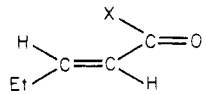
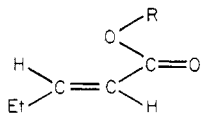
to be larger with the esters than with the ketones.

A second factor that explains the greater double bond stabilizing ability of the formyl group is steric. Electronic factors should favor the coplanar transoid conformation of **2t**, **4t**, **6t**, and *trans*-3-hexen-2-one shown in **7**, which



7

is analogous to the preferred conformations of acrolein, 1,3-butadiene, and glyoxal.[14] When X is hydrogen there will be the least steric hindrance to coplanarity. When X is methyl more hindrance is expected than when X is methoxyl, because of the preference of esters for eclipsing the carbon–oxygen double bond with the carbon–oxygen single bond,[15,16] as in **8**. Perhaps there is greater steric



8

strain in the $\alpha,\beta$-unsaturated ester. Observations on *tert*-butyl formate show that although detectable fractions of this species are in other conformations, most of the material is in a conformation in which the carbonyl group is eclipsed by the O–Bu bond.[17,18] Steric repulsions are estimated to have expanded the C–O–C angle in this conformer to greater than 120°.[18,19] Our ester **4t** probably exists largely in a similar conformation, but the expanded C–O–C angle and possible presence of small amounts of a second conformer have not made the equilibrium constants for eq 4 much different from those for eq 5 at a given temperature.

However, there do appear to be significant differences in rates of isomerization between the two esters. On the assumption that at 59 °C **3** is twice as reactive as at 45 °C and **1** is half as reactive as at 80 °C, the relative rates of DBU-catalyzed equilibration at 59 °C are 1:13:14 000 for **3**, **5**, and **1**, respectively.

To calculate $D$ values, Skoglund[20] has added the equilibrium constants reported here plus all the additional values that would be found in the literature to the compilation reported earlier.[2] In the least-squares treatment, the carbomethoxy, carbo-*tert*-butoxy, and all other $CO_2R$ groups were treated as a single substituent. Values of 0.43 and 0.05 were used for $\sigma_{p\text{-}CO_2R}$ and $\sigma_{p\text{-}CH_2CO_2R}$, respectively. For $\sigma_{p\text{-}CHO}$ and $\sigma_{p\text{-}CH_2CHO}$, the values used were 0.44[21] and 0.05, respectively. $D_{CO_2R}$ was found to be 3.14 kcal/mol and $D_{CHO}$ to be 4.32 kcal/mol.

In the conjugated isomers there should be inhibited rotation around the bond between the carbonyl group and the $\alpha$-carbon atom. This will tend to make the entropy of reaction negative. The $\Delta S$ value obtained for the pentenals is positive, but the experimental uncertainty is so large that we are not sure that this fact is significant. It is not obvious to us why $\Delta S$ should be more positive for the pentenals than for the esters. Both esters have negative $\Delta S$ values, as expected. The more negative value for the *tert*-butyl esters suggests that the bulky *tert*-butyl group gives increased interference with rotations around single bonds in the conjugated isomer. It is also possible that there is significance in the curvature of the van't Hoff plot for the *tert*-butyl ester that is seen in Figure 1.

**Registry No.** **1c**, 53448-06-9; **1t**, 58838-14-5; **2c**, 1576-86-9; **2t**, 1576-87-0; **3c**, 81643-00-7; **3t**, 81643-01-8; **4c**, 81643-02-9; **4t**, 81643-03-0; **5c**, 36781-66-5; **5t**, 20515-19-9; **6c**, 15790-87-1; **6t**, 15790-88-2; *trans*-2-pentenoic acid, 13991-37-2; *trans*-2-pentenoyl chloride, 33698-85-0; 3-pentenoic acid, 5204-64-8.

