Table I. Conditions and Results of the Hydrolysis of Thiamin Analogues at 25.0 °C and 1.0 M Ionic Strength[a] in the Presence and Absence of *p*-Nitrobenzenethiolate Ion[b]

[substrate]$_0$, M[c]	pH	[buffer base], M	[$^-SC_6H_5$-NO_2]$_0$, M	k_2, M^{-1} s^{-1}	sulfide[d,e] product, %
IV					
	9.65	0.010 CO_3^{2-}		0.298	
	11.04	0.02 PO_4^{3-}		0.307	
2.48×10^{-3}	11.48	pH-stat		0.317	
	12.54	satd $Ca(OH)_2$		0.316	
4.78×10^{-6}	11.04	0.02 PO_4^{3-}	1.1×10^{-5}	0.286	55
2.39×10^{-5}	11.04	0.02 PO_4^{3-}	5.6×10^{-5}	0.277	80
2.39×10^{-5}	12.54	satd $Ca(OH)_2$	5.2×10^{-5}		35
V					
	9.30	0.010 CO_3^{2-}		2.66	
	10.34	0.050 CO_3^{2-}		2.59	
	10.75	0.24 CO_3^{2-}		2.33	
4.70×10^{-5}	9.89	0.005 CO_3^{2-}	5.5×10^{-5}	2.83	>90
1.59×10^{-4}	10.34	0.050 CO_3^{2-}	1.9×10^{-4}	3.05	>90
7.3×10^{-4}	11.04	0.02 PO_4^{3-}	7.3×10^{-4}		>90
4.7×10^{-5}	11.04	0.02 PO_4^{3-}	7.2×10^{-5}		75
9.4×10^{-6}	11.04	0.02 PO_4^{3-}	1.4×10^{-5}		45

[a] Maintained with KCl. [b] Wavelengths for kinetic studies: 273 for IV and 255 or 310 nm for V. Second-order rate constant is given by $k_\Psi/[OH^-]$; $pK_W = 14.00$. [c] Between 2 and 9×10^{-5} M unless indicated otherwise. [d] The change in the thiolate anion concentration at 406 nm (ϵ 14 800) measures the amount of sulfide formed. [e] For rate constant ratios in keeping with values suggested here see: Cho, M. J.; Pitman, I. H. *J. Am. Chem. Soc.* 1974, *96*, 1843.

group and phosphorus.[10] Significantly, although there is no kinetic dependence on PO_4^{3-}, it is present in the product. In carbonate buffer II is an alcohol, resulting indirectly from decarboxylation of a carbonate monoester or directly from reaction with solvent.[11]

Competition experiments with *p*-nitrobenzenethiolate ion are most revealing. When this nucleophile is present to about the same extent as either substrate, a new product forms; II has this nucleophile bonded to its methylene group as a sulfide. Most significantly, although sulfide may be produced as a major product, second-order rate constants for hydrolysis are unaffected (Table I). Moreover, the amount of sulfide formed shows no significant dependence on the leaving group in spite of a 9-fold variation in hydrolysis rate constants between substrates. Thus, hydroxide ion catalyzes the formation of sulfide substitution product.

Identification of the sulfide product is based on its ultraviolet spectrum and its subsequent reactivity toward sulfite ion. Sulfide product produced at pH 11 in a reaction with V was diluted with sulfite ion and its reactivity measured. The rate constant for substitution by sulfite ion (eq 1) is essentially the same as that (0.0162 M^{-1} s^{-1}, 25.0 °C, 340 nm) found for authentic sulfide in a separate experiment.

Preparative experiments also provide evidence for a sulfide product. Both substrates (100 mg) when added to a small excess of *p*-methoxybenzenethiolate ion in 0.1 M hydroxide ion give product II (Nuc = $SC_6H_4OCH_3$-*p*) in 90% isolated yield.[12]

Our results clearly eliminate a single step S_N2 mechanism of substitution. Instead, one or more intermediates must be present which are trapped by thiolate ion or PO_4^{3-} *after* the rate-limiting step. Hydroxide ion reacts with starting material before or during the rate-limiting step to initiate the process.

