was systematically regenerated in potassium carbonate by interaction between the oxaphosphetane anion and the solid phase (Figure 2).

It was clear that the capacity of this anion on the regeneration of potassium carbonate could be used in other reactions which would not involve a solid base in stoichiometry.[28]

We observed a quantitative transformation of furfural with a quantity of $K_2CO_3 \cdot 1.5H_2O$ significantly lower than the stoichiometry required for phosphonate (Table III). Potassium carbonate would first act by classical acid–base interaction followed by regeneration of its active basic sites by the intermediate oxaphosphetane anion at the interface. Such an interfacial process could only be explained by the intervention of water molecules, which dilate superficial meshes of the solid and therefore promote these interactions between species weakly monoadsorbed on the solid and molecules in the dioxane organic phase.

Conclusion

This study points out the importance of a perfect knowledge of structures of solid bases and reactive intermediate species formed at the surface or at the interface in reactions proceeding by anionic activation. In these conditions, the Wittig–Horner reaction is controlled by the structure of phosphorus carbanionic species whose nature depends on the structure of solid bases. This novel approach makes it possible to optimize reactions of this type and determine their mechanisms.

Experimental Section

^1H NMR spectra were recorded on a Varian T-60 spectrometer with TMS as internal standard. ^{31}P NMR spectra were recorded on a Brucker WH90 spectrometer with 85% H_3PO_4 as external standard. Mass spectrometry was carried out on a Girdel Chromatograph coupled with a Nermag R 10-10 spectrometer by chemical ionization (CH_4).

1,4-Dioxane (Prolabo) was distilled over $CaCl_2$ and kept on 4-Å molecular sieves. 1,4-Dioxane-d_8, toluene-d_8, and DMSO-d_6 (1-mL ampules) were used directly (CEA, France). The carbonyl substrates and ethyl (diethylphosphono)acetate were commercial products (Fluka). Furfural and benzaldehyde were distilled under reduced pressure in the presence of K_2CO_3 before use. Activated $Ba(OH)_2$ or $Ba(OH)_2 \cdot H_2O$ was prepared by heating[18] $Ba(OH)_2 \cdot 8H_2O$ (Prolabo) at 200 °C for 3 h. The product was ground and kept in a dessicator in the presence of NaOH. $K_2CO_3 \cdot 1.5H_2O$ and $Cs_2CO_3 \cdot 3H_2O$ (Fluka) were used directly.

The nature and number of active sites of the solid bases were determined with 2,6-di-*tert*-butyl-4-methylphenol, and 1,3-dinitrobenzene was used to titrate reducing sites. The bases did not show acidic or oxidizing sites after titration with pyridine and phenothiazine.[18c]

General Method for Synthesis of Ethyl Acrylates. Reactions were carried out in a 100-mL round-bottomed flask equipped with a reflux condenser, mechanical stirrer, and thermometer. The solid base, 1, and aldehyde (see tables for molar quantities) were added sequentially to dioxane, and water was added. The mixture was stirred at 70 °C in a thermostated bath.

The composition of the reaction mixture was determined periodically with an Intersmat Chromatograph IGC 120 DFL (flame ionization) equipped with an OV 101 5% column on Chromosorb W/AW 80/100. The temperature range 140–280 °C was programmed to increase 20 °C/min with a nitrogen gas flow of 25 mL/min. Injector and detector temperatures were 250 and 280 °C, respectively. Yield of 3-(2-furyl)-2-propenoate was determined by GC with hexadecane as internal standard.