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# $^1$H NMR Evidence for High Barriers to Amino Group Rotation in 4-Aminopyrimidines, Including Thiamin, at Low pH in Water[1]

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*Received September 1, 1981*

The $^1$H NMR spectrum of thiamin (**1**), 4-aminopyrimidine (**2**), 4-amino-5-(methoxymethyl)-2-methylpyrimidine (**3**), and thiothiamin (**4**) was recorded at a variety of concentrations, temperatures, and pH's in 80:20 (v/v) $H_2O$–$^2H_2O$ employing correlation spectroscopy and Redfield 2–1–4 sequences at 360 and 500 MHz. At pH's 1.5 to 3.0 units below the p$K$ for N1 protonation, two amino hydrogen resonances were observed to persist at temperatures below about 10 °C for **1**, 26 °C for **2**, 40 °C for **3**, and 15 °C for **4**, indicative of hindered amino group rotation under these conditions. The concentration and temperature dependence of the behavior of the two NH resonances at low pH suggest that the increased barrier is not due to intermolecular interactions but simply to the favorable resonance interaction between the amino group nitrogen lone pair and the pyrimidine ring once the latter is N1 protonated. The barrier to amino group rotation in N1′-protonated thiamin was estimated to be 14.6 kcal/mol at pH 1.56, 12 °C, in 1 M KCl solution.

The possibility that the aminopyrimidine portion of thiamin (**1**) diphosphate (the vitamin $B_1$ coenzyme) has a catalytic function was raised by Schellenberger,[3] whose studies demonstrated that the coenzyme devoid of the

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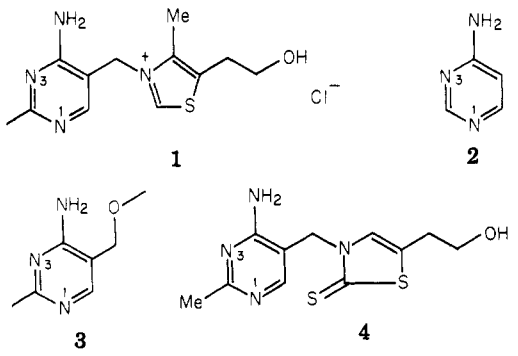

1 2



3 4

amino group lacked catalytic activity. While such exocyclic amino groups in aminopyrimidines are very weak bases, we had earlier suggested that attaching a positive charge to a ring nitrogen could accelerate several steps in the reaction sequences mediated by 1, as well as turn the amino group into a Brønsted acid and its conjugate base into a nucleophile.[2] A similar suggestion was advanced by Sable and co-workers, who demonstrated that a $CF_3$ group in place of $CH_3$ at the 2'-position of thiamin would convert the amino group into a Lewis acid.[4] That the exocyclic amine in 1 is a weak base was demonstrated by Sable's group earlier when they found that the $NH_2$ protons constitute a single, well-resolved resonance in a wide pH range in $H_2O$,[5] implying relatively slow exchange of these hydrogens with the solvent hydrogens. It was later found that N1 methylation of 1 and 2 slowed down amino rotation in $Me_2SO$-$d_6$ to the point where two distinct NH resonances could be observed.[2] Zoltewicz et al. also reported observation of two NH resonances in 1 in $CH_3OH$ below −40 °C.[6] It is here reported that in four different 4-aminopyrimidines, including thiamin (1), at pH's 1.5 or more units below the p$K$'s for N1 protonation and in $H_2O$, $NH_2$ rotation is slowed down such that two NH resonances are clearly observed. A barrier to amino group rotation in 1 could be estimated at low pH in $H_2O$. These observations are different from any previously reported: the experiments were performed in water near room temperature (0–40 °C), unlike previous studies from this laboratory and that of Zoltewicz et al.,[6] and at low enough concentrations to reduce the effects of exchange broadening, which at high concentrations of 1 does not allow observation of two resonances.[5] This report constitutes the first direct evidence for restricted amino group rotation in water in 4-aminopyrimidines near ambient temperatures. These studies were made possible by the ability to study resonances pertaining to protons involved in hydrogen bonding at low concentrations of substrate in aqueous medium employing either correlation spectroscopy[7] or Redfield's 2-1-4 techniques[8] at high magnetic field strengths.

