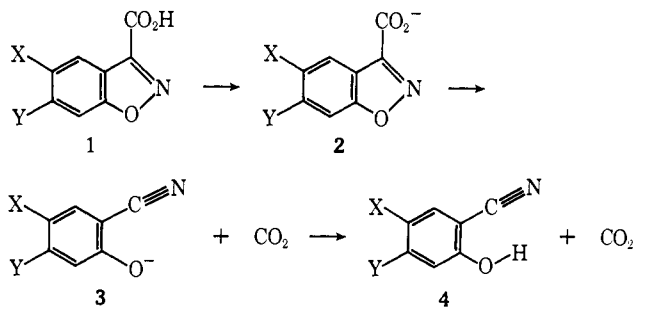
Decarboxylation of Benzisoxazole-3-carboxylic Acids. Catalysis by Extraction of Possible Relevance to the Problem of Enzymatic Mechanism

Sir:

As part of a mechanistic study of benzisoxazole decompositions[1] we have examined the reaction **1** → **4**,[2] which provides a striking example of acceleration of rate by solvent.[3] In water the substances **1a–g** undergo



1 **2** **3** **4**

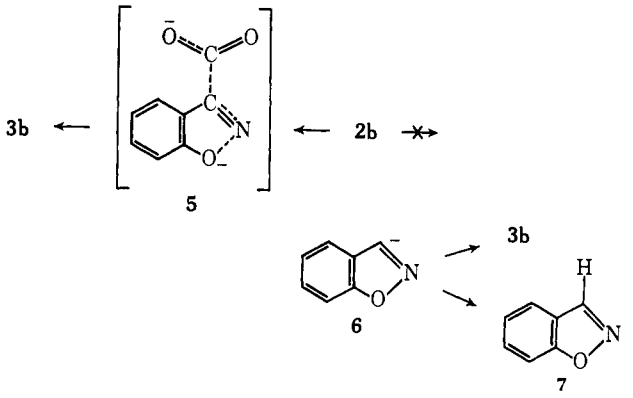
a, X = H; Y = NH_2
b, X = Y = H
c, X = H; Y = OMe
d, X = H; Y = Cl
e, X = H; Y = NO_2
f, X = NO_2; Y = H
g, X = NO_2; Y = NO_2

a slow ($t_{1/2}$ for **1b** 7 days at 30°), quantitative decarboxylation to yield **3** or **4**. Over the aqueous pH range the rates are given by expression 1 where K_a is the measured dissociation constant of **1**. For decarboxylation of **2b** H_2O, μ = 1, 30–50°, $\Delta H^{\pm}$ =

$$k_{obsd} = k_0 \frac{K_a}{K_a + H^+} \qquad (1)$$

32 kcal/mol and $\Delta S^{\pm}$ = 19 eu; rates are unaffected by changes in salt concentration, nor is a rate increase observed at pH 2 when phosphoric acid concentration is changed from 0.005 to 0.5 *M*. When **2b** was decomposed in tritiated 0.5 *M* phosphoric acid no tritiated **7** was detected, implying a product ratio of **3b** to **7** of at least 10^5; *ca.* 10^9 sec^{-1} may be assumed for the protonation rate constant of **6** under these conditions,[4] and consequently the conversion **6** to **3b** must occur with a rate constant of at least 10^{14} if **6** lies on the path connecting **2b** and **3b**. The transformation **2b** → **3b** is thus established as occurring *via* the transition state **5**. The Hammett ρ of 1.4 observed for the reactions of **1a–g** in water, 30°, indicates that appreciable negative charge appears at the ring oxygen of **5**.

The conversion of **1** to **4** in water is thus seen to involve a slow transformation of **2** to **3** which is uncatalyzed and unaffected by small medium changes. On the other hand dramatic rate accelerations result if water is replaced by aprotic solvents. For most of the solvents of Table I no rate change occurs when tetramethylguanidine is replaced by the weaker and



3b ← **5** → **2b** (↛)

6 → **3b**, **7**

differently structured base, triethylamine, and it thus seems likely that the reported rates apply to dissociated salts.

Table I.[a] Rates of Decarboxylation of 6-Nitrobenzisoxazole-3-carboxylate (**2e**)

Solvent	k, sec^{-1}	ρ[b]	Solvent	k, sec^{-1}	ρ
H_2O	7.3×10^{-6}	1.4	MeCN[c]	2.9	1.9
MeOH	2.5×10^{-4}	1.6	DMSO[d]	10	2.0
$HCONH_2$	7.4×10^{-4}		Me_2CO[c]	24	2.2
EtOH	1.0×10^{-3}	1.9	DMF	37	2.0
C_6H_6[c]	4.8×10^{-3}		TMSO	64	2.1
HCONHMe	8.1×10^{-3}		DMAc	160	2.4
$MeNO_2$	5.8×10^{-1}	1.9	NMP	250	2.1
C_6H_5CN[c]	2.5		HMPA	700	2.4

[a] Temperature 30°; TMSO = tetramethylene sulfone, NMP = N-methylpyrrolidone, HMPA = hexamethylphosphoramide; fast rates were measured with a Durrum–Gibson stopped-flow spectrometer by mixing equal volumes of solvent containing 10^{-4} *M* **1** and 0.001 *M* p-toluenesulfonic acid with solvent containing 0.0015 *M* tetramethylguanidine. [b] ρ values are based on rates for **1a–e**. [c] Solvent gave a slower rate when tetramethylguanidine was replaced by excess triethylamine. [d] Rate constants of 3.0, 2.8, and 3.9 sec^{-1} were observed in DMSO containing, respectively, 0.25 *M* $LiClO_4$, $NaClO_4$, and $KClO_4$.

