloride dihydrate dissolved in a minimum amount of 12 *M* HCl. After 5 min at 0°, the mixture was stirred 2.5 hr at 20°, then diluted with 400 ml of ethyl acetate, followed cautiously by 200 ml of saturated aqueous bicarbonate. The pH was brought to 8 (NaOH) and, after stirring for 10 min, the organic phase was separated, dried, and evaporated to yield 1.0 g (92%) of yellow crystals of 3-carbomethoxy-4-aminobenzisoxazole: mp 138.0–139.5°; NMR ($CDCl_3$) 4.1 (s, 3), 5.5 (s, 2), 6.47 (d, J = 8, 1 Hz), 6.89 (d, J = 8, 1 Hz), 7.34 (t, J = 8, 1 Hz).

A solution of 1.0 g (5.2 mmol) of the amine in 20 ml of water and 7 ml of sulfuric acid was stirred at 3–5° during the slow addition of 0.38 g (5.3 mmol) of sodium nitrite in 20 ml of water. After 30 min at 2–5°, the solution was poured into a stirred solution of 370 g of cupric nitrate trihydrate in 600 ml of water and treated with 0.75 g (5.2 mmol) of cuprous oxide, following the general procedure of Lewin and Cohen.[9] After 20 min, the solution was extracted four times with dichloromethane. Pooling, drying, and evaporating yielded 0.85 g of light yellow needles which were purified on a silica gel dry column (3.7 × 50 cm) using chloroform as developent. The zone of R_f 0.7–0.8 was collected and eluted yielding 0.64 g (64%) of 3-carbomethoxy-4-hydroxybenzisoxazole as pale yellow needles, mp 146–148°.

A solution of 0.50 g of this phenol in 10 ml of 50% sulfuric acid was heated 42 hr at 55° and then extracted with 3 × 30 ml of ether. The extracts were pooled, washed with water, dried, and evaporated to yield crude acid. Recrystallization from 4 ml of ethyl acetate and 50 ml of hexane at 0° yielded 0.29 g of 3-carboxy-4-hydroxybenzisoxazole: mp 165° dec; NMR (acetone-d_6) 6.78 (d, J = 8, 1 Hz), 7.20 (d, J = 8, 1 Hz), 7.66 (t, J = 8, 1 Hz), 9.6 (s, 1); uv (H_2O, pH 2, monoanion) 306 nm (ϵ 2600), (H_2O, pH 13, dianion) 325 (5200); pK_{a1} = 0; pK_{a2} = 11. Anal. Calcd for $C_8H_5NO_4$: C, 53.62; H, 2.81; N, 7.53. Found: C, 53.30; H, 2.94; N, 7.53. Decomposition of this substance in aqueous or nonaqueous solvents gave a substance identical with 2,6-dihydroxybenzonitrile by mixture melting point and uv absorption at pH 1.5 and 12.5.

2,6-Dihydroxybenzonitrile. A mixture of 0.25 g (1.8 mmol) of 2,6-dihydroxybenzaldehyde and 0.60 g (5.3 mmol) of hydroxylamine-*O*-sulfonic acid in 25 ml of water is stirred at 20° for 45 min (homogeneous) and then treated with 50 ml of dichloromethane and 0.8 g (9.5 mmol) of sodium bicarbonate.[10] After 30 min, the organic phase is separated and the aqueous phase stirred 30 min with an additional 50 ml of dichloromethane. The pooled organic phases were dried and evaporated, and the crude residue was dissolved in 3 ml of ethanol and 8 ml of 2 *M* NaOH. After 1 hr, acidification and extraction with dichloromethane and ether, followed by drying and evaporation, yielded crystals which were dissolved in 20 ml of ethyl acetate. The resulting solution was decolorized with charcoal, heated to boiling, treated with 20 ml of cyclohexane, concentrated to 30 ml, and filtered to remove a trace of brown material. Dilution to 40 ml with cyclohexane, concentration to 25 ml, and cooling yielded 0.15 g (60%) of yellow needles, mp 203–204°. Sublimation raised the mp to 209°. Anal. Calcd for $C_7H_5NO_2$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.50; H, 3.74; N, 10.54.

3-Carboxy-6-hydroxybenzisoxazole. The hydrolysis procedure described above for the 4-hydroxy derivative was applied to 3-carboethoxy-6-hydroxybenzisoxazole. The crude product (92%) was recrystallized by forming a saturated solution at 20° in ethyl acetate containing a drop of acetic acid, diluting with petroleum ether, and cooling to 0°: mp 201–202° dec; uv (H_2O, pH 3, monoanion) 289 nm (ϵ 8500), (H_2O, pH 10, dianion) 312 (11800); pK_{a1} = 1.3; pK_{a2} = 8. Anal. Calcd for $C_8H_5NO_4$: C, 53.62; H, 2.81; N, 7.82. Found: C, 53.43; H, 2.86; N, 7.62.