At the end of the reaction, the solid phase was separated by filtration; addition of Silica 60H (Merck) or Celite gel to the bottom of the fritted tube aided retention of small particles of the solid. The solvent was evaporated in a rotavapor, and the product was purified by distillation or flash chromatography (silica gel, hexane/ether, 8:2). Physical properties of ethyl cinnamates agreed with literature data. Ethyl 3-(2-furyl)-2-propenoate has been described.[10a]

IR Spectra of Adsorbed Phosphorus Carbanions. The adsorption of the phosphorus reagent was carried out under the same conditions as the reaction: 1 (2.3 mmol) was mixed with 2 mL of deuterated solvent, 0.04 mL of D_2O, and $Ba(OH)_2 \cdot H_2O$ (1.2 mmol) or alkaline carbonate (3 mmol) at 70 °C for 25–40 min, depending on the base. The solid was filtered and dried under vacuum. The IR spectrum of the solid was recorded on pellets comprising 12 mg of the solid in 170 mg of KBr in a Brucker IFS spectrometer with a single Fourier transformed beam (1000 accumulations). The liquid phase was analyzed by ^{31}P NMR. Adsorption of furfural and other carbonyl substrates on the solid base were determined the same way in the absence of the phosphorus reagent.

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Secondary Deuterium Kinetic Isotope Effects in the Cleavage of Thiamin and *N*-Methylthiaminium Ion: First Evidence To Identify the Rate-Limiting Step

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Thiamin and 1'-methylthiaminium ion deuterated at the 6'- and *N*-methylene positions were cleaved by sulfite ion in aqueous phosphate at 25 °C. Observed secondary kinetic isotope effects (standard deviation of the ratio) were inverse for the 6'-position, 0.95 (0.09) and 0.95 (0.03), respectively, and normal for the *N*-methylene group, 1.08 (0.09) and 1.10 (0.03), respectively. These results confirm the multistep mechanism first proposed by us (*J. Am. Chem. Soc.* **1977**, *99*, 3134). They prove for the first time that sulfite ion adds to the 6'-position and that fragmentation of the CH_2–thiazole bond in the resultant adduct contributes to the rate in the multistep mechanism.

Thiamin (**1a**) and its *N*-methyl derivative **1d** undergo nucleophilic substitution at the heterobenzylic methylene group in the presence of aqueous sulfite ion by an unusual, multistep mechanism.[1] One sulfite ion adds to an elec-

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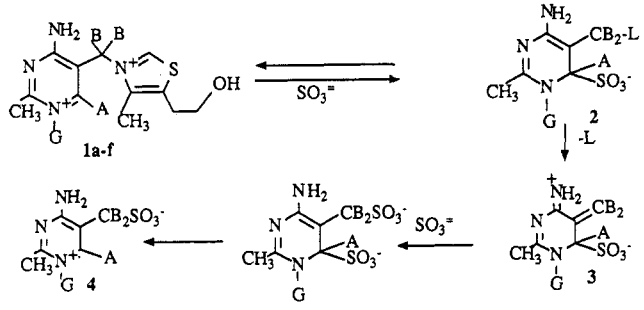
Scheme I



trophilic pyrimidinium ring to give intermediate **2** that loses the thiazole leaving group to form a second intermediate **3**. A second sulfite ion, the one appearing in the observed substitution product, then captures **3** to give an adduct. Aromatization of this adduct by loss of the first sulfite ion gives the aromatic substitution product **4**, Scheme I, an $S_N(AE)$ mechanism.

Evidence for this complex process includes (a) trapping of an intermediate, presumably **3**, by various nucleophiles in fast steps that do not affect the overall rate of substitution,[1] (b) isolation of trapped products,[2,3] and (c) demonstration of the required second-order sulfite ion kinetics. The second-order sulfite ion term is only observed under very special conditions. In the case of thiamin, the second-order process is found only when the sulfite ion concentration is low enough so that capture of an intermediate by the pyrimidine nitrogen of thiamin becomes competitive with sulfite ion trapping.[2,4] In the case of a thiamin analogue possessing a thiolate ion leaving group in place of the thiazole, common ion retardation by added thiolate ion brings about a change from the usual first-order to second-order sulfite ion kinetics.[3]

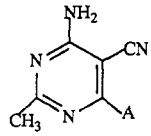
We now present the first evidence in the form of secondary hydrogen–deuterium kinetic isotope effects (KIE), k_H/k_D, to demonstrate that both the addition of sulfite ion and subsequent cleavage of the methylene–thiazole bond contribute to the rate under the usual conditions where sulfite ion reacts by a first-order process. Sulfite ion must add to the 6-position of the pyrimidine ring in a fast, reversible step. A normal KIE was found for the methylene unit, and an inverse effect for the 6′-position of the thiamin **1** (G = H) and its *N*-methyl derivative **1** (G = CH_3).