It seems likely that sulfite and hydroxide ions both add to the pyrimidine ring to give similar intermediate III. While some may have wished to attribute "unique" properties to sulfite ion because of its ability to form sultone intermediate VI from III, this view is untenable because hydroxide ion cannot form such a structure. Yet reactivities of the two ions are quite similar toward a substrate with a common leaving group. This is revealed by a comparison of second-order rate constants for the hydrolysis of V and the sulfite ion substitution of a derivative of V having G = H.[2] Because yields of thiolate ion trapped products do not depend significantly on the identities of the two leaving groups, it seems probable that the leaving group has departed before the second nucleophile attacks, i.e., III eliminates its leaving group before reacting with a second nucleophile. Hence, the likely mechanism is one in which nucleophile adds to pyrimidine ring present in its cationic form, then follows loss of the leaving group, addition of the nucleophile which appears in the product, and rearomatization.

The multistep pathway of substitution found for thiamin and its analogues with sulfite and now with hydroxide ion suggests this mechanism is a general one. Our observations raise the question of whether thiaminase II, thiamin hydrolase,[13] reacts similarly.

Acknowledgment. Our work was kindly supported by Grant AM-17442 from the National Institute of Arthritis, Metabolism and Digestive Diseases.

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[10] Gaydou, E. M.; Llinas, J. R. *Org. Magn. Reson.* **1974**, *6*, 23.

[11] Carbonium ions react with water by a general base-catalyzed process. See Ritchie, C. D., Wright, D. J., Huang, D-S., Kamego, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 1163 and references given therein.

[12] Nitrothiolate ion was selected for kinetic studies because of its favorable ultraviolet spectrum, while the methoxy ion gives a highly water-insoluble product.

[13] Evans, W. C. *Vitam. Horm. (N.Y.)* **1975**, *33*, 467.

Identification of a Biradical as the Reactive Form of the 2-Isopropylidenecyclopentane-1,3-diyl Singlet Species

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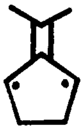
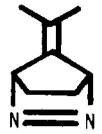
The chemistry of 2-isopropylidenecyclopentane-1,3-diyl (**1**) can be dissected into reactions of two molecular spin states, a singlet and a triplet.[1-3] Although the triplet (**1**-T) is clearly a biradical, a subtle and vexatious uncertainty has veiled the true nature of the singlet species, which might be formulated as a biradical, **1**-S, or as its bicyclic valency tautomer, 5-isopropylidenebicyclo[2.1.0]pentane (**2**). The recent synthesis of the hydrocarbon **2**, a thermally labile but observable substance,[4] now makes possible a kinetically based identification of the biradical **1** rather than the bicyclic hydrocarbon **2** as the reactive entity in the cycloadditions of the singlet with olefins.



1

2



3

Thermal decomposition of hydrocarbon **2**, prepared[4] by photolysis of a degassed acetone solution of diazene **3** in the absence of a trapping olefin, can be followed by nuclear magnetic resonance (NMR) spectroscopy at 270 MHz. The reaction occurs with clean first-order kinetics and gives the previously reported[1] dimers of **1**. The temperature dependence of the first-order rate constant, measured at eight points from −58 to −26 °C, gives the Arrhenius parameters $E_a = 13.7$ kcal/mol and log $A = 9.6$ (A in s^{-1}). These

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[1] Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 446 and references cited therein.

[2] Corwin, L. R.; McDaniel, D. M.; Bushby, R. J.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 276.

[3] Duncan, C. D.; Corwin, L. R.; Davis, J. H.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 2350.

[4] Rule, M.; Lazzara, M. G.; Berson, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 7091.