From the work of Parker and others,[5] carboxylic acid anions are believed to be much less stable, relative to resonance-stabilized phenolate anions, in dipolar aprotic than in protic solvents, and solvent rate accelerations for anion-exchange reactions are frequently known to show the pattern and magnitude of those of Table I. This example of a large solvation effect is notable for its ease of study and for its accommodation of rate-enhancing substituents which have a minimal effect on the environment at the site of reaction. Thus the Hammett ρ values reveal that the largest sensitivity of rate to substituent is shown by substrate in the most activating solvent, an expected result, since electron-withdrawing substituents must further delocalize the charge of **5** and increase its differentiation from **2** by solvent.

The appearance of the water-immiscible benzonitrile among the activating solvents prompts the question whether marked rate increases can be realized simply by extraction of a suitable salt of **2** from water into a second phase. If the major determinant of solvent rate accelerations is the instability of highly localized, hy-

(1) D. S. Kemp, *Tetrahedron*, **23**, 2001 (1967); M. T. Link, Ph.D. Thesis, Massachusetts Institute of Technology, 1968.

(2) H. Lindemann and H. Cissée, *Justus Liebigs Ann. Chem.*, **469**, 44 (1929); for reviews, see K. H. Wünsch and A. J. Boulton, *Advan. Heterocyclic Chem.*, 277 (1967); A. Quilico, *Chem. Heterocyclic Compounds*, **17**, 161 (1962).

(3) Substances **1a–g** were prepared by the methods of ref 2; new compounds gave satisfactory elemental analyses.

(4) M. Eigen, *Angew. Chem. Int. Ed. Engl.*, **3**, 1 (1964).

(5) A. J. Parker, *Advan. Phys. Org. Chem.*, **5**, 173 (1967); A. J. Parker and R. Alexander, *J. Amer. Chem. Soc.*, **90**, 3313 (1968); R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *ibid.*, **90**, 5049 (1968).

drogen-bond free anions in aprotic solvents, then an extraction into a nonaqueous phase containing water at unit activity should result in a negligible rate increase.

In fact, when **2e** is stirred rapidly at pH 10, 25°, in a water–benzonitrile emulsion containing 0.2 *M* tetraethylammonium chloride, **3e** is formed with a half-time of *ca.* 1 sec, and the presence of benzonitrile results in a rate acceleration of 10^5. Both the tetraethylammonium salts of **3e** and of models for **2e** are extracted quantitatively from water into benzonitrile. However, even with the potassium salt of **2e**, which together with the salt of **3e** is largely in the water phase, a rate acceleration of at least 100-fold results upon addition of benzonitrile. These results imply[6] a very small solvent activity coefficient for **5** in benzonitrile, relative to water.

Together with recent findings on the structure of hydrated ions in aprotic solvents[7] these extraction experiments suggest changes in the interpretation of the nature of at least some large solvent rate effects. More importantly, they provide evidence for a catalytic effect of probable relevance to many bioorganic mechanisms. Benzonitrile may be regarded as a model enzyme for the transformation **2** → **3**, and similar medium effects may be expected to play integral roles in actual enzyme-catalyzed processes involving charged substrates or intermediates.

(6) Reference 5a, p 181.

(7) C. H. Langford and T. R. Stengle, *J. Amer. Chem. Soc.*, **91**, 4016 (1969).

(8) A. P. Sloan Fellow, 1968–1970. Financial support through National Institutes of Health Grants GM 13453 and GM 15944 and National Science Foundation Grant GP 8329 is gratefully acknowledged.

(9) National Science Foundation Predoctoral Fellow, 1966–1969.

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Base Catalysis of Thiazolium Salt Hydrogen Exchange and Its Implications for Enzymatic Thiamine Cofactor Catalysis

Sir:

The hydrogen exchanges of hetercyclic cations have received much attention[1] since Breslow's observation[2] of the base-catalyzed equilibration in water of the 2 proton of thiazolium salts and the application of his finding to the elucidation of several thiamine-dependent enzyme processes.[3] Since heterocyclic ylides appear to be largely inductively stabilized, they may provide an interesting foil for the more exhaustively studied enolates[4] for formulations of the mechanics of aqueous proton transfers involving carbon acids.