Results

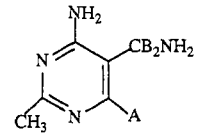
Deuterated Substrates. Our synthesis of the required deuterated substrates has as the key step the Raney nickel reduction of a 5-cyanopyrimidine **5a** in the presence of deuterium gas. This reduction adds deuterium atoms at the methylene side chain to yield an aminomethyl precursor of thiamin. Subsequent, time-honored cyclization at this chain introduces the thiazolium ring of thiamin.[5]

Starting material **5a** was prepared by cyclizing acetamidine with (ethoxymethylene)malononitrile.[6] Although it was possible to make the 6-deuterio derivative using deuterated (ethoxymethylene)malononitrile,[7] about half of the deuterium was lost when the 5-cyano group was reduced catalytically with hydrogen in the next step. An alternate method therefore was selected.

	A	B	G
a	H	H	H
b	D	H	H
c	H	D	H
d	H	H	CH_3
e	D	H	CH_3
f	H	D	CH_3
g	D	D	-



5 a,b



6 a-c,g

6-Deuterio-5-(aminomethyl)pyrimidine **6b** was made by reduction of cyanide **5a** with Raney nickel and hydrogen to give the corresponding protio compound **6a** that then was treated with the nickel, this time in the presence of deuterium gas. The second exposure to the catalytic reduction resulted in the replacement of the isotope at the 6-position. The ratio of deuterio to protio products was 9 to 1.

Similarly, reduction of **5a** with the nickel catalyst in the presence of deuterium gas gave trideuteriopyrimidine **6g** having the isotope at both the 6-position and the methylene side chain. Most of the label was removed from the 6-position again using nickel and hydrogen to form **6c** having the CD_2 unit.

All (aminomethyl)pyrimidines **6** were cyclized using the classical synthesis of thiamin proceeding by way of the ammonium dithiocarbamate salt **7** to produce a thiazole thione **8** that then is desulfurized.[5] Isolation of the dithiocarbamate proved to be beneficial, giving rise to higher yields of products. We present our synthesis of labeled thiamin because many of the details of this old preparation are not found in the original patent literature[8] or are scattered among derivative preparations,[5] not always in journals readily accessible.[9]

Our deuteration reactions need to be placed in perspective. Direct deuterium exchange is not known with Raney nickel and deuterium gas but some examples using "deuterized" Raney nickel made with $NaOD/D_2O$ have been reported, e.g., the reduction of an alkyne.[10] Aromatic and aliphatic hydrogen–deuterium exchange effected by heating compounds in D_2O with deuterated Raney nickel without additional deuterium gas have been reported.[11]

Selective deuteration with Raney nickel and D_2O[12] has heretofore not been observed for heterocyclic compounds. Therefore, the scope of our observations concerning annular hydrogen exchange was explored. They are described in the Experimental Section.

Prior to our work, deuterium had been introduced into the 2′-methyl group of thiamin quite easily using acidic D_2O[13] and of course into the 2-position of the thiazolium ring.[14] Curiously, hydrogen–deuterium exchange is not a viable means of introducing the isotope into the 6′-position of the pyrimidine ring in contrast with the ease of such substitution for pyridinium ions[15] in alkaline solution and the high temperature but neutral pH approach for pyridines.[16,17]

Kinetic Studies. Substrates were cleaved under pseudo-first-order conditions by sulfite ion in a phosphate buffer at 1 M ionic strength maintained with KCl. The reactions were followed spectrophotometrically as reported earlier,[18] making the usual pH corrections for partial