Rate Measurements. Rate constants for the reaction of triethylamine and tetrabutylammonium acetate with benzisoxazoles were obtained in dry solvents at 5×10^{-5} *M* substrate concentration, using catalyst concentrations in the range of 5×10^{-2} to 10^{-3} *M*.

Because of the slowness of the reaction rate in water at 30° decomposition of 4- and 6-hydroxybenzisoxazoles was carried out at 50°. Extensive hydrolysis of product nitrile to amide occurred as a complication, and final absorbance values were calculated from the extinction coefficient of product. Generally, reliable rate data could be obtained only over 1 half-life of the reaction, the problem being most acute at high pH. For this reason, the 6-hydroxy compound **5** was not studied above pH 6.

Solvent Activity Coefficients. 1. Potassium Hydroxide. A 1.0 *M* aqueous solution of KOH was extracted carefully with an equal volume of benzonitrile. The layers were separated, and the benzonitrile phase was centrifuged to remove traces of aqueous emulsion and then was extracted with three equal volumes of distilled water. The pH of the combined aqueous layers was 9.0; therefore, $[KOH]_{PhCN} = 3 \times 10^{-5}$ and $\log w_{\gamma}s_{K^+}w_{\gamma}s_{OH^-} = 9$.[11]

2. Benzonitrile. After equilibration of 10 ml of benzonitrile and 10 ml of tritiated water, 0.1 ml of the benzonitrile, and 0.1 ml of unlabeled water was counted, showing 1.8×10^3 cpm; a sample consisting of 0.1 ml of dry benzonitrile and 0.1 ml of tritiated water showed 1.8×10^5 cpm. The concentration of water in benzonitrile is therefore 0.55 *M*. The uv absorption of a similarly equilibrated aqueous phase was used to determine the concentration of benzonitrile in water as 0.012 *M*.

3. 4-Nitrosalicylonitrile Anion. An aqueous solution 0.01 *M* in 4-nitrosalicyclonitrile potassium salt and 0.04 *M* in KOH was extracted with an equal volume of benzonitrile. After centrifugation and fourfold dilution, an optical density of 0.34 was observed (ϵ 2850). The relationships of eq 1 were applied to obtain log

$w_{\gamma}s_{K^+}w_{\gamma}s_{RO^-} = 3.3$, $RO^- =$ 4-nitrosalicylonitrile anion. By a similar procedure, the value of $w_{\gamma}s_{Et_4N^+}w_{\gamma}s_{RO^-}$ was found to be 0.8.

In the organic phase, for only one extractable anion:

$$[\text{anion}]_{PhCN} = [\text{cation}]_{PhCN}$$

$$w_{\gamma}s_{A^+}w_{\gamma}s_{B^-} = \frac{[\text{anion}]_w[\text{cation}]_w}{[\text{anion}]_{PhCN}[\text{cation}]_{PhCN}} = \frac{[\text{anion}]_w[\text{cation}]_w}{[\text{anion}]_{PhCN}{}^2} \quad (1)$$

The distribution coefficient for partitioning of tetraethylammonium bromide between water and benzonitrile was determined: log $w_{\gamma}s_{Et_4N^+}w_{\gamma}s_{Br} \geqslant 5.0$. Distribution coefficients for the starting material (**1**) could only be approximated. For the potassium ion experiment, the ratio of rate constants observed for the extraction experiment to that observed for the substrate in wet benzonitrile is 1.4×10^{-3}, which then roughly equals the concentration ratio of starting material anion for the extraction. The concentration of potassium ion in the aqueous phase was 0.05 *M*; that in the organic phase must equal the concentration of the most abundant anion which is the product and which therefore varies throughout the experiment. An average value is in the range of $1\text{-}2 \times 10^{-4}$ *M*, whereupon log $w_{\gamma}s_{K^+}w_{\gamma}s_1 = 5.4$. The concentration ratio of transition states is equal to the ratio of reaction rates in the two phases.[11] For the tetraethylammonium ion experiment, the rate in benzonitrile is the overall rate constant times the overall concentration (since reaction takes place significantly only in benzonitrile); the rate in water must equal the starting material concentration in water times the aqueous rate constant, 7.3×10^{-6} sec^{-1}. A similar calculation applies to the potassium ion experiment, with the complication that the experimental rate constant varied from 2×10^{-3} at 25% reaction to 8×10^{-4} at 75% reaction, presumably reflecting the change in potassium ion concentration in the organic phase as the more readily extracted product is formed. A value of log $w_{\gamma}s_{Et_4N^+}w_{\gamma}s(\mathbf{2})$ of between −2.4 and −2.7 is obtained in the former case and, with an average rate constant of 7×10^{-4} sec^{-1}, the latter case gives $0.3 < w_{\gamma}s_{K^+}w_{\gamma}s(\mathbf{2}) < 0.8$. Although there are uncertainties in these calculations, it may be noted that the critical cation partition ratio is bounded by the product and buffer salt partition ratios and cannot deviate from the indicated values by more than a factor of ca. 5.