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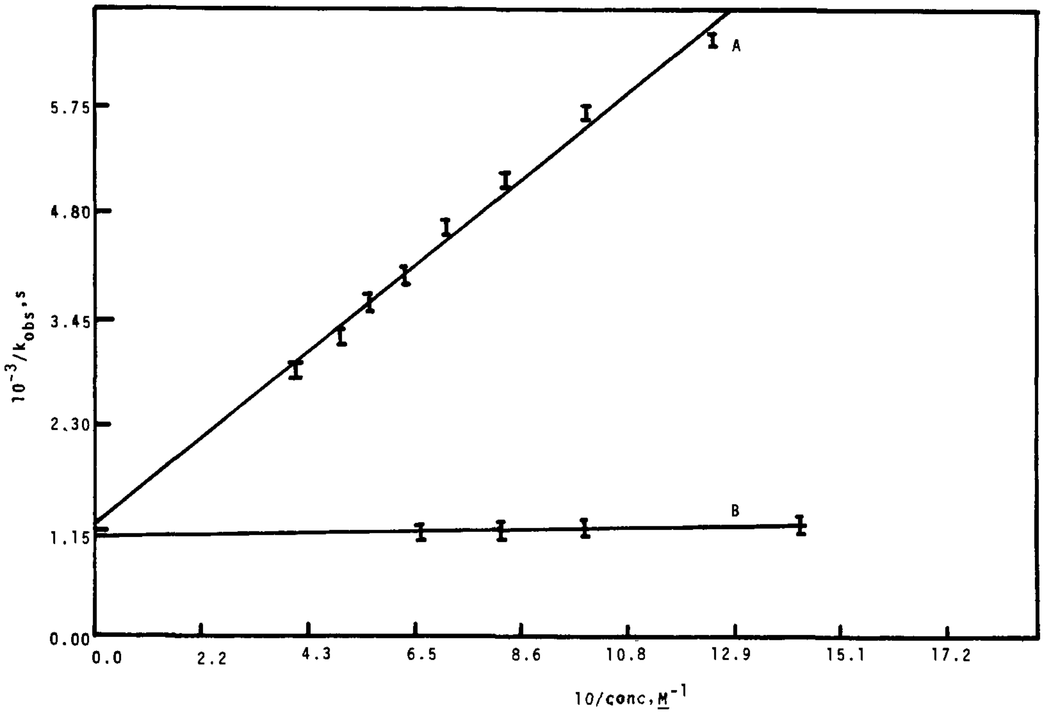


Figure 1. Dependence of the reciprocal of the pseudo-first-order rate constant, k_{obsd}, on the reciprocal of the concentration of trapping agent acrylonitrile (A) or maleic anhydride (B) in the reaction with **2** at -55 °C in acetone-d_6 solvent.

values are essentially the same as those obtained earlier[4] for reactions in two other solvent systems.

Incorporation of a large excess of a conjugated olefin such as acrylonitrile into the reaction mixture increases the rate of disappearance of **2**. The product is the same mixture of cycloadducts, **4** and **5**, as is obtained upon capture of the singlet species when it is generated by deazetation of diazene **3** in acrylonitrile.[1-3] Fused adducts (**4**) are the major products in both instances.

The formation of cycloadducts **4** and **5** from the hydrocarbon **2** may be formulated with either of two hypothetical mechanisms which predict different kinetic behavior: (a) Direct bimolecular collision of **2** with the olefin would result in second-order kinetics. (b) Reversible interconversion of **2** and a singlet biradical **1-S** followed by capture of **1-S** by the olefin predicts second-order kinetics when the capture step is rate determining, first-order kinetics when the ring-opening step is rate determining, and intermediate behavior when the rate-determining step is not well-defined[5] (Scheme I).

Under the pseudo-first-order conditions of the present experiments, mechanism a predicts a linear response of the pseudo-first-order rate constant, k_{obsd}, to the acrylonitrile concentration, [M]. The steady-state approximation applied to mechanism b predicts the relationship of eq 1, which may be converted to linear

$$k_{obsd} = k_1k_2[M]/(k_{-1} + k_2[M]) \qquad (1)$$

form as its reciprocal, eq 2. Exclusive operation of mechanism

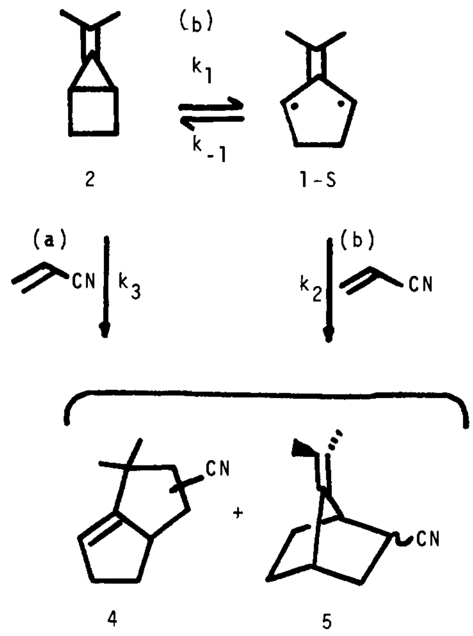
$$1/k_{obsd} = (k_{-1}/k_1k_2[M]) + 1/k_1 \qquad (2)$$

b thus would lead to a linear plot of $1/k_{obsd}$ vs. 1/[M] with a finite intercept ($1/k_1$). Note that the double-reciprocal plot also would be linear for mechanism a (bimolecular collision), but as eq 3 shows, it would have a zero intercept.

$$1/k_{obsd} = 1/(k_3[m]) \qquad (3)$$

The reaction of **1** with a 10-fold excess of acrylonitrile at -55 °C[6] in acetone-d_6 can be followed by the same kinetic technique described for the dimerization of **1**. A double-reciprocal plot of the data (Figure 1) is linear with an intercept of 1.186 × 10^3 s. A Scatchard plot of the same data (Figure 2), which should emphasize any curvature masked by the double-reciprocal plot,[7] also is linear.