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Table I. Conditions and Secondary Kinetic Hydrogen-Deuterium Isotope Effects for the Reaction of Thiamin (1a) and *N*-Methylthiaminium Ion (1d) with Sulfite Ion in Phosphate Buffer at 25.0 °C and 1 M Ionic Strength with KCl[a]

isotope position	pH range	$10^5 k_{obs}$, s^{-1}	free $10^2[SO_3^{2-}]$, M	no. of runs	av $10^2 k_2$,[b] M^{-1} s^{-1}
		Thiamin			
6′-H	6.25–7.01	7.72–19.7	1.57–3.62	4	11.8 (0.8)
6′-D[c]	6.27–7.01	8.27–19.9	1.61–3.62	3	12.4 (0.9)
CD_2[d]	6.26–6.90	8.59–17.6	1.59–3.35	4	10.9 (0.6)
	6′-position, k_H/k_D = 0.95 (<90% CL); methylene, k_H/k_D = 1.08 (90% CL)				
		N-Methylthiaminium Ion			
6′-H	6.24–7.03	139–593	1.45–3.45	6	4.12 (0.08)
6′-H	6.92–6.94	142–154	3.54–3.59	9	4.13 (0.12)
6′-D[c]	7.00–7.03	141–150	3.38–3.45	4	4.24 (0.11)
6′-D[c]	6.91–6.94	152–156	3.51–3.59	9	4.33 (0.04)
CD_2[d]	6.25–7.02	126–568	1.48–3.43	4	3.73 (0.07)
	6′-position, k_H/k_D = 0.95 (99.9% CL); methylene, k_H/k_D = 1.10 (99.9% CL)				

[a] pK_a of HSO_3^- is 6.59; pK_a of thiamin is 5.28 (I = 1.0). [b] Standard deviation in parentheses. [c] 90% D. [d] 85% CD_2 and 35% 6′-D.

protonation of sulfite ion and thiamin in order to obtain the pH-independent second-order rate constant.[1] Reaction conditions and the mean values of second-order rate constants are listed in Table I along with standard deviations that refer to variations between individual runs.

At the suggestion of a referee, additional runs were carried out. They comprise 18 experiments performed on the *N*-methyl substrate focusing on the KIE for the 6′-position. The composition of the phosphate buffer was maintained constant, and the protio and deuterio compounds were examined in an alternating order to minimize any temperature fluctuations. Conditions and individual results are described in detail in the Experimental Section. The composite results are listed separately in Table I. An increase in precision was gained. But the addition or elimination of the old data from the new has little influence on the final values of the KIE and so all 28 runs are included in the final statistics for the 6′-position.

The present second-order constant for protio thiamin, 0.118 M^{-1} s^{-1}, is similar to our older value, 0.192 M^{-1} s^{-1}, obtained by an analytical method based on NMR with D_2O as the solvent.[1] For the *N*-methyl compound the new and old values of 0.0412 and 0.0410[18] M^{-1} s^{-1} also are in agreement.

In Table I are the KIE values along with the associated confidence limits (CL) comparing statistically the differences between the mean values of the second-order rate constants for the protio and deuterio forms of each substrate.[19] The question was asked, is there a statitically meaningful difference between k_H and k_D? In the case of the *N*-methyl compound where there are appropriate data it did not matter whether individual runs on protio and deuterio compounds were paired and the differences between paired runs were compared or whether the mean values of the second-order constants for protio and deuterio compounds each treated as an independent group were analyzed. The conclusions were the same. With a high degree of confidence (99.9% CL) we are able to state that the k_H nd k_D values for both the 6′-position and methylene position of the *N*-methyl substrate are different. However, the confidence limits for thiamin itself are considerably lower, being <90% for the 6′-position and >90% for the methylene chain. The experimental uncertainties in the second-order constants for thiamin are high in part because two pH-dependent corrections must be made, one reflecting the degree of protonation of thiamin, the other for free sulfite ion. This is not the case for the *N*-methyl analogue where only a single pH correction to give the amount of free sulfite ion is needed.

Importantly, the pattern of KIE's is the same for both substrates. Therefore, the conclusions about the reaction mechanism are expected to be the same for both.