Rate Measurements for Extraction Experiments. A 100-ml aqueous stock solution of 3-carboxy-6-nitrobenzisoxazole and either KOH or KOH and tetraethylammonium bromide was prepared; 5 ml of this solution was vigorously stirred at 30° and treated with an equal volume of benzonitrile. At an appropriate time, the mixture was quenched with 10 ml of methanol containing a small amount of methanesulfonic acid, diluted to 25.0 ml, and a portion was transferred to a cuvette containing a drop of tetramethylguanidine. Rates in mixtures of this ratio of methanol:benzonitrile were very slow.

Relationships between Solvent Induced Rate Acceleration and Solvent Catalysis

Unlike catalysis, solvent induced rate acceleration is defined by a single experiment, in which a substrate is observed to react more rapidly when dissolved in a given pure solvent than a reference solvent. A demonstrated solvent induced rate acceleration need not imply the possibility of solvent catalysis. Thus, thermodynamic work may be required to transfer the substrate from the reference to an accelerating solvent, cancelling any lowering of activation energy which results from the solvent change. Because a variety of experiments, both conceptual and practical, can be envisaged to achieve solvent catalysis, a detailed discussion is appropriate. It is meaningless to compare experiments in catalysis without agreeing on a reference state and, for the purposes of this discussion, we take this to be a dilute aqueous solution of substrate. By solvent catalysis we mean a method by which a solvent induced rate acceleration can be used to effect catalysis of the decomposition of substrate, initially present in dilute aqueous solution, without input of thermodynamic work or coupling with other irreversible processes.

For the reaction **1** to **3**, a natural choice of reference solvent is water, in which the reaction is slowest. More generally, water appears to be a natural choice for anion decompositions. For most anions hydrogen bonding appears to be a major stabilizing factor in solvation[12] and the major factor which inhibits reactivity.[2] The most severe test of solvent catalysis is surely that which operates with anions which are initially in their most stable, unreactive state, i.e., in aqueous solution.

Other choices of reference state are of course possible. Many examples of phase transfer catalysis[13] involve a starting state in which anions are in an anhydrous crystal lattice,[14] clearly of higher thermodynamic potential than a dilute aqueous solution. Other phase transfer phenomena[15] involve a reference state in which the anion and reactant of a bimolecular displacement are present in separate phases, and a key catalytic feature is bringing these into a common phase where reaction can occur. Although it is likely that catalysis in the sense of the above definition plays a role in many of the reported cases of phase transfer catalysis, its contribution may be relatively small.[16] Thus Herriott and Picker report a catalytic effect of 10 for the reaction of thiophenoxide with 1-bromooctane.[16]

Three factors determine the relationship between solvent rate acceleration and solvent catalysis: (1) the balance between starting material destabilization and transition state stabilization for the change, water to accelerating solvent; (2) the balance between solvent induced stability changes at the reacting sites and those for the molecule as a whole; and (3) a possible tendency of anions which are strongly hydrogen bonded to carry water molecules from water across solvent boundaries into aprotic solvents.

In the extreme case of a very small reactant which is uncharged, the issue is settled by the first factor. Catalysis can be observed only to the degree that the transition state is stabilized by the solvent transfer. Solvent rate accelerations which are solely the result of starting material destabilization will be precisely mirrored in unfavorable partitioning of starting material into the accelerating solvent and identical reaction rates will be observed in aqueous and nonaqueous phases.

Molecules of a size which have regions remote from the sites of reaction, or charged molecules whose counterions can be selected to yield favorable distribution properties, belong to a more versatile class. Hypothetically a suitable choice of remote substituent or counterion could balance unfavorable partitioning properties of the reactive regions of the molecule by those of the molecule as a whole. Were this the only consideration, any rate acceleration observed in pure solvents should be convertible to catalysis, e.g., with the help of a semipermeable membrane which passes substrate molecules but excludes solvent.