## Results

**4-Aminopyrimidine (2).** The pH dependence of the chemical shifts of most proton resonances (360 MHz, 0 °C) is shown in Figure 1. The curves imply a p$K_a$ of 5.7 ± 0.2, in excellent accord with the 5.7 p$K_a$ reported for the conjugate acid[9] (protonation presumably at N1). Most unusual, however, was the appearance of two NH resonances at a pH well below the p$K_a$. Below pH 4 the chemical shifts were no longer pH dependent. The temperature dependence of the spectrum was monitored at both 360 (pH 2.07) and 500 MHz (pH 1.03) and indicated that *all* resonances shifted downfield with increasing temperature. At 500 MHz, two NH resonances were clearly visible at low pH, even at 23 °C, and rather than coalescing, each resonance appeared to broaden as the temperature was raised. Up to 30 °C, no clear coalescence of the two NH resonances was detectable, but the resonances became too broad to be monitored above this temperature. The two NH resonances detected at this low pH were also moving downfield with increasing temperature, albeit less than the CH resonances. The pH dependence of the chemical shifts of the two NH resonances was also examined in great detail at 1 °C, 23 mM concentration of 2 between pH 2.6 and 4.65. Under these conditions, the two NH resonances started to broaden with increased pH, coalesced to a single broad resonance at pH 4.45, and sharpened somewhat at pH 4.65. The chemical shift of the broadened single NH resonance at pH 4.45 was intermediate between the chemical shifts of the two NH resonances observed at pH 4.25 and below. Also, a limited number of experiments were performed at 1 °C and five times lower concentration of 2. At lower concentration, two NH resonances were discernible to a higher pH. These differences could not be quantitated, since the NH resonances broadened and shifted simultaneously as the pH was increased. Nonetheless, it was clear that the line width increased with increasing concentration of 2 during the coalescence process brought on by the increasing pH.

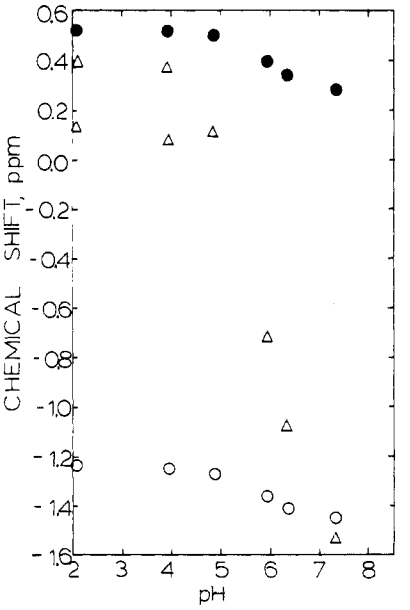


**Figure 1.** The pH dependence of the chemical shift of 15 mM 2, 0 °C, in 80:20 (v/v) $H_2O$–$^2H_2O$ at 360 MHz. The chemical shifts are quoted upfield (−) or downfield (+) from one doublet whose chemical shift is pH independent for $NH_2$ (△), singlet (●), and the other doublet (○).

**4-Amino-5-(methoxymethyl)-2-methylpyrimidine (3).** The $^1H$ NMR spectrum of 3 was discussed earlier.[2]

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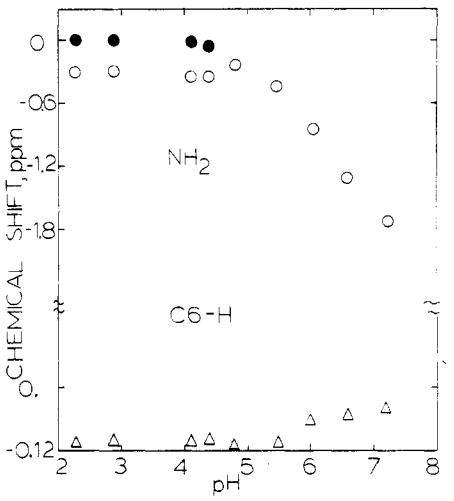


**Figure 2.** The pH dependence of the chemical shifts of the C6 H and C4 $NH_2$ resonances in 10 mM **3** at 5 °C in 80:20 (v/v) $H_2O$–$^2H_2O$ at 360 MHz. Relative chemical shifts are quoted rather than from an internal standard.

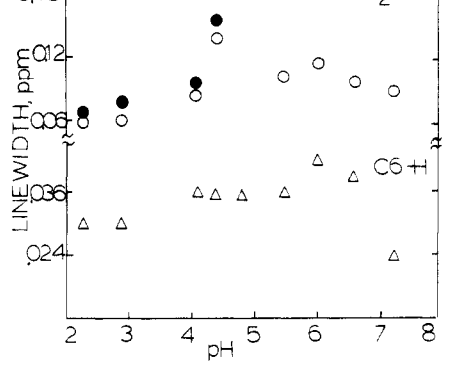


**Figure 3.** The pH dependence of the line width of the C6 H and C4 $NH_2$ resonances in 10 mM **3** at 5 °C in 80:20 (v/v) $H_2O$–$^2H_2O$ at 360 MHz.