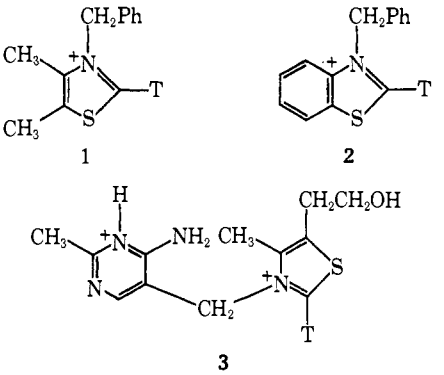
(1) R. A. Olofson, J. M. Landesberg, K. M. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.*, 88, 4265 (1966); R. A. Olofson and J. M. Landesberg, *ibid.*, **88**, 4263 (1966); R. A. Olofson, J. S. Michelman, and W. R. Thompson, *ibid.*, **86**, 1865 (1964); P. C. Haake, L. P. Bausher, and W. B. Miller, *ibid.*, **91**, 1113 (1969); H. A. Staab, M.-Th. Wu, A. Mannschreck, and G. Schwalbach, *Tetrahedron Lett.*, 845 (1964); H. W. Wanzlich, *Angew. Chem.*, **74**, 127 (1962).

(2) R. Breslow, *J. Amer. Chem. Soc.*, 79, 1762 (1957).

(3) For reviews, see: (a) R. Breslow, *Ann. N. Y. Acad. Sci.*, **98**, 445 (1962); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. II, Benjamin, New York, N. Y., 1966, pp 214–226; (c) F. H. Westheimer in "The Enzymes," Vol. I, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed, 2nd ed, Academic, New York, N. Y., 1959, p 287.

(4) For reviews, see: (a) M. Eigen, *Angew. Chem. Int. Ed. Engl.*, **3**, 1 (1964); (b) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter X; W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 3.

We wish to report kinetic isotope effects and approximate Brønsted coefficients for aqueous exchange reactions of the thiazolium salts **1** and **2**. From the tabulated data it is clear that the Brønsted β values for these exchanges are nearly unity and that hydroxide



catalysis overwhelms reactions with other bases over the entire aqueous pH range. Since the rate constant for protonation of thiazolium ylides may be assumed to be 10^{10}–10^{11} M^{-1} sec^{-1},[4a,5] from the water catalytic constants of Table I, one can estimate pK_a values

Table I. Detritiation of **1**, **2**, and **3** in H_2O, 30°, μ = 1.0 (NaCl)

Salt	Catalyst	k, M^{-1} sec^{-1}	k_H/k_T	Brønsted β
1-Br$^-$	OH$^-$	6.0×10^4	2.7[a]	
	Acetate[b]	$<1 \times 10^{-5}$		>0.9
	Water[c]	$<3 \times 10^{-11}$		
2-Br$^-$	OH$^-$	1.8×10^6	4.8[a]	
	Acetate[b]	8×10^{-4}		
	Methoxyacetate[b]	6×10^{-5}		>0.9
	Water[c]	6×10^{-9}		
3-2Cl$^-$	OH$^-$	7.5×10^5		
	Water[c]	$\sim 1 \times 10^{-9}$		

[a] Measured in D_2O; rate of disappearance of the 2-proton nmr signal gave k_H; appearance of DTO gave k_T. [b] For **1**, pH 3.5, catalysis by 0.1 *N* acetate did not exceed 15% of overall rate; for **2**, acetate catalysis (0.1 *N*) contributed 40% to the rate at pH 3.3, and methoxyacetate catalysis (0.1 *N*) 30% at pH 2.4. [c] At pH 1.0 and 0, rate constants of 1.5×10^{-8} and 3.3×10^{-9} sec^{-1} were observed for detritiation of **1**; at pH 0.8, a rate constant of 6.6×10^{-7} sec^{-1} was observed for the detritiation of **2**; at pH 1.0 and 0, rate constants of 2.8×10^{-7} and 9.7×10^{-8} sec^{-1} were observed for detritiation of **3**. Water catalytic constants were estimated by subtracting the hydroxide contribution, k_{OH}-[OH$^-$], from each of the above values.

for the thiazole 2 protons of **1**, **2**, and **3** to be 18–20, 16–18, and 17–19, respectively. From the hydroxide catalytic constants, the rates of protonation of the ylides of **1**, **2**, and **3** by water may be estimated to be 10^{10}–10^{11} sec^{-1}, 10^9–10^{10} sec^{-1}, and 10^9–10^{11} sec^{-1}. These values lie close to diffusion-controlled limits, and the observed isotope effects are probably best regarded as determined by equilibrium, not kinetic, factors.[6]

(5) This assumption rests on the probable localized character of thiazole ylides and on Eigen's nearly universal finding of diffusion control for rates of proton transfers involving hydronium ion. Should the reprotonation rates be slower, the pK_a values are overestimated, but the finding of a nearly constant catalytic constant for ylide protonation remains valid; the minute isotope effects observed for **1** and **2** are difficult to rationalize.