However, if solvent rate acceleration is the result of destabilization of starting material in aprotic solvents through loss of hydrogen bonding at the reactive site, then hydrated substrate may be expected to be unreactive in all solvents. A catalytic experiment involving an anhydrous accelerating solvent then could succeed only with a membrane which excludes both solvent and hydrated substrate. An experiment involving partitioning between water and a solvent saturated with water is expected to fail. (For a classification of the catalytic possibilities, see Table I.)

The latter experiment (Table IB) is the easiest of the possibilities to execute, and we selected it for our studies of the reaction **1** to **3**, despite its likelihood of failure, for the above arguments appear to apply to this reaction. In it, a

Table I. Possible Catalysis Experiments Involving the Partitioning of a Substrate between Water and an Accelerating Solvent

Nonaqueous solvent state and transfer conditions	Practical problems	Hydrogen bonding of substrate in nonaqueous solvent	Experimental outcome	Interpretation
A. Dry accelerating solvent				
1. No solvent transfer; no hydrated substrate transfer	Requires a very selective semipermeable membrane; operationally very difficult	Not possible; no water	Catalysis	Catalysis depends only on a favorable distribution coefficient, controllable by substituent or counterion
2. No solvent transfer; transfer of hydrated substrate	Requires selective membrane; operationally difficult	Uncertain; depends on relative affinity of solvent and substrate for water	Uncertain	Ambiguous; any observed rate acceleration is accompanied by irreversible water transfer
B. Wet accelerating solvent; solvents mutually saturated	Requires an accelerating solvent which does not mix with water	Yes	No catalysis	Unambiguous; inhibition by hydrogen bonding to substrate
		Yes	Catalysis	Unambiguous; H bonding to substrate unimportant; rate attributable to TS stabilization

carboxylate anion (**1**) is converted into carbon dioxide and the highly delocalized phenolate anion **3**. Parker's estimates of ionic distribution coefficients imply that carboxylate anions are strongly destabilized by a transfer from protic to aprotic media, while **3**, and presumably transition state **2**, is expected to show a much smaller energy change and perhaps a stabilization.[2,17] A variety of experiments, particularly those of Kolthoff,[18] establishes that carboxylate anions form strong hydrogen bonded complexes with added protic species in dipolar aprotic solvents.

Despite these arguments against the prospects of catalysis, large catalytic effects are demonstrated in the next section for a simple extraction experiment involving the conversion **1** to **3**.

Results

A. Catalysis by Extraction. As described in the preceding section, the planned catalysis experiment involves partitioning of a salt of **1** between water and a suitable immiscible solvent. Although other solvents doubtless could have been chosen, benzonitrile proved to be convenient, and all our extraction studies were conducted with it.[19] At mutual saturation, benzonitrile is 0.5 *M* in water, and water, 0.012 *M* in benzonitrile. In dry benzonitrile, salts of 3-carboxy-6-nitrobenzisoxazole decarboxylate at 30° with a rate constant of 2.5 $\sec^{-1}$, or 3×10^5 times faster than the rate in water. The possibility of catalysis by simple extraction into a wet solvent is established by the remarkable finding that the rate constant in benzonitrile saturated with water is reduced by only a factor of 5. A similar observation obtains for the acetate ion catalysis of deprotonation of benzisoxazole, which is slowed by only 15-fold by the addition of 0.13 *M* water to benzonitrile (Table II).

Realization of extraction catalysis was achieved using two cations, tetraethylammonium and potassium. When an aqueous solution of 5×10^{-4} *M* 3-carboxy-6-nitrobenzisoxazole was made 0.01 *M* in potassium hydroxide and 0.1 *M* in tetraethylammonium bromide and overlayered with an equal volume of benzonitrile, a rate constant of ca. 4×10^{-1} $\sec^{-1}$ was observed for the overall system, or 5×10^4 times faster than the rate in pure water. Control experiments established that addition of benzonitrile to water up to the point of saturation did not affect the rate, which was independent of the method of agitation, as long as vigorous stirring was maintained. Neither tetraethylammonium bromide nor potassium hydroxide was significantly extracted into the organic phase although, under the experimental conditions of a large excess of organic cation in the aqueous phase, both **1** and **3** were largely present in the benzonitrile.

