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.

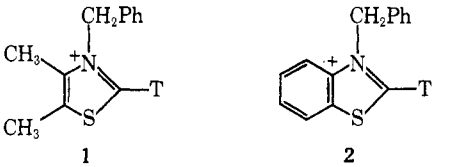
(1) R. A. Olofson, J. M. Landesberg, K. M. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.*, **88**, 4265 (1966); R. A. Olofson and J. M. Landesberg, *ibid.*, **88**, 4263 (1966); R. A. Olofson, J. S. Michelman, and W. R. Thompson, *ibid.*, **86**, 1865 (1964); P. C. Haake, L. P. Bausher, and W. B. Miller, *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



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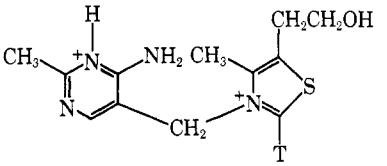

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catalysis overwhelms reactions with other bases over the entire aqueous pH range. Since the rate constant for protonation of thiazolium ylides may be assumed to be 10^{10}–10^{11} M^{-1} sec^{-1},[4a,5] from the water catalytic constants of Table I,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

The ylides from **1**, **2**, and **3** are stronger bases than hydroxide by only 2–4 pK_a units, yet react with water with limiting rates. It therefore seems likely that an Eigen plot[4a] of log k *vs.* ΔpK_a for these reactions will show an abnormally small pK_a region for which neither forward nor reverse rates are limiting. We conjecture that high rates for proton transfers with small driving forces will prove general for highly localized carbanions reacting in protic media, and that the moderate activation required for proton transfers between oxygen anions of comparable strength[4a] may reflect the strengths of hydrogen bonds to these anions, rather than a general property of aqueous proton transfers.

The above data set limits on the rates of reactions catalyzed in water by thiazolium yields. For example, for diffusion-controlled reaction of the ylide from **1** with a substrate S at pH 7, the maximum rate is (10^{-2}–10^{-3})[S][**1**] M sec^{-1} in water and (10^{-1}–10^{-2})[S][**1**] M sec^{-1} in 50% ethanol.[7] The observed rate constant for formation of benzoin from 1 M benzaldehyde at 30° in 50% ethanol containing 0.1 M **1**, pH 7.5, is 3×10^{-6} M^{-1} sec^{-1}, which is only 10^4–10^5 slower than the maximum estimated above for rate-determining ylide attack.

By contrast, yeast pyruvate decarboxylase, a thiamine pyrophosphate dependent enzyme, reacts with 0.01 M pyruvate at pH 6, 30°, with a turnover number of *ca.* 50 sec^{-1}.[8] The enzyme-mediated reaction of thiamine with pyruvate is thus seen to be at least 10^4 times faster than the maximum rate possible with **1** in water, and 10^3 times faster than the maximum possible with **3**.[9] Although this comparison involves assumptions which might result in order of magnitude errors, the scale of this rate ratio establishes the presence within the enzyme of a far higher concentration of thiamine ylide than can be realized in water. Thus a major role of the enzyme must be to change the relative thermodynamic stabilities of thiamine and its ylide, perhaps by juxtaposing an oxyanion and the thiamine cation in a relatively nonpolar environment. Conversely, the rapid uncatalyzed reaction observed in water between the ylide of **1** and the relatively unreactive carbonyl compound, benzaldehyde, together with the high β for ylide formation (which precludes general-base-catalyzed rate increases of any magnitude), independently imply that marked mechanistic catalysis during enzymatic addition of thiamine to pyruvate is rather unlikely. It appears that pyruvate decarboxylase may catalyze the initial step of its reaction sequence simply by providing a medium which shifts an equilibrium.

(6) For discussion of a related situation, see E. A. Walters and F. A. Long, *J. Amer. Chem. Soc.*, **91**, 3733 (1969).