Figure 2 presents the pH dependence of the chemical shifts of the NH and C6 H resonances. The pH dependence of both curves reflects the 5.9 $pK_a$ (25 °C) determined according to potentiometric titrations.[2] When the pH was lowered from 4.8 to 4.5, the resonance corresponding to the $NH_2$ group changed from a single peak with a chemical shift which is pH dependent to a set of two peaks with pH-independent chemical shifts. Figure 3 presents the pH dependence of the line width at half maximal peak height for the resonances corresponding to $NH_2$ and C6 H at 5 °C, 360 MHz, and 10 mM **3** in the absence of any buffer. A line-broadening factor of 10 Hz was employed, so that line widths greater than 0.03 ppm (10/360) are interpretable. In particular, the line width of resonances corresponding to both C6 H and $NH_2$ maximize at pH 6 near the 5.9 $pK_a$ for N1 protonation. Such a maximum in the line width of the $NH_2$ resonance of 1 had been observed near pH 5 for 1[5] (1 has a $pK_a$ for its N1′-protonated conjugate acid that is nearly an entire unit lower than the corresponding $pK_a$ for **3**). As the pH was lowered, there was observed new broadening of the $NH_2$ resonance, with a new maximum observed between pH 4.8 and 4.3. The initial concentration of **3** (titrated with dilute HCl) was the only species present in solution. As the pH was lowered further, a pH-independent line width was obtained at pH 2.3.

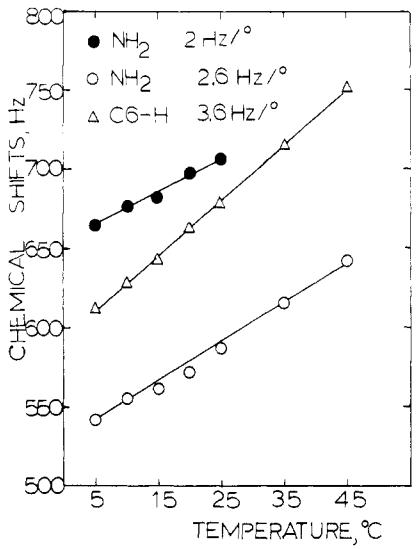


**Figure 4.** The temperature dependence of the chemical shifts (360 MHz) of C6 H and C4 $NH_2$ in 10 mM **3** at pH 3.0 in 80:20 (v/v) $H_2O$–$^2H_2O$. The slopes of the lines for the NH's are smaller than the slope of the line for C6 H.

To gain more information about the origins of the increased barrier to amino group rotation observed at a pH well below ring protonation, concentration and temperature dependencies of the two NH resonances were also examined. At pH 3.0 and 5 °C in the concentration range of 2.9–18 mM **3**, the appearance and chemical shifts of the two NH resonances were virtually unchanged. Nor was there significant change in the line width of the resonances, perhaps a slight decrease with increased concentration. Figure 4 illustrates that separate NH resonances were clearly observable at pH 3 (10 mM **3**) over a wide range of temperatures, to well above 25 °C at 360 MHz (Figure 4) and to over 40 °C at 500 MHz. Above these temperatures the two resonances became too broad to monitor but clearly still did not coalesce. The line width increased with temperature as expected, since it is proportional to the rate of exchange ($2\pi\Delta\nu = \tau^{-1}$) with medium protons. The slope of the chemical shift vs. temperature plots was found to be greater for the C6 H than for the two NH resonances. All these resonances were found to move to lower field with increasing temperature. It should be also recalled that $N^1$-$CH_3$-**3** in $Me_2SO$-$d_6$ gave rise to two NH resonances separated by approximately 0.8 ppm.[2]

**Thiamin (1).** At pH 3.44 and 5 °C, a 10 mM solution of thiamin gave rise to a single NH resonance. At the lower pH of 1.56 and in the presence of 1 M KCl (to allow lowering the solution temperature to below 0 °C), the amino region of the spectrum of approximately 5 mM thiamin gave the temperature-dependent behavior illustrated in Figure 5. At the point of coalescence of the two NH resonances (flat-top at 12 °C), the lifetime (= $1/2\,k$; $k$ is the rate constant in one direction) of the proton in the two environments can be calculated to be about 12 ms. This value, with the assumption of a transmission coefficient of unity in the Eyring expression, allows an estimate of about 14.6 kcal/mol for the activation energy for amino rotation at 12 °C. This constitutes the first observation of two NH resonances in thiamin in water. As with the other 4-aminopyrimidine analogues, the observation requires low concentration, low temperature, and an N1′-protonated ring.