The observed KIE (standard deviation of the ratio[20]) for the 6′-position of thiamin and its *N*-methyl derivative are inverse, being 0.95 (±0.09) and 0.95 (±0.03) respectively, while that for the methylene group is normal, 1.08 (±0.09) and 1.10 (±0.03), respectively.

The KIE may be corrected for incomplete deuteration using standard probability treatment and the geometric mean relationship for the methylene group which consists of two equivalent isotopes.[21] In this way, the observed KIE of 1.08 for the two isotopes in **1a**/**1c** increases to 1.10 or 1.05 for each one of the two isotopes at the methylene unit and for **1d**/**1f** it changes from 1.10 to 1.13 or 1.06 per isotope. Moreover, the true KIE for the methylene group must be slightly larger than reported because there is a small contribution from the inverse isotope effect at the 6′-position, owing to the presence of a small amount of deuterium. The residual deuterium (35%) could not be removed from this position without decreasing the isotopic content of the methylene group as well.

Discussion

An inverse KIE is found for the 6′-position and a normal KIE for the bridging methylene group, Table I. These observations are consistent with our multistep mechanism given in Scheme I.[1] Sulfite ion adds to the annular 6′-position to give **3** and this is followed by cleavage of the thiazole ring from the adduct to form intermediate **4**. While we postulated the addition to the 6′-position of the pyrimidinium ring[1] and this is reasonable on electronic and steric grounds, the present isotope effect data constitute the first experimental evidence to show that addition of sulfite ion to this position does indeed take place during the reaction. Prior to this we had observed the NMR spectrum of a sulfite ion adduct of a model of thiamin in aqueous solution, a pyrimidine derivative without a leaving group, 4-amino-5-cyano-1,2-dimethylpyrimidinium iodide.[22] Sulfite ion added to the less hindered, unsubstituted 6-position.

The KIE value for the addition step is small, especially if this is considered to be a preequilibrium reaction. Thus, an equilibrium isotope effect (EIE) for the addition step might be approximated by the value of 0.899 for the ad-

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dition of hydride ion to the 4-position of a pyridinium ion[23] or by the value of 0.84 estimated from fractionation factors using chloride ion to model sulfite ion.[24,25]

We offer three explanations for the low value. (1) Perhaps the addition of sulfite ion takes place to more than one annular position and these adducts also give rise to product. The underlying principle behind addition is that the nucleophile should add so as to give an adduct without positive charge on the ring, i.e., to positions 2′, 4′, and 6′. However, because the other two sites offer more steric hindrance, the 6′-position is expected to be favored, as demonstrated by our model compound.[22] Any competing addition would decrease the value of the observed KIE. (2) The hybridization in adduct **3** may not be exactly sp^3 and so the change on bonding is not from sp^2 to sp^3 but rather something less. In the adduct, particularly of the *N*-methyl substrate, the sulfonic acid group is adjacent to substituents which may cause this large group to adopt a position tilted away from these groups toward the ring causing the C–S bond to be richer in p-orbital character, and the C–H richer in s than that for a purely tetrahedral structure. Since the change in hybridization is less than normal, the EIE value is less than usual. (3) Loss of the leaving group from adduct **2** in the subsequent step to give **3** may not be entirely rate limiting. Reversion of the adduct back to starting materials may be competitive with loss of the leaving thiazole ring. That is, although the addition of sulfite ion may be reversible, it need not be a true preequilibrium process. If two steps are each partially rate limiting, then the isotope effect will be a weighted average of the isotope effects for each step.[26] In our case this is the average of inverse and normal effects in the direction of the forward reaction.

The elimination step to give **4** in our proposed mechanism is an S_N1 reaction in which a neutral group departs. However, our KIE of 1.06 per atom in the methylene group is similar to those observed for benzylic positions in S_N2 reactions[27] and is smaller than those often found for authentic S_N1 reactions.[28] The value by itself therefore does not discriminate between the $S_N(AE)$ and S_N2 mechanisms. But there is no ambiguity concerning our proposed scheme. The independent evidence cited in the introduction as well as the inverse KIE found for the 6′-position offer rigorous proof of the multistep pathway.