(7) Calculated from the observed exchange rate in 50% ethanol, assuming the ylide protonation rate to be that observed in water.

(8) J. Ullrich, J. H. Wittorf, and C. J. Gubler, *Biochim. Biophys. Acta*, **113**, 595 (1966).

(9) It should be noted that **1** may be a more appropriate model for enzymatically bound thiamine pyrophosphate than the protonated thiamine **3**.

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

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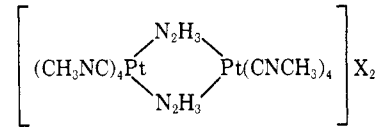
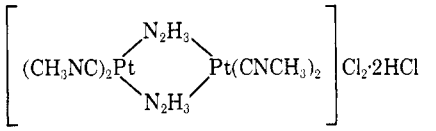
Palladium and Platinum Complexes Resulting from the Addition of Hydrazine to Coordinated Isocyanide

Sir:

In 1925 Chugaev and coworkers reported[1] that treatment of tetrakis(methyl isocyanide)platinum(II) with hydrazine produced a red, crystalline complex, A, which was formulated on the basis of analytical and conductivity data as **1**. Treatment of this salt with hydrochloric acid led to the evolution of methyl isocyanide and the formation of yellow crystals, B, which were formulated as **2**. The yellow crystals, B, could be converted back into the the red form, A, by



1, X = Cl^-, I^-, ClO_4^-, N_3^-



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treatment with methyl isocyanide and aqueous base. Since compounds containing coordinated molecular nitrogen[2a] or diazene[2b] have been prepared by treating certain transition metal complexes with hydrazine, we suspected that Chugaev's nitrogen-rich compounds might also contain an oxidized form of hydrazine. However, investigation has revealed that these complexes contain a novel ligand which is formed by the insertion of hydrazine into two methyl isocyanide moieties.

We have confirmed the experimental findings of Chugaev, *et al.*[1] In addition analogous complexes have been prepared with palladium(II), but not with nickel(II). Methylhydrazine, phenylhydrazine, or hydroxylamine also react with tetrakis(methyl isocyanide)-platinum(II) to produce analogs of A; these complexes also yield analogs of B on treatment with hydrochloric acid. Both A and B and their analogs exhibit infrared absorptions in the 3400–3300-cm^{-1} region which indicate the presence of N–H groups. The infrared spectra of A and its analogs also exhibit two bands in the 2330–2370-cm^{-1} region which are assigned to the CN stretch of two *cis* methyl isocyanide ligands, but no infrared absorptions are found in the region 3000–1650 cm^{-1} for B and its analogs. Consequently it is apparent that the formation of these compounds has involved a reaction of the isocyanide triple bond. In order to ascertain the nature of the product, an X-ray study has been carried out on the palladium analog of B.

The complex $[(CH_3)_2C_2N_4H_4]PdCl_2$ crystallizes as very fine, yellow needles in the orthorhombic space

(1) L. Chugaev, M. Skanavy-Grigorieva, and A. Posniak, *Z. Anorg. Allg. Chem.*, **148**, 37 (1925).

(2) (a) A. D. Allen, F. Bottomley, R. O. Harris, V. P. Reinsalu, and C. V. Senoff, *J. Amer. Chem. Soc.*, **89**, 5595 (1967); Yu. G. Borod'ko, V. S. Bukreev, G. I. Kozub, M. L. Khideke', and A. E. Shilov, *Zh. Strukt. Khim.*, **8**, 542 (1967); A. D. Allen and J. R. Stevens, *Chem. Commun.*, 1147 (1967); J. E. Fergusson and J. L. Love, *ibid.*, 399 (1969); J. T. Moelwyn-Hughes and A. W. B. Garner, *ibid.*, 1309 (1969); (b) G. C. Dobinson, R. Mason, G. B. Robertson, R. Ugo, F. Conti, D. Morelli, S. Cenini, and F. Bonati, *ibid.*, 739 (1967).