**Thiothiamin (4).** This compound was examined since it has a pyrimidine ring identical with that of thiamin; however, the thiothiazolone carries no charge, in contrast to the positive charge on the thiazolium ring of **1**. Figure

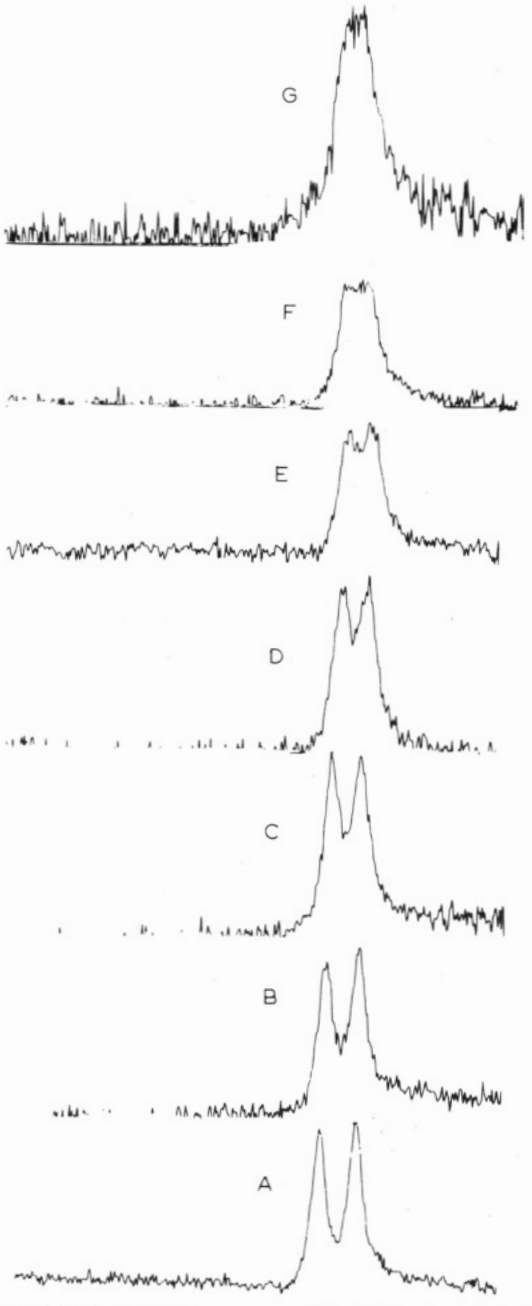


**Figure 5.** The C4′ $NH_2$ resonance(s) of thiamin (**1**) at 5 mM concentration, pH 1.56, at −2 (A), 2 (B), 6 (C), 8 (D), 10 (E), 12 (F), and 14 °C (G) in 1 M KCl in 80:20 (v/v) $H_2O$–$^2H_2O$ at 360 MHz employing the Redfield 2–1–4–1–2 technique.[8]

6 demonstrates the pH dependence of the chemical shifts and of the line width of the NH resonance(s) at 5 °C, 10 mM concentration of **4**. The titration curves are incomplete due to the greatly reduced solubility of **4** above pH 5. Nevertheless, it is clear that the chemical shift behaves with an approximate p$K$ of 5 ± 0.3, very similar to that of **1**. Below pH 3, there were again observable two NH resonances. Both the chemical shift and line-width behavior are similar to those observed for **3**. The chemical shift of C6 H is virtually pH independent, whereas the line width varies slightly but systematically in a fashion parallel to that of the NH resonance. At pH 1.92, two NH resonances were observable between 0 and 15 °C, harder to resolve but still readily discernible at 15 °C. The chemical shifts of both C6 H and $NH_2$ resonances moved to lower field at higher temperature. Finally, in $Me_2SO$-$d_6$, the $NH_2$ resonance of **4** appeared as a single peak, but on addition of an equivalent of HCl, two peaks of equal area and