The isotope effect found for the methylene group clearly shows that departure of the leaving thiazole contributes to the observed rate constant in the multistep process. But it is small in size. A number of reasons for this reduced magnitude are possible. (1) There is likely to be in the transition state considerable double bond character betwen the primary carbon and the pyrimidine ring due to charge delocalization, and this would decrease the size of the KIE.[29] (2) Perhaps steric effects associated with neighboring substituents prevent significant rehybridization of the methylene group during bond cleavage in the transition state. This too would serve to decrease the magnitude of the isotope effect. (3) As stated above, if loss of the thiazole ring were not entirely rate limiting, then the KIE would be diminished.[26] (4) There is 35% deuterium at the 6′-position in addition to label at the side chain providing an inverse KIE prior to bond cleavage and thereby decresing the overall value.

In related studies, an inverse KIE (0.89, 90 °C) was found for the rate-limiting addition of hydroxide ion to the 6-position of 1,3-dimethyl-5-[(4-nitrophenyl)methyl]uracil leading to substitution at the methylene side chain following rapid loss of the nitrophenoxide ion. At low pH when the rate becomes independent of pH and the mechanism becomes S_N1, loss of the nitrophenoxide ion is rate limiting, and this step has a normal KIE (1.25).[30]

Conclusion

We have observed KIE's for two steps, the first inverse, the second normal. Because both KIE's are small we cannot say whether (a) or (b) is true. (a) The addition of sulfite ion to thiamin is rapidly reversible and this is followed by rate limiting loss of the triazole ring. (b) Addition of the nucleophile and loss of the leaving group each are partially rate limiting.

With this report a more detailed mechanism of the reaction between thiamin and sulfite ion is established.

Experimental Section

The general method for the hydrogenation or deuterogenation of pyrimidinenitriles **5** and aminomethylene compounds **6** is as follows: Raney Ni (Merck, 50% with water; about 1 g; the quality of the catalyst did not greatly alter the deuteration results) was washed twice with water and DMF and suspended in DMF (30 mL, saturated with gaseous ammonia). The nitrile **5** (1 g, 7.5 mmol) or aminomethylene compound **6** (1 g, 7.2 mmol) was added, and the solution was hydrogenated (deuterogenated) at 4 bar for 4 h at 50 °C. Deuterogenation in monodeuteriomethanol did not influence the amount of exchange, in contrast to another report where D_2O was used.[11] Almost identical exchange results were obtained omitting ammonia gas in the solvent, yielding only somewhat more secondary amine. To reach an exchange level higher than 60–70%, the supply vessel filled with hydrogen (deuterium) had to be purged and refilled after 1, 2, and 3 h. The solution was filtered from the catalyst, and the solvent was distilled in vacuo. The residue was dissolved in hot toluene (80 mL), the solution was filtered, and the solvent volume was reduced to 5 mL. The yield of aminomethylene compound **6** was 80–90%. The extent of deuteration was checked by ^1H NMR spectroscopy. After a short reduction time (1 h) residual nitrile was not deuterated at C-6, indicating that the exchange process at the 6-position took place on the reduced product only.

About the same result was found with methanol or ethanol solvent in which the starting materials are not very soluble. Even in DMF, a good solvent, the exchange process did not take place with 10% Pd on charcoal (100 mg). The extent of deuteration is as follows: **6b**, 90% 6-D; **6c**, CD_2 85% and 6-D 35%; **6g**, 90% CD_2 and 90% 6-D. The melting point of all **6** compounds was 155–157 °C.