Table II. Rate Constants for the Decarboxylation of 4 and 5

Solvent	T, °C	k, $\sec^{-1}$ 5	4	1, (X = 6-MeO)
Water (pH 4.5, μ = 1)	50	6.6×10^{-5}	1.3×10^{-6}	6.4×10^{-5}
Water (pH 12.5, μ = 1)	50		4.8×10^{-5}	
Acetonitrile	30	1.7×10^{-1}	3.8×10^{-7}	2.3×10^{-1}
Acetonitrile	50		6.8×10^{-6}	
Me_2SO	30	6.9×10^{-1}	3.6×10^{-5}	1.0
DMF	30	9.2×10^{-1}	8.9×10^{-6}	4.7
DMAc	30	6.2×10^{-1}	1.2×10^{-5}	7.9

With no tetraethylammonium ion present and only 0.05 *M* potassium hydroxide as a source of cations, roughly 0.1% of starting material is extracted into the benzonitrile; under these conditions, an average rate constant of ca. 7×10^{-4} $\sec^{-1}$ was observed, which corresponds to an acceleration of a 100-fold.

Although the data available from these experiments are imprecise, it is nonetheless informative to use them for further calculations. Following Parker,[2] we define $w_\gamma s_{X^+} w_\gamma s_{Y^-}$ as the distribution coefficient (eq 2) for transfer of the salt X^+Y^- from benzonitrile to water. Expression 2

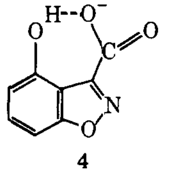
$$w_\gamma s_{X^+} w_\gamma s_{Y^-} = (H_2O_{\gamma X^+}PhCN)(H_2O_{\gamma Y^-}PhCN) = \frac{[X^+]_{H_2O}[Y^-]_{H_2O}}{[X^+]_{PhCN}[Y^-]_{PhCN}} \qquad (2)$$

can be used to characterize the extraction of starting materials and transition states, while the expression of products must be multiplied by the equilibrium concentration ratio for carbon dioxide in these solvents. The latter is not available for benzonitrile but can be estimated as log $w_\gamma s_{CO_2} = -0.5$, which is the value observed for benzaldehyde or for nitrobenzene.[20] Expression 1 was evaluated directly for products by uv assay. For the experiment using tetraethylammonium ion, the fraction of starting material in the aqueous phase is estimated at 10-50%, and the concentration of tetraethylammonium ion in the benzonitrile is estimated at 5×10^{-4} *M;* very roughly then, log $w_\gamma s_{Et_4N^+} w_\gamma s(\mathbf{1}) = 2.5$. For the experiment with potassium cation, the concentration to starting material in benzonitrile can be calculated from the observed rate of reaction and the known rate constant for reaction in wet benzonitrile, in which all of the reaction occurs. A value log $w_\gamma s_{K^+} w_\gamma s(\mathbf{1})$ of 5.4 is obtained.

Following an argument of Parker,[2] one can obtain estimates of $w_\gamma s$ for the transition state. Since starting materials in the two phases are at equilibrium, and each starting material, by the assumption of activated complex theory, must be in equilibrium with its corresponding transition state, the transition state concentrations in the two phases are necessarily also at equilibrium values, even though no transition state ever crosses the phases boundary. The ratio of transition state concentrations must therefore equal the ratio of overall rates of reaction in each solvent phase. The rate in the organic phase is equal to the overall reaction rate for the system; the rate in water may be estimated as the product of the concentration of starting material in water and the known rate constant for reaction in water. For reaction using tetraethylammonium cation, respective values of 2.5, −2.5, and 0.3 are obtained for log $w_{\gamma}s_{\mathrm{Et_4N^+}}w_{\gamma}s_{\mathrm{X^-}}$ for starting material (**1**), transition state (**2**), and product (**3**). For the potassium case, the corresponding values are 5.4, −0.7, and 2.8. In both cases, relative to either starting materials or products, the transition state is seen to be orders of magnitude more stable in benzonitrile.

The results and conclusions of this section may be summarized as follows. The feasibility of catalysis by extraction of the conversion **1** → **3** has been established by the observation that the reaction proceeds very rapidly in benzonitrile saturated with water. Cation dependent extraction catalysis has been demonstrated to result in rate accelerations in the range of 10^2 to 10^4. The rate effects which lead to catalysis result from energy changes on extraction which are peculiar to the transition state and are not shared with starting materials or products. Although the exact balance between transition state stabilizing and starting material destabilizing effects cannot be decided from this evidence alone, the observation that relative stabilizing effects are greater for the transition state than the product makes it certain that a large part of the rate enhancement must be attributed to special stabilizing interactions of the reacting bonds of the transition state with benzonitrile molecules.

