resulted gave the known phosphonate **2** and 1 equiv of triethylamine hydrochloride.

Several attempts to prepare a diamide such as **8** were unsuccessful. Treatment of **5** with 2 equiv of 3,4-dichloroaniline afforded only the carboxamide derivative **4j** upon workup. Similarly, treatment of **7** with 2 equiv of *p*-toluidine gave only carboxamide **4** after workup.

Experimental Section[10]

Infrared spectra were obtained on a Perkin-Elmer 727B spectrophotometer. ^{1}H NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 solutions with a Varian T-60 or EM-360 spectrometer; chemical shifts are reported in parts per million downfield from Me_4Si. Combustion analyses were performed by Atlantic Microlabs, Atlanta, Ga.

1-Ethoxy-2,1-benzoxaphosphol-3-one 1-Oxide (1). A solution of 17.8 g (0.069 mol) of 2-(diethoxyphosphinyl)benzoic acid (**2**) in 27 mL of purified thionyl chloride[11] was refluxed under a nitrogen blanket for 0.75–1.0 h. The pale straw-colored solution was cooled and concentrated to dryness in vacuo. A few milliliters of benzene was added to the residue, and the solution was concentrated again to remove residual thionyl chloride. Purification was completed by holding the product under vacuum (0.55 mm) at room temperature for 1 h. A white crystalline product (14.1 g, 97%), mp 104–107 °C, was obtained: NMR ($CDCl_3$) δ 1.4 (t, 3, J = 7 Hz), 4.1–4.7 (q, 2), and 7.8–8.3 (m, 4). The product was stored in a stoppered flask under vacuum until used.

General Procedure for 2-Phosphonobenzamide Derivatives.[4] A solution of 3.5 g (0.0165 mol) of 1-ethoxy-2,1-benzoxaphosphol-3-one 1-oxide (**1**) and 0.033 mol of amine in 25 mL of chloroform was refluxed for 1 h. The solution was cooled and concentrated to a glass-like residue on a rotary evaporator. This material, the monoethyl phosphonate ester, was hydrolyzed in 10 mL of ethanol containing 3 mL of 0.5 M hydrochloric acid and about 10 mL of water. The hydrolysis was complete after heating for 0.5 h on a steam bath. The product (**4**) crystallized from the solution; or if not, it was concentrated to dryness and crystallized from aqueous ethanol or ethylacetate–cyclohexane.

General Procedure for 2-Aryl-1-ethoxy-2-azaphosphinolin-3-one 1-Oxide Derivatives (6). A solution of 0.012 mol of amine or hydrazine and 0.025 mol of triethylamine in 50 mL of benzene was added dropwise with stirring to a solution of 0.012 mol of 2-(chloroethoxyphosphinyl)benzoyl chloride (**5**) in 50 mL of benzene. A slight exotherm occurred during the addition period. The mixture was then heated to reflux for 1.5–2 h. The mixture was cooled to room temperature, and triethylamine hydrochloride was filtered off. The benzene filtrate was washed with 50 mL water, dried over sodium sulfate, filtered, and concentrated to dryness. The residue was crystallized from ethyl acetate–cyclohexane.

Registry No.—**1**, 67873-07-8; **2**, 22537-93-5; **4a**, 67872-84-8; **4b**, 67872-86-0; **4c**, 67872-88-2; **4d**, 67872-90-6; **4e**, 67872-92-8; **4f**, 67872-93-9; **4g**, 67872-95-1; **4h**, 67872-97-3; **4i**, 67904-76-1; **4j**, 67872-99-5; **4k**, 67873-00-1; **4l**, 67873-01-2; **4m**, 67873-03-4; **5**, 67873-08-9; **6a**, 67904-77-2; **6b**, 67904-78-3; **6c**, 67873-04-5; **6d**, 67873-05-6; **6e**, 67873-06-7.

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Restricted Rotation of the Amino Group Bonded to Thiamin and to 2-(1-Hydroxyethyl)thiamin and the Question of Intramolecular Amino Group Catalysis

John A. Zoltewicz,* Thomas D. Baugh, and Roy W. King

Department of Chemistry, University of Florida, Gainesville, Florida 32611

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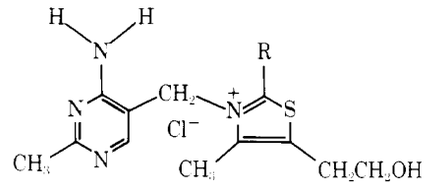
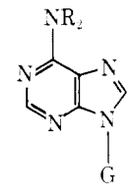
A controversy of long standing concerns the role of the amino group of thiamin or vitamin B_1 (**1**) and its biochemically important derivative 2-(1-hydroxyethyl)thiamin (**2**).[1] The



1. R = H
2. R = CH(OH)CH$_3$



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dispute deals with whether or not this substituent serves as a base in intramolecular deprotonation reactions[2-4] involving both enzymic and nonenzymic systems. It is said that the amino group of **1** may deprotonate the thiazolium ion ring at position 2 to produce an ylide and that the amino group of **2** may remove a proton from the carbinol carbon of the 1-hydroxyethyl substituent to form an "enamine" intermediate.