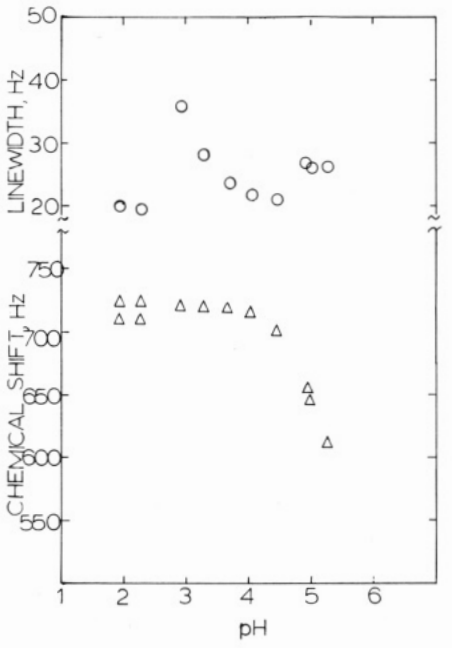


**Figure 6.** pH dependence of the line width and chemical shift (360 MHz = 1 ppm) of the C4′ $NH_2$ resonance in 10 mM thiothiamin (**4**), 5 °C, in 80:20 (v/v) $H_2O$–$^2H_2O$.

separated by approximately 0.4 ppm became apparent.

## Discussion

The observation of two distinct resonances for the amino hydrogens (each integrated to one proton equivalent) implies that the rate of amino group rotation is slow on the NMR time scale.[10] Since in the four compounds here studied such slowing down of the amino group rotation is only observed well below (1.5 to 3 pH units) the p$K_a$, it must be emphasized that on all aminopyrimidines studied to date, including nucleic bases[11] and thiamin,[12,13] first protonation takes place on a ring nitrogen rather than on the amino nitrogen.[14] First protonation on thiamin,[13] and very likely also on the other 4-aminopyrimidines studied herein,[2] takes place at N1 in aqueous medium. The restricted amino rotation in water is observed when any of the four species here discussed is N1 protonated. Also, restricted rotation was observed over a range of temperatures and concentrations; hence, the increased barrier is not due to intermolecular interactions. The aromatic and NH resonances of compounds **2**–**4** moved to lower fields at higher temperatures (see, for example, Figure 4). Such observations on heteroaromatic molecules in water are the result of ring-current effects and have been interpreted as being due to vertical stacking interactions.[15]

Restricted rotation around exocyclic amino groups in related compounds was first reported by Becker et al.,[16] who demonstrated that in N3-protonated or N3-alkylated cytosinium (**5**), but not in the neutral precursors, there

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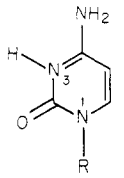
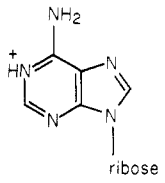
exist two NH resonances in nonaqueous solvents. Later,



5, R = H or alkyl

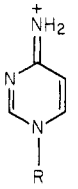
Raszka reported[17] that at 0 °C in water even neutral cytosine in cytidine and in 5'-cytidine monophosphate gives rise to two NH resonances; hence, there exists a substantial barrier to amino group rotation. It was also shown that in 2 N mineral acid, adenosine (6) also gives rise to two



6

NH resonances at low temperature (conditions under which the adenine ring is at least monoprotonated).

It has now been amply demonstrated in this laboratory that in the 4-aminopyrimidines, including thiamin, introduction of a positive charge at N1 (by protonation or alkylation) greatly increases the barrier to amino group rotation in water. The resonance contribution 7 accounts for this increased barrier.



7, R = H or alkyl

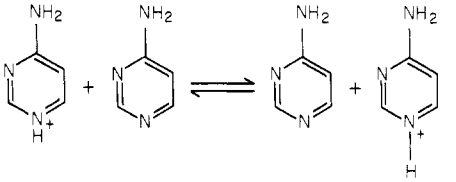
The following arguments can be made concerning the observation of two NH resonances only at pH's well below the pK's for N1 protonation. (1) General acid–base autocatalysis of the exchange of the $NH_2$ protons with protons from the aqueous medium broadens the $NH_2$ resonance; hence, one must employ low concentrations, high magnetic fields, and low temperatures to observe the inherent magnetic nonequivalence of the two NH resonances, reflecting an increased barrier to rotation. (2) There are several contributions to the complex dependence of the line width of the NH resonance(s) on pH (see, for example, Figure 3 on compound 3). Near the N1 protonation p$K$ there was observed a maximum in line width. This is probably a result of the exchange of the amino hydrogens of an N1-protonated molecule of 3 with solvent hydrogens and catalyzed by neutral 3.[5] As the pH was lowered further, there was observed broadening again, which upon still further lowering of the pH finally led to two distinct NH resonances. Very detailed experiments on the pH dependence of this phenomenon on 2 (and 3) clearly demonstrated that the behavior observed was due to an enhanced rate of exchange of the $NH_2$ protons between two environments ($N^1$-H-$2^+$ and 2) with increasing pH.[10,18–20]