B. The Influence of Hydrogen Bonding on Aprotic Solvent Catalysis of the Decarboxylation of 1. Our approach to a resolution of the role of hydrogen bonding in the reaction **1** → **3** is the synthesis and study of 3-carboxy-4-hydroxybenzisoxazole (**4**), a substance which contains its own protic environment. If hydrogen bonding is not an important determinant of solvent rate acceleration, then **4** should show exactly the same pattern of solvent effects as **5**. Large deviations from that pattern should reveal the magnitude of the effect of hydrogen bonding since **4** and **5** would be expected to behave similarly in protic media.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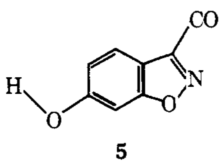
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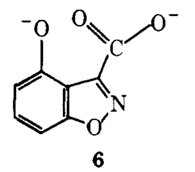

6

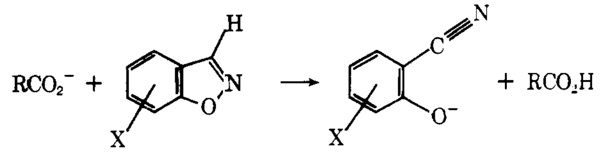
The first and third columns of Table II establish that the 6-hydroxy- and 6-methoxy-3-carboxybenzisoxazoles behave essentially identically in water, acetonitrile, and Me_2SO, although an unexplained deviation of tenfold in rate is observed in DMF and DMAc. The second column provides data which establish the internally hydrogen bonded 4-hydroxy-3-carboxybenzisoxazole to be essentially inert to the catalytic effects of solvent change which are so striking a feature of all other representatives of the class **1**. This extreme effect clearly establishes the relevance of hydrogen bonding as a potent inhibitor of solvent catalysis of the reaction.

Details of the aqueous decomposition of **4** provide further evidence pertinent to this point. The dianion **6** is electronically deactivated, relative to **4** and, barring factors attributable to change in hydrogen bonding, **6** would be expected to be less reactive than **4**. Strikingly, it is a factor of nearly 40-fold more reactive. The conclusion seems unavoidable that the intramolecular hydrogen bond of **4** is a still more potent inhibitor of decarboxylation than are the intermolecular hydrogen bonds formed to the carboxylate anion of **1** by water molecules in water. *From the general behavior of **4**, one can conclude that an anion **1** which is strongly hydrogen bonded will be inert to reaction in any solvent, and the rapid reaction observed in wet benzonitrile implies that as much as 20% of **1** in this solvent must be free of hydrogen bonding.*

Concerning the nature of the inhibition by hydrogen bonding, a pertinent observation is a $\Delta H^{\ddagger}$ value of 27.5 kcal/mol and a $\Delta S^{\ddagger}$ value of +4 eu which are observed for the decarboxylation of **4** in acetonitrile. It will be recalled that nearly invariant $\Delta S^{\ddagger}$ values of +20 eu were found to characterize the decarboxylation reactions of **1** in all solvents.[1]

C. The Generality of Solvent Catalysis of the Decomposition of 1. Central to the interpretation of the results of the preceding sections is the premise that the transfer of charge from the carboxylate anion of **1** to the phenolate anion of **3** and the differing solvation patterns of these anions are the keys to the solvent rate acclerations. Although this assumption finds much precedent in the work of Parker with a variety of nucleophilic substitution reactions, one still could argue that the analogy with his work is forced. Thus, in Parker's cases, carboxylate anions are merely converted to esters, and thereby retain much of their structural features while, in the reaction **1** → **3**, the conversion involves a C-C bond fission and conversion of the anion to carbon dioxide. Conceivably the similarity of solvent effects in the two cases is misleading and, in the benzisoxazole case, the solvent effects are more dependent on internal factors such as the pattern of breaking bonds at the transition state than on the solvation state of starting materials.

Fortunately, the issue can be easily tested, for reaction **7** → **3**, catalyzed by acetate, can be studied in many solvents including benzene using the readily available, anhydrous salt, tetrabutylammonium acetate. Rate constants for the reaction **7** → **3** in six solvents are reported in Table III; those in water are estimated values for three of the substrates, the rates in acetate buffers being too slow for convenient measurement.