We report results of the first low temperature NMR investigation of **1** and **2**. Our observations reveal that rotation of the amino groups in these molecules is markedly restricted. Moreover, with a knowledge of the barrier to rotation and with information on related molecules already in the literature, we are able to estimate for the first time the pK_a of the amino substituents. These estimates allow us to make clear statements about intramolecular general base catalysis in enzyme-free systems.

Results and Discussion

Hydrochlorides of both salts are sparingly soluble in dry methanol but readily yield 0.3 M solutions when neutralized and buffered by 0.4 M 1,4-diazabicyclo[2.2.2]octane (Dabco).[5,6] At ambient temperatures, the signals of the amino protons are broad, owing to rapid exchange with the solvent.[2] But as the temperature is lowered and the rates of proton exchange decrease, these signals sharpen considerably, having, for example, a width at half-height of 8 Hz at −20 °C. Additional cooling leads to a separation of the singlet into two separate signals; integration with respect to the carbon-bonded proton of the pyrimidine ring shows that each signal is associated with one proton. As temperatures are reduced well below that for coalescence, differences in chemical shifts increase; the signal at lower field undergoes a larger shift. Relevant data for the reversible changes are given in Table I.

Variations in chemical shifts below coalescence largely reflect hydrogen bonding. In order to determine whether Dabco influences the chemical shifts of the amino protons, a sample

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Table I. Coalescence Temperatures and Chemical Shifts of the Amino Group Protons of 1 and 2 in CH_3OH

compd	coalescence temp, °C	chemical shifts, δ (Hz[a])
1	−34 ± 0.8[b]	−44 °C: 7.69, 7.45 (10.5) −54 °C: 7.83, 7.47 (12.5)
2	−40 ± 0.5[b]	−49 °C: 7.82, 7.38 (15) −58 °C: 7.94, 7.43 (16)

[a] Width at half-height. [b] Average of 2 determinations.

of 1 liberated from its hydrochloride prior to use and free of Dabco was examined. Shift differences and also the coalescence temperature were the same as before, suggesting that the solvent rather than Dabco is chiefly involved in hydrogen bond formation. A small but significant contribution to the line width is due to J_{HNH}.[7]

Signals of the diastereotopic methylene protons of **2** dissolved in CD_3OD were observed over a range of temperatures down to −55 °C. No significant change in chemical shift or coupling constant was detected for these or other carbon-bonded protons. Similarly, no change was found for 1 in CH_3OD.[8] Importantly, chemical shifts and coupling constants for both compounds in methanol are essentially the same as those for aqueous solutions buffered to neutralize hydrochlorides. There is no evidence of thiazole ring cleavage[9] or cyclization,[10] which is reported for highly basic solutions. Chemical forms of samples in methanol are correctly symbolized by **1** and **2**.

Rate constants of 65 and 92 s^{-1} as well as free energy barriers of 11.9 and 11.4 kcal mol^{-1}, respectively, are calculated in the usual way at the coalescence temperatures using chemical shift differences observed approximately 20 °C below coalescence. Rate constants include a small correction to reflect premature coalescence of the wide peaks.[11]

Observed barriers to rotation must primarily reflect conjugation between the amino group and the electron-withdrawing pyrimidine ring, which gives rise to a partial exocyclic double bond and not to interactions between the amino group and the adjacent thiazolium ion ring. This conclusion is supported (a) by mutually complementary X-ray structural and NMR chemical shift data which indicate that the main conformations of both molecules, although different, have the amino group directed away from the neighboring thiazolium ion ring,[4,12] (b) by the similar barriers for **1** and **2**, and (c) by a similar free-energy barrier for rotation of the dimethylamino group in the related compound 4-dimethylaminopyrimidine, which does not have an adjacent substituent.[13]