In order to check the general applicability of the deuteration method the following compounds (100 mg) were treated as above for 3 h with Ni (100 mg) and D_2 (4 bar) in methanol or DMF (10 mL) solvent under the same conditions and found to be unchanged: thiamin, thiamin disulfide, 4-amino-2-methyl-5-(hydroxymethyl)pyrimidine, 4-amino-6-methyl-5-(aminomethyl)pyrimidine, 4-amino-2,6-dimethyl-5-(aminomethyl)pyrimidine, cytosine, thymidine, and adenosine. Some exchange took place in the following molecules: 4-amino-5-(aminomethyl)pyrimidine (20% D at C-2,6), 6-methyluracil (25% D at C-5), 4-amino-2,6-dimethyl-5-(hydroxymethyl)pyrimidinium chloride (15% D at 2-CH_3). Hence the exchange reaction seems to be highly specific to **6**.

***N*-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]dithiocarbamate, Ammonium Salt (7b,c).** Amine **6** (1.3 g, 9.4 mmol) was suspended in a mixture of ethanol (4 mL) and concentrated

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ammonia (0.65 mL). Gaseous ammonia also was bubbled into the mixture until everything dissolved. A solution of carbon disulfide (0.72 g, 9.4 mmol) in 16 mL of ethanol was added, and the mixture was left to precipitate 7 for 3 h: yield 2.1 (97%), mp 246 °C dec. **7b** and **7c**: ^{1}H NMR (Me_2SO-d_6) (nondeuterated compound) δ 2.27 (3 H s, CH_3), 4.50 (2 H, s, CH_2), 6.20 (4 H, b, NH_4), 6.80 (3 H, b, NH_2 + NH), 7.82 (1 H, s, CH). **7b**: $C_7H_{12}DN_5S_2$ (232.3). **7c**: $C_7H_{11}D_2N_5S_2$ (233.4).

3-[(2-Methyl-4-amino-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-2-thiothiazolone (8b,c).[5] A solution of **7b,c** (2.1 g, 9.1 mmol) in warm DMF/H_2O 1:1 (13 mL) was cooled to 20 °C, sodium iodide (0.8 g, 5.2 mmol) and 3-chloro-4-oxypentyl acetate (1.7 g, 9.5 mmol) was added, and the solution was stirred for 6 h. A precipitate was isolated from the cooled (4 °C) mixture, redissolved in HCl (13 mL, 10%), and heated on a steam bath for 15 min. The cold solution then was neutralized with NaOH (10%), and **8b,c** was isolated, heated with ethanol (20 mL), and isolated again, yield 1.4 g, 52%; mp 240 °C (lit.[8] 238–9 °C). ^{1}H NMR (DCl, TSS-standard), nondeuterated **8**: δ 2.27 (3 H, s, CH_3), 2.60 (3 H, s, CH_3), 2.90 (2 H, t, CH_2CH_2), 3.76 (2 H, t, CH_2OH), 5.33 (2 H, CH_2-bridge), 7.52 (1 H, s, CH).

Thiamin-6′-d_1 and *N*-CD_2 Hydrochloride (1b and 1c).[5] To an ice-cold suspension of thiothiazolone **8b,c** (1.4 g, 4.7 mmol) in water (4.5 mL) and concentrated hydrochloric acid (0.24 mL) was added slowly hydrogen peroxide (1.65 g, 30%, 14.5 mmol). The clear solution was heated to 60 °C, and sulfate was precipitated with a solution of barium chloride (1.14 g, 5.5 mmol) in water (5 mL). The filtrate was brought to dryness, taken up in hot ethanol (7.5 mL), and **1b,c** crystallized after cooling, yield 1.3 g (83%, over all 42%), melting point, of the raw material: **1b**, 238 °C, 90% D at C-6′; **1c**, 239 °C, 85% D at the methylene bridge and 35% D at 6′. Recrystallization raised the melting point to 250 °C. **1b**, $C_{12}H_{16}DN_4OSCl$·HCl (338.3); **1c**, $C_{12}H_{15}D_2N_4OSCl$·HCl (339.3).

1′-Methylthiaminium-6′-d_1 and *N*-CD_2 Perchlorate (1e and 1f). The procedure was essentialy the same as that[31] described for the nondeueterated material: 0.34 g (1 mmol) of **1b** yielded 250 mg (52%) of **1e**, mp 209 °C, $C_{13}H_{19}Cl_2DN_4O_9S$ (480.3); 1.2 g (3.5 mmol) of **1c** yielded 0.95 g (55%) of **1f**, mp 216–18 °C. ^{1}H NMR analysis revealed that **1e** was 90% deuterated at C-6′, **1f** 85% at the methylene bridge; 35% of C-6′ was still deuterated.