7 **3**

The data of Table III establish that an exceedingly large rate increase for the reaction **7** → **3** results if the solvent is changed from protic to aprotic. The measured ratio of rate constants for decomposition of 5,7-dinitrobenzisoxazole in acetonitrile and water is 3 × 10^7. Given the success of a linear Bronsted equation for correlating rates of the deprotonation reactions of benzisoxazoles,[21] we regard the likely accuracy of the estimated rate constants for acetate reactions in water to be high. Using these values, one can compare the log rate ratio for reaction in water and acetonitrile; for **1** → **3** the 5-nitro case gives 5.8; for **7** → **3**, the value is 7.3. Similarly, the hydrogen case gives 5.1 for **1** → **3** and 5.8 for **4** → **3**. For the acetate catalyzed reaction, **7** → **3**, the log rate ratios for acetonitrile and water reactions show the trend, 6.2, 5.8, 7.3, and 7.4 as the benzisoxazole substituent is varied from H to 5,7-dinitro. As with the conversion **1** →

Table III. Rate Constants for the Reaction of Benzisoxazoles with Tetrabutylammonium Acetate in Organic Solvents (T 30°)

	Log k_2, M^{-1} sec^{-1}					
Substituent	Water[a]	CH_3CN	PhH	$Me_2C{=}O$	PhCN	PhCN + 0.13 M H_2O
H	−5.57*	0.18	1.52	1.52	1.26	0.08
5-Chloro	−5.08*	1.15	2.41	2.68	2.15	1.00
5-Nitro	−3.85*	3.45	4.30	5.18	>4	3.36
5,7-Dinitro	−1.70	5.72				

[a] Rate constants in water were estimated from the known pK_a values of the phenols and the measured rate constant for the reaction of sodium acetate in water with 5,7-dinitrobenzisoxazole, with the method of ref 11.

Table IV. Solvent Effects on Rate Constants for Reaction of 5-Nitrobenzisoxazole and Triethylamine (T 25°)

Solvent	k_2, M^{-1} sec^{-1}	Log k_2
Water[a]	0.82	−0.09
Formamide	0.37	−0.43
Acetonitrile	1.8	0.25
Me_2SO	4.3	0.63
DMF	2.8	0.45

[a] T 30°, pH 10.

3, the reaction **7** → **3** is thus seen to become more sensitive to solvent change as the benzisoxazole is made more reactive.

This effect is in accord with the observation of Parker that, relative to other carboxylate anions, acetate ion has the largest change in activity on passage from water or methanol to dipolar aprotic solvents.[2] A carboxylate group bound to a polarizable aromatic group such as a benzisoxazole would be expected to show a smaller change. The benzene anomaly may reflect incomplete dissociation (or formation) of a tetramethylguanidinium ion pair in this solvent for the reaction **1** → **3**; alternatively, acetate ion may show a very large activity change in this nonpolar solvent.

That large rate accelerations with solvent change are not general features of the deprotonation reactions of benzisoxazoles is shown by the data of Table IV; rather than a change of more than 10^7, observed for acetate catalysis, rate constants for catalysis by triethylamine vary by only a factor of 2 from water to acetonitrile and by a factor of 5 for any solvent change. As kinetic bases reacting with benzisoxazoles in water, triethylamine surpasses acetate by roughly 10^4; in acetonitrile, acetate ion is superior by 10^3.

Discussion and Summary

The following points have been established. (1) A large rate acceleration for the reaction **1** → **3** is observed in benzonitrile saturated with water, with pure water as reference solvent. (2) Extraction of **1** from water to benzonitrile results in cation dependent rate accelerations of 10^2 to 10^4 fold. Relative to water, wet benzonitrile stabilizes the transition state **2** more than the product **3**. (3) By means of the model **4**, a strong hydrogen bond to the carboxylate anion of **1** has been shown to inhibit the conversion to **3** in all solvents. (4) The solvent rate acceleration seen for **1** → **3** is also observed for the acetate catalyzed reaction **7** → **3**.

Confining attention only to results 1 and 2, one can propose only three formal rationalizations. One could postulate that, contrary to data of Parker and others, destabilization of carboxylate anions through loss of hydrogen bonding is not a major determinant of the large rate accelerations observed in dry aprotic solvents, and therefore water in wet solvents has little effect on rate. Rejecting this position, one could argue for either of two alternatives. One is that hydrogen bonding exists in wet benzonitrile, does effect carboxylate stabilization, but is without effect on activation energies because of a fortuitous extra lowering of transition state energy which results from the presence of water. The other is that despite the demonstrated affinity of carboxylate groups for protic species, a significant fraction of **1** in fact must lack hydrogen bonds in wet benzonitrile. From result 3, the first two of these rationalizations must be rejected. The third therefore must be correct.