On the assumption that the barrier to rotation reflects not only electron delocalization but also the basicity of the amino site, we make the following comparison which provides estimates of the pK_a values. The free-energy barrier to rotation of the amino substituent of adenines (**3**) is in the range 12.5–13.5 kcal/mol.[14] The pK_a of the amino group of **3**, recently estimated with the aid of a linear free-energy relationship, is about −2 to −3.[15] Therefore, in view of the similar rotational barriers for **1** and **2**, the pK_a values of their amino substituents are likely to be alike as well,[16] placing them near that for water and well outside the range of catalytically active sites in chemical and biochemical reactions.[25]

In reactions not involving enzymes, the amino group of **1** has not been found to serve as a kinetically significant general base toward the adjacent thiazolium ion ring. Deprotonation of **1** at position 2 to give an ylide is catalyzed essentially by lyate ion; the Brønsted β value is about 1.[18] Deprotonation of **2** at the carbinol carbon to give an enamine has been studied less extensively; this reaction is general base catalyzed.[2] Experimental evidence is not yet available to indicate whether or not the amino group of **2** can serve as an intramolecular base in competition with other bases.

Our estimate of the very low basicity of the amino groups of these molecules along with the increasingly advanced view that intramolecular general base catalysis offers only a very modest kinetic advantage, usually less than about a factor of 100 over a similar bimolecular reaction,[17] allows us to make the following statements. In the case of **1**, the absence of intramolecular catalysis in ylide formation is not surprising. The low basicity and the small kinetic advantage associated with intramolecularity as well as the large β value all militate against the amino group competing successfully with lyate ion in such a reaction. The same considerations apply to **2**. Although the expected smaller β value helps to minimize low reactivity associated with low basicity, we suggest that it will be difficult to find conditions where the amino group will compete with lyate ion and/or buffer base in enamine formation.[19]

Our view is not in conflict with a well-established intramolecular reaction involving the amino group of **1**. Thus, when the hydrochloride of **1** is added to an alkaline solution, a transient yellow color appears. This color is associated with an intermediate formed by the addition of the amino group to the C-2 position of the thiazolium ring, leading to a new six-membered ring.[9,20] Here the amino group serves as a nucleophile and not as a general base. Unlike intramolecular proton transfer with its "loose" transition state, an intramolecular nucleophilic reaction may enjoy a sizable kinetic advantage due to its intramolecularity.[17] We suggest this is the case for the process leading to the yellow, six-membered ring intermediate.

If intramolecular proton transfer were to take place in an enzymic reaction involving **1** or **2**, then it is clear that the enzyme must provide substantial activation in order to overcome the intrinsic low reactivity of the amino group associated with its very weak basicity. The ways by which an enzyme might provide the necessary activation are quite reasonable.[21] So, the problem of intramolecular amino group catalysis in enzymic systems is yet to be resolved.

Experimental Section

2-(1-Hydroxyethyl)thiamin was available from another study.[6] Thiamin chloride was liberated from its hydrochloride (Sigma) using triethylamine.[22] Methanol was dried before use; samples contained a few pellets of 3Å molecular sieves to keep them dry. Wet samples slowly underwent degradation, presumably hydrolytic cleavage of the thiazolium ring.

Spectra were recorded on a Varian XL-100. Numerous scans were taken above and below the coalescence temperature. The performance of the instrument was always optimized, with care being taken to avoid saturation by varying the rf power. Sweep times were 500–1000 s, and the sweep widths were 50–250 Hz. Temperatures were determined using the data of Van Geet.[23] Curiously, **1** was stable in the presence of the Dabco buffer but not in its absence. The chloride-free base of **1** in cold, dry methanol rapidly cleaved, forming a precipitate and the disubstituted thiazole in a reaction reminiscent of that in methanol–water.[22,24]

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Methylation of Acids with Pentamethoxyphosphorane

Donald B. Denney,* Robert Melis, and Anil D. Pendse

Department of Chemistry,
Rutgers, The State University of New Jersey,
New Brunswick, New Jersey 08903

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Several years ago it was reported that pentaethoxyphosphorane reacts with a variety of acidic materials to give the ethylated derivatives.[1] It has also been reported that triphenyldiethoxyphosphorane will effect cyclizations of various glycols and amino alcohols.[2] These reactants have some decided advantages over more common reagents. They do not require acids or bases as catalysts, nor are acids or bases generated during the course of their reactions. Another advantage of these reagents is that blocking groups are often not required. The major disadvantage that these reagents have had is their relative inaccessibility. They could only be prepared by allowing the appropriate trivalent phosphorus compound to react with diethyl peroxide. The prospect of working with large quantities of diethyl peroxide has successfully thwarted further development of these reagents.