Kinetics. Pseudo-first-order kinetics were carried out spectrophotometrically as reported earlier.[18] However, for the more extensive study on the 6′-position of **1d** and **1e** a variation on the reported method was employed. A stock solution of phosphate buffer (0.0184 M Na_2HPO_4 and 0.0276 M KH_2PO_4) was made up with KCl to an ionic strength of 0.828 and kept under argon. To a 1-cm cell containing about 2 mg of **1d** or **1e** was added 3 mL (3.140 g) of buffer under argon. Following thermal equilibration of the cell in the thermostatted compartment for 15 min 100 ± 0.2 μL of 1.61 M stock Na_2SO_3 was added by a pipet dispenser with disposable tip. The change in the absorbance (about 0.250) was observed at 292 nm. Ten points were taken 10 min after mixing, covering a span of about 3 half-lives. Infinity values were measured but were corrected as needed by a least-squares computer program fitting the correlation coefficient to a value better than 0.9999. These infinity corrections in general were very small. The pH was measured immediately after a run with a PMX 2000 meter. The accuracy of the pH measurements is of the order 0.005. Ten pairs of kinetics runs were taken, but one pair was discarded because unaccountably the pH of the solution with the nondeuterated sample was 0.5 too high. The deuterated and nondeuterated substrates were measured alternately in order to minimize any temperature variation. The results are summarized as follows where the order of the data is run number and isotope identity/10^3k_{obs}, s^{-1}/pH/10^3k_2, M^{-1} s^{-1}. The fractional amount of free sulfite ion was calculated as earlier,[18] the second-order constant being given when k_{obs} is divided by the free sulfite ion concentration. 1H/1.53/6.94/42.6, 2D/1.56/6.93/43.7, 3D/1.56/6.94/43.5, 4H/1.51/6.94/42.0, 5H/1.45/6.93/40.6, 6D/1.56/6.93/43.6, 7H/1.54/6.93/43.1, 8D/1.52/6.92/42.9, 9D/1.52/6.91/43.3, 10H/1.44/6.92/40.6, 11H/1.45/6.94/40.3, 12D/1.53/6.93/42.8, 13H/1.42/6.93/39.8, 14D/1.53/6.93/42.9, 15D/1.54/6.91/43.9, 16H/1.49/6.93/41.7, 17D/1.56/6.93/43.7, 18H/1.46/6.93/40.8.

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Functionalization of Olefins by Alkoximidoylnitrenes

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(*N*-Cyano- and *N*-(methylsulfonyl)alkoxycarbimidoyl)nitrenes, generated in situ from the corresponding azides by 300-nm UV light, convert a variety of olefins cleanly and stereospecifically to the corresponding aziridines. These can readily be hydrolyzed to N-unsubstituted aziridines or ring-opened to allylic isoureas. The nitrenes can also be generated by thermolysis at 80 °C. The azides add to norbornene to give triazolines, which lose nitrogen to give the *exo*-aziridines.

Introduction

Additions of nitrenes to olefins have been studied since 1962.[1] Carbonylnitrenes, sulfonylnitrenes, alkoxynitrenes, phosphorylnitrenes, and certain (*N*-acylamino)nitrenes give aziridines.[2-4] Nevertheless, there are relatively few examples of intermolecular nitrene additions to olefins for actual use in synthesis. This might be due to a combination of circumstances. For example, (alkoxycarbonyl)-nitrenes can be made conveniently and efficiently (below 0 °C if so desired) by α-elimination[5] or photolysis, and at 80 °C by thermolysis, from stable precursors which themselves do not react with olefins. Still, (alkoxycarbonyl)-nitrenes are not very suitable for making aziridines. Being too reactive, they give appreciable quantities of various

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