Scheme I



The observations of a linear double-reciprocal dependence and a finite intercept are consistent with the exclusive operation of the two-step mechanism b. The diylophilic reactivity of acrylo-

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[5] Note that a mechanism involving *irreversible* ring opening **2** → **1-S** followed by bimolecular capture of **1-S** (**1-S** + olefin → products) would display first-order kinetics. A mechanism involving reversible hydrocarbon ⇌ biradical interconversion (**2** ⇌ **1-S**) and bimolecular capture of hydrocarbon **2** would lead to second-order kinetics and would be indistinguishable from mechanism a by the present technique.

[6] The temperature in the NMR spectrometer probe, measured with a methanol standard, was constant (±0.2 K) during each run. However, because of unavoidable fluctuations in operating conditions, the temperature varied from run to run by as much as 1.5 K. Small corrections to the observed rate constants were applied to bring the measurements to a common temperature of 218.1 K.

[7] Scatchard, G. *Ann. N.Y. Acad. Sci.* **1949**, *51*, 660.

[8] Rule, M.; Berson, J. A. *Tetrahedron Lett.* **1978**, 3191.

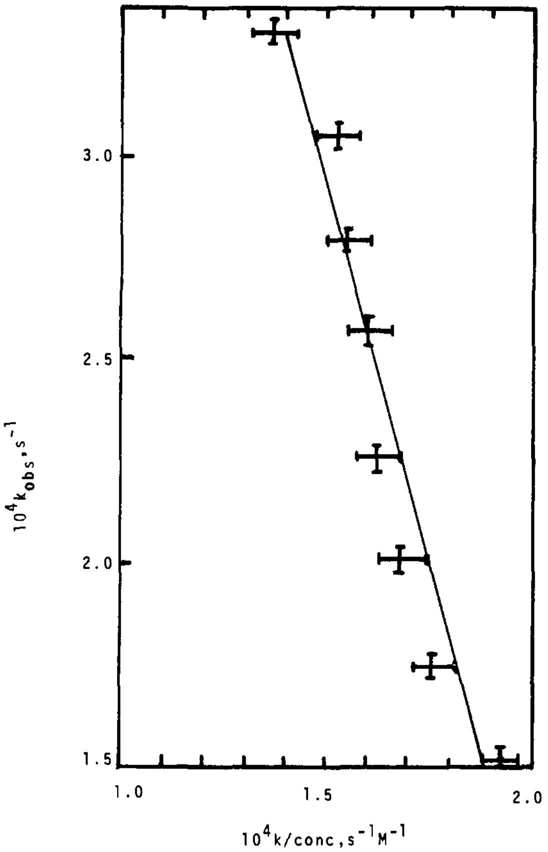

Figure 2. Scatchard plot of the acrylonitrile data of Figure 1 (A).

nitrile evidently is in an intermediate range, since neither the first-order nor the second-order extremes of behavior predicted by mechanism b is observed.

One could hope to achieve the first-order extreme with a trapping agent more reactive than acrylonitrile. Previous direct competition studies[1,3] have shown that at 60 °C, maleic anhydride is 52 times more reactive toward the singlet than is acrylonitrile. If this preference persists or increases at the temperature of the present experiments (−55 °C), a change in kinetic behavior with maleic anhydride might be expected. Indeed, Figure 1 shows that the pseudo-first-order rate constant is virtually insensitive to the concentration of maleic anhydride in the experimental range. This constancy is characteristic of mechanism b when the rate-determining step is unimolecular formation of the reactive intermediate (**2** → **1**-S).

It is a distinguishing feature of mechanism b that a common reactive intermediate is formed, regardless of the trapping agent. Accordingly, the intercepts, $1/k_1$, of the double-reciprocal plots for all trapping agents should be the same. As Figure 1 shows, this requirement is met. The values of k_1 from the acrylonitrile and maleic anhydride plots are 8.43 and 9.06×10^{-4} s^{-1}, which agree within 7%.