Another approach has been to use the phosphorane formed from trimethyl phosphite and methyl vinyl ketone. This material has been shown to be an excellent methylating agent toward acids, phenols, and thiophenols.[3]

Recently a new route to phosphoranes has been developed, and it overcomes the problems associated with the diethyl peroxide route.[4] Pentamethoxyphosphorane (**1**) can be prepared by this method, which consists of allowing trimethyl phosphite (**2**) to react with 2 mol of methyl benzenesulfenate (**3**) at −78 °C in pentane.

$$\underset{\mathbf{2}}{(CH_3O)_3P} + 2\underset{\mathbf{3}}{C_6H_5SOCH_3} \rightarrow \underset{\mathbf{4}}{(CH_3O)_4PSC_6H_5}$$

$$\xrightarrow{3} \underset{\mathbf{1}}{(CH_3O)_5P} + \underset{\mathbf{5}}{(C_6H_5S)_2}$$

$$\underset{\mathbf{7}}{(CH_3O)_3P{=}O} + \underset{\mathbf{8}}{C_6H_5SCH_3} \leftarrow \underset{\mathbf{6}}{(CH_3O)_4P^+} + C_6H_5S^-$$

The reaction is rapid and leads to the production of **1** and diphenyl disulfide (**5**) along with trimethyl phosphate (**7**) and thioanisole (**8**). The contaminants most likely arise from dissociation of the first intermediate, the thiooxyphosphorane **4**, into the ion pair **6**.[5] The ion pair decomposes by S_N2 attack of thiophenoxide on carbon to give **7** and **8**.

Purification of **1** is effected by removing precipitated **5** by filtration at −78 °C. Extraction of the pentane solution with propylene carbonate removes more **5** and **7**. Distillation affords **1** (57%), which is usually contaminated with small amounts of **8** (3–7%). Pentamethoxyphosphorane is fairly stable thermally. After 71 h of heating at 80 °C, only a small amount of decomposition to trimethyl phosphate had occurred. After 184 h, 45% phosphate and 55% phosphorane were present. Pentamethoxyphosphorane is very hydrolytically unstable. It hydrolyzes immediately on contact with water.

Pentamethoxyphosphorane reacts with acids to give the permethylated products in the indicated isolated yields: benzoic acid, 90%; phenol, 92%; hydroquinone, 69%; salicylic acid, 85%; 2,4-dimethylphenol, 77%; and thiophenol, 90%. These reactions were conveniently conducted by adding **1** to the acid in methylene chloride, or in some cases no solvent was employed. In the case of thiophenol, the reaction is quite exothermic and the reactants were mixed at −78 °C and allowed to warm to room temperature. The products of the reactions are methanol, trimethyl phosphate, and the methylated compound. If the methylated compound is water insoluble, then trimethyl phosphate and methanol can be removed merely by washing with water.

Pentamethoxyphosphorane reacted slowly with 2,6-di-*tert*-butylphenol (7 days) at room temperature to produce 88% of 2,6-di-*tert*-butylanisole. At 80 °C, 86% of 2,6-di-*tert*-butylanisole was produced in 26 h.

Several nitrogen acids have been allowed to react with **1**; thus, succinimide and **1** reacted to give *N*-methylsuccinimide in 76% yield, phthalimide yielded 64% of *N*-methylphthalimide, and uracil gave 1,3-dimethyluracil in 88% yield.

The reactions of **1** with carbon acids are currently under study, and the results will be reported later. Earlier, it was shown that pentaethoxyphosphorane ethylates diethyl malonate on carbon and ethyl acetoacetate on oxygen.[1]

Experimental Section

All ^1H NMR spectra were recorded with a Varian T-60 NMR spectrometer. GLC analyses were conducted with F and M Model 700 and Varian 90-P gas chromatographs. Melting points were recorded with a Mel Temp apparatus and are uncorrected.

Preparation of 1. A 2-L three-neck flask equipped with a dropping funnel and a mechanical stirrer was charged with 125.0 g (1.120 mol) of methyl benzenesulfenate[4b] and 700 mL of dry pentane. The flask was cooled in a dry ice–acetone bath under an atmosphere of argon. Over a period of 1.5 h, 69.50 g (0.560 mol) of freshly distilled trimethyl phosphite in 50 mL of dry pentane was added dropwise with vigorous stirring. An additional 75 mL of pentane was added to facilitate stirring of the heterogeneous reaction mixture; diphenyl disulfide precipitated from the pentane at −78 °C. The reaction mixture was allowed to warm to room temperature and was stirred for an hour. The reaction mixture was cooled to −78 °C, and the pentane solution was separated from diphenyl disulfide by forcing it through a filter stick

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