Table I. Conditions under Which Two NH Resonances Are Observed in Compounds 1–4 in Water

| compd (concn, mM) | p$K_a$ | pH below which 2 NH resonances are obsd | $\Delta\nu$,[a] Hz (at 360 MHz) | temp, °C, below which 2 resonances are clearly discerned |
|---|---|---|---|---|
| 1 (5) | ~4.9 | 2.0 | 19 | <10 |
| 2 (15) | 5.7 | 4.5 | 94 | >25 |
| 3 (10) | 5.9 | 4.5 | 120 | >40 |
| 4 (10) | ~5 | 3.0 | 12 | >15 |

[a] Difference in chemical shift between the two clearly resolved NH resonances at a temperature at least 10 °C below coalescence.

If the lifetime of the proton on N1 in $N^1$-H-$2^+$ is long on the NMR time scale and the barrier to amino group rotation is high on this same time scale, two distinct NH resonances will be observed. Once the lifetime of this proton is shortened (but the barrier still remains the same), for example, by the following processes,



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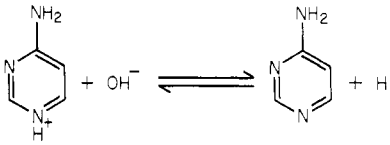

(2)

with increasing pH, the two resonances will first broaden and then coalesce and sharpen again, precisely what was observed. The evidence indicating that an increased concentration of 2 brought on coalescence at a lower pH suggests that eq 1 contributes significantly to the pH-dependent coalescence phenomenon either through direct or solvent-mediated proton transfer.[21] A rate constant for the two-site exchange process could be estimated as $2.2 \times 10^2$ $s^{-1}$ (from the expression $\tau\Delta\nu = \sqrt{2}/2\pi$, where $\tau$ is the lifetime of the proton in each environment, and $\Delta\nu$ is the chemical shift difference between the two environments well below the coalescence temperature), at pH 4.45 and 1 °C, at which a flat-topped resonance was observed.[20] At this pH, with the known p$K_a$ of N1-protonated 2 this first-order rate constant provides a second-order catalytic rate constant of $1.0 \times 10^5$ $s^{-1}$ $M^{-1}$ for eq 1 and $8 \times 10^{11}$ $s^{-1}$ $M^{-1}$ for eq 2, assuming one or the other to be exclusively responsible for the pH-dependent coalescence phenomenon. The unacceptably large value obtained for eq 2 confirms that eq 1 provides the predominant pathway for the pH-dependent coalescence phenomenon.[22] Since $\Delta\nu$ for 1 and 4 is much smaller than for 2 and 3 (Table I), the mechanism also accounts, in part, for the fact that two NH resonances in the former two compounds can only be observed nearly three units below the pK's for N1 protonation. As the pH was lowered further, a pH-independent

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(18) Emsley, J. W.; Feeney, J.; Sutcliffe, L. H. "High Resolution Nuclear Magnetic Resonance Spectroscopy"; Perganion Press: Oxford, 1965; Vol. I, Chapter 9.
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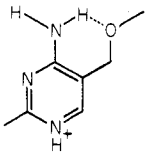
(20) Bovey, F. A. "Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1969; Chapter 7.
(21) Grunwald, E.; Loewenstein, A.; Meiboom, S. *J. Chem. Phys.* **1957**, *27*, 630–640.
(22) The author is grateful to an anonymous referee for pointing to such an explanation as a possible one of the observed data. The results here presented should serve as just one more warning that apparent changes with pH need not reflect microscopic ionization constants. For example, the onset of two NH resonances at pH 4.3–4.5 for compounds 2 and 3 does not reflect anything about the true microscopic ionization constants listed in Table I.

line width was observed for the two NH resonances. The line width at these low pH values was still greater than that of the C6 H resonance, indicating that the N1-protonated species still was undergoing amino hydrogen exchange with solvent hydrogens.