Mechanism b treats the singlet biradical **1**-S kinetically as a local minimum in a potential-energy surface, not as a transition state. In this model, a finite barrier opposes the ring-closure step **1**-S → **2**. Independent experimental evidence for the existence of such a barrier in the singlet species derived by photolytic deazetation of the diazene **3** already has been deduced[4] from the temperature dependence of the distribution of photoproducts (**2** vs. **1**-T).

We now find further confirmation in the observation that photolysis of diazene **3** in the presence of 2 M acrylonitrile at −78 °C gives a mixture of 80% of hydrocarbon **2** and 20% of cycloadducts **4** and **5**, with **4** predominant. Moreover, the same experiment using 1.0 M maleic anhydride instead of acrylonitrile gives <5% of **2** and >95% of the analogous cycloadducts. The origin of the cycloadducts cannot be a simple thermal reaction of hydrocarbon **2** with the trapping olefin, since control experiments show that process to be immeasurably slow at −78 °C.

These results indicate the formation of a discrete, trappable intermediate[9] in the thermolysis of **2** and in the photolysis (and thermolysis[1-3]) of **3**. This species cannot be a bicyclo[3.1.0]hex-1-ene (**6**), since derivatives of this ring system behave in an

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entirely different manner.[8] Nor can the triplet **1**-T be the intermediate, since its chemistry is also different.[1-3] It is difficult to propose candidates other than **1**-S for the role of the singlet species, the identification of which now brings to a total of four (**1**-S,**1**-T,**2**, and **6**) the explicitly recognizable entities of the 2-isopropylidenecyclopentane-1,3-diyl family.

The present work rules out any explanation of the observed[1,10,11] regiospecificity of the singlet cycloadditions in terms of direct $[_2\pi_s + {}_2\pi_s + {}_2\sigma_s]$ reaction of the bicyclic hydrocarbon **2** with the olefin. A more general explanation[10,11] based on the frontier MO properties of biradical **1**-S clearly is preferred.

The slope and intercept of Figure 1 give the ratio $k_{-1}/k_2 = 3.7$ M. We are not aware of other examples in which competition between intramolecular ring closure and intermolecular capture of a hydrocarbon singlet biradical has been demonstrated kinetically.

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(9) (a) The value of $k_1 = 8.75 \times 10^{-4}$ s^{-1} at 218.1 K corresponds to $\Delta G^‡ = 15.6$ kcal/mol for the ring opening **2** → **1**-S. $\Delta S^‡$ would be expected to be near zero for this reaction,[9b] so that $\Delta H^‡ \simeq 15.6$ kcal/mol. This is significantly *higher* than the value $E_a - RT = 13.3$ kcal/mol observed for the pyrolysis of **1** in the absence of a trapping agent. Nevertheless, the apparent discrepancy does not exclude **1**-S as a common intermediate for the two processes. It can be shown that the observed activation energy, E_a, for the pyrolysis of **2** in the absence of trapping agent is given by $E_a \simeq E_1 - E_{-1}$ where E_1 and E_{-1} are the activation energies for the formation and recyclization of **1**-S. The "discrepancy" of ~2.3 kcal/mol (15.6–13.3) then would be a measure of E_{-1}. (b) Gajewski, J. J.; Chow, S. D. *J. Am. Chem. Soc.* **1977**, *99*, 5696. Roth, W. R.; Wegener, G. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 758.

(10) Siemionko, R.; Shaw, A.; O'Connell, G.; Little, R. D.; Carpenter, B. K.; Shen, L.; Berson, J. A. *Tetrahedron Lett.* **1978**, 3529.

(11) Siemionko, R.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 3870.

Oxygen-Atom Transfer from Iodosobenzene to Ketenes, α-Keto Carboxylic Acids, and Ketones

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Recently, Groves et al.[1] showed that iodosobenzene, $C_6H_5I{=}O$, could serve as a source of an oxygen atom for a porphyrin, which in turn effected olefin epoxidation and alkane hydroxylation. Furthermore anaerobic oxygenation of cytochrome P450 has been achieved by using $C_6H_5I{=}O$ as the oxygen-atom donor.[2,3]

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† On a leave of absence from Kurukshetra University, Kurukshetra, India.

(1) J. T. Groves, T. E. Nemo, and R. S. Myers, *J. Am. Chem. Soc.*, **101**, 1032 (1979).

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