This explanation requires that equilibrium 3

$$(R\text{-}CO_2^- \cdot H_2O)_s \rightleftarrows (RCO_2^-)_s + (H_2O)_s \qquad (3)$$

is strongly solvent dependent. Since the chemical potentials of water in pure water and in water-saturated benzonitrile are identical, a simple thermodynamic cycle establishes that for the fraction of $(RCO_2^-)_s$ in the organic phase to increase, its affinity for water in that phase must decrease from the affinity seen in pure water. This surprising result finds some support in other studies. Grunwald[22] has argued from thermodynamic evidence that, in dioxane-water mixtures, the solvation shell of anions is similar in composition to that of the bulk solvent, no selective affinity for water being detected. Similar conclusions have been reached by Stengle et al.[23] for Me_2SO-water and acetonitrile-water mixtures, using an NMR technique.

It is now clear that the reaction **1** → **3** is sensitive to all of the factors which have been invoked previously to explain solvent rate accelerations, and yet the balance between these effects which lead to catalysis appears to be more subtle than could have been predicted from earlier work. Hydrogen bonding at the carboxylate site of **1** results in selective stabilization which inhibits the reaction. Hydrogen bonding also appears to alter the structure of the transition state **2**. From the observed rate data, it is likely that the value of $w_\gamma s$ for the water-benzonitrile partitioning of the transition state derived from **4** must differ by at least 10^5 from that observed for **2**. Moreover, the entropy of activation of only +4 eu observed for the decomposition of **4** must be contrasted with the value of +20 eu which was observed for all decompositions of **1**. Hydrogen bonding appears to result in a tighter transition state which is not as susceptible to stabilization by dipolar aprotic solvation.[24] Thus a peculiarity of wet benzonitrile which allows the existence of anions, free of hydrogen bonds, results directly or indirectly in the catalysis observed in the extraction experiment.

By contrast, the nonhydrogen bonded transition state **2** is highly susceptible to stabilization in aprotic solvents—strikingly, to a greater degree than the polarizable product **3**. Dispersion interactions between solvent and transition state must be the source of this stabilization. Grunwald has discussed the relevance of these effects to related problems[26] and, in this connection, it is important to recall the range of rate constants observed for **1** to **3** among ethers as solvents and the rate maxima observed with certain solvent mixtures.[1] Energy changes for **2** are undoubtedly maximal for certain structural patterns of solvation and, since a transition state is expected to be an unusually polarizable molecule in the vicinity of certain of its bonds, the precise matching of complementary regions of solvent polarizability may have large stabilizing effects. Until it becomes possible to tailor rigid solvent environments for the reaction, this point must remain speculative.

An intriguing final point concerns the transition state structure **2** in protic media. The 60-fold slower rate observed for **4** vs. **5** or **1** (X = 6-MeO) in water as a solvent implies that the internal hydrogen bond of **4** is a more effective inhibitor of reaction than are intermolecular hydrogen bonds.[27] The +20 eu observed for the decarboxylation of **1** in water[1] is most consistent with a nonhydrogen bonded transition state. Conceivably, the reactions of **1** in protic media involve a medium-dependent equilibrium which generates a minute amount of nonhydrogen bonded **1**, followed by conversion of the latter to a transition state. Rate variation among protic solvents can then be rationalized in terms of solvent effects on either equilibrium.

Although other systems must be tested to support the premise, we think it likely that the catalytic features of the conversions **1** to **3** and **7** to **3** are general features of anionic transformations and some anion-cation reactions. To the degree that such reactions appear in enzymatic transformations, the conclusions of this study must be relevant to development of a mechanistic understanding of enzymes. Probably the clearest analogy now available is provided by Leinhard's observation of a solvent induced rate acceleration for the decarboxylation of the TPP pyruvate adduct.[28]

Two of our findings may be useful for the synthesis of working enzyme models. Because transition state stabilization effects which result from solvation can exceed those for products, it is probable that product inhibition need not be a serious complication for related systems designed for practical catalysis. Because the hydrogen bonding tendencies of anions are functions of solvating environment and reactive anions are thereby accessible in the proper solvent, even in the presence of water, solvent rate accelerations can be rendered catalytic.

A major uncertainty which remains is the nature of the solvent which can be employed in catalytic experiments. Benzonitrile can be saturated with water at low concentrations, presumably retaining much of its anhydrous structure. As a nitrile, it can be classed as a protophobic solvent.[29] It is possible that wet protophylic solvents,[29] such as amides and sulfoxides, may prove to be noncatalytic, even when laden with large hydrophobic groups to render them water immiscible. Given our lack of a satisfactory intuitive model for solvation in solvent mixtures, the issue awaits experimental resolution.

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