Finally, it is instructive to consider the temperature below which two amino resonances are observable (Table I) as a qualitative measure of the barrier to amino group rotation. First, 1 with a p$K$ similar to that of 4, but with a larger $\Delta\nu$ than 4, has a lower coalescence temperature than 4. The positively charged thiazolium ring of 1 compared to the neutral thiothiazolone of 4 could be the source of the greater barrier to amino rotation in 4. The amino groups of 2 and 3 at low pH's gave rise to two NH resonances ($pK_a$'s for their conjugate acids are 5.7 and 5.9, respectively) even at 25 and 40 °C, respectively. Coalescence of the two resonances was not visible in either one, rather line broadening with increased temperature. Both 2 and 3 likely have higher barriers to amino rotation than 1. Also, 3 exhibits less broadening at the same concentration than 2 at 25 °C; therefore, the barrier in 3 must be larger than in 2. This could be the result of intramolecular stabilization depicted in 8. The barrier to amino



8

rotation estimated for N1′-protonated thiamin at 12 °C in water is about 14.6 kcal/mol, a value consistent with those reported in nonaqueous solvents for some related compounds[23,24] and larger than the nearly 12 kcal/mol measured for neutral thiamin at −40 °C in methanol.[6] The barrier to amino group rotation in compounds 2–4 when N1 protonated is even larger than in thiamin itself but could not be determined, since coalescence was not observed.

These studies demonstrate the need to perform such experiments in water at very low concentrations of compounds to avoid complications due to various exchange phenomena that would mask the subtle changes here described.

(23) See references in ref 6.
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## Experimental Section

**Materials.** 4-Amino-5-(methoxymethyl)-2-methylpyrimidine (3) was a gift from Merck Sharpe & Dohme Research Laboratories, Inc., Rahway, NJ. Thiothiamin (4) was a gift from Hoffmann-La Roche Inc., Nutley, NJ. Deuterated solvents were purchased from Stohler Isotope Chemicals and Aldrich Chemical Co. 4-Aminopyrimidine was purchased from Calbiochem.

**Methods.** Solution pH's were adjusted on small volumes employing a Radiometer GC 2321 or Ingold microelectrode. $^1$H NMR studies were performed (a) at 360 MHz at the NIH facility at the University of Pennsylvania, School of Medicine, in the proton correlation mode[7] or employing the Redfield technique,[8] and (b) at 500 mHz at the Francis Bitter National Magnet Laboratories of MIT employing the Redfield 2–1–4 pulse technique.[8] The data at 360 and 500 MHz were collected in 80:20 (v/v) $H_2O$–$^2H_2O$ at variable temperature. The temperature quoted is accurate to ±1 °C. Typically, at each temperature the sample was equilibrated in the probe for at least 10 min prior to recording of the data. The deuterium oxide is required for a stable lock signal. All pH's quoted pertain to apparent readings at a glass electrode and have an uncertainty of less than ±0.1 unit. The solution pH's were always adjusted with HCl or NaOH solutions; hence, $Cl^-$ was the only anion employed.

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**Registry No.** 1, 59-43-8; 2, 591-54-8; 3, 769-82-4; 4, 299-35-4.

# Relative Migratory Aptitudes of Alkyl Groups in the Iodination of Ethenyltrialkylborates. A Conformational Analysis

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Relative migratory aptitudes of various alkyl groups have been determined in the iodine-induced rearrangement of bromomagnesium ethenyltrialkylborates. Trialkylboranes of types $R_{3-n}BR'_n$, *B*-R-9-BBN, and $CH(CH_3)_2C(CH_3)_2BRR'$ were complexed with vinylmagnesium bromide and then iodinated. Alkyl rearrangement to the ethenyl terminus, followed by deiodoboration, produced a mixture of 1-alkenes. The overall migratory aptitude order is cyclohexyl > *sec*-butyl > isobutyl > *n*-butyl, bicyclooctyl > thexyl. The magnitude of the migratory aptitude ratios after statistical correction varies with the alkyl substitution pattern in the borate. The migration order is most conveniently explained by consideration of relative conformational stability in the iodinated intermediates before rearrangement.

The electrophilic iodine-induced rearrangement of α,β-unsaturated organoborates is a valuable method for producing substituted alkenes[1–3] and alkynes.[4] However, there remain the synthetic and theoretical problems of

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