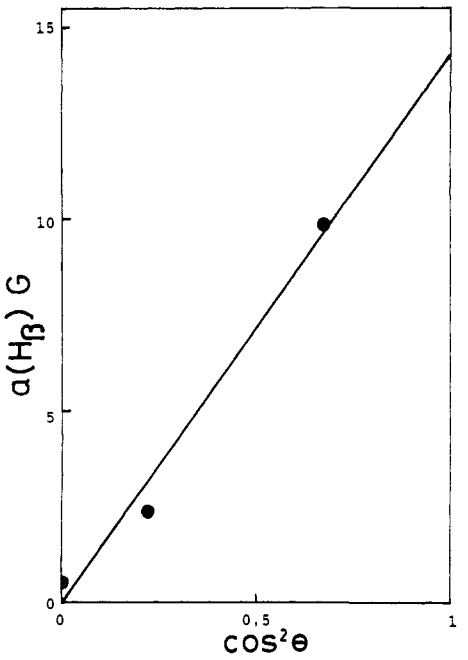

Figure 3. Relationship between the β-proton hfsc's of the 1-norbornyl radical and the dihedral angles θ.

sponding constant for planar radicals. The β-proton hfsc's of 1-adamantyl and bicyclo[2.2.2]oct-1-yl radicals (6.58 and 6.64 G, respectively)[10] are about twice as large as the values predicted from the relationship in Figure 3. Thus the B value seems to have a large dependence on the degree of nonplanarity at the radical site.

The bridgehead proton hfsc in the 1-norbornyl radical (2.45 G) is somewhat smaller than the hfsc of the bridgehead proton in the bicycl[2.2.2]oct-1-yl radical (2.69 G),[10] although the H_4 in the former is closer to the radical site than the bridgehead proton in the latter radical. The calculated value of $a(H_4)$ for the 1-norbornyl radical in Table I increases with increasing flattering of the radical site and with the closer approach of C_4 to C_1. This suggests that the odd electron is delocalized onto the bridgehead hydrogen atom through a "through-space" mechanism (i.e., rear-lobe overlap, homohyperconjugation[11]) in the case of the 1-norbornyl radical, whereas in the bicyclo[2.2.2]oct-1-yl radical a "through-bond" interaction is dominant.[10] When the "through-space" interaction between C_1 and C_4 was artificially turned off in performing INDO calculations, the calculated $a(H_4)$ of the 1-norbornyl radical (Z = 0.0 Å) decreased from 2.46 to 0.56 G. On the other hand $a(H_4)$ of the bicyclo[2.2.2]oct-1-yl radical[12] was calculated to increase from 3.20 to 6.83 by omitting the "through-space" interaction between C_1 and C_4 in the INDO calculation.[13] These results also support conclusions on the odd electron delocalization mechanisms mentioned above. This type of interchange of the dominant interaction accompanying the change of the number of bridging carbon atoms has been predicted in a theoretical study of the interaction between lone pairs in bridgehead diazabicyclic alkanes.[14]

The further experimental confirmation of the assignments of the hfsc's in the 1-norbornyl radical as well as theoretical studies on the effects of "through-space" and "through-bond" interactions on long-range hfsc's are in progress and will be published in the near future.

Acknowledgment. The authors wish to thank Dr. H. Morishima for the fabrication of an ESR cavity with slits. We are grateful to Professor J. K. Kochi and Drs. R. Konaka and S. Terabe for their invaluable help with the instrumentation. We are indebted to Professor Y. Deguchi for giving them a chance to use the JEOL JEC-6 computer for the simulation of ESR spectra and to Dr. P. J. Krusic for critical reading of the manuscript.

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Takashi Kawamura,* Masaji Matsunaga, Teijiro Yonezawa
Department of Hydrocarbon Chemistry
Faculty of Engineering, Kyoto University
Sakyo-ku, Kyoto 606, Japan
Received October 7, 1974

Mechanism of the Reaction of Dithiols with Flavins

Sir:

We are extending the work of Gascoigne and Radda[1] on the aqueous reaction of flavins (e.g., 3-carboxymethyllumiflavin (I) which cannot undergo ionization at N(3) (riboflavin $pK_a \sim 10$)[2]) with dithiols (e.g., dithiothreitol (DTT)). We confirm that the reaction is first order in flavin and dithiol. Linear buffer catalysis is observed between pH 7 and 11 and a change in rate determining step occurs below pH 7 and above pH 11. Our results support the mechanism depicted in Scheme I, in which a C(4a) adduct is formed. This scheme may be compared with mechanisms suggested previously by others.[1,3]

Data (open circles) for the solvent reaction are compared in Figure 1 with a theoretical curve (solid line) based on best fit values for the rate constants for attack processes and for breakdown of the covalent intermediate.[4] The correspondence between curves a0, a1, a2, and b in Figure 1 and the rate constants of Scheme I is presented in Table I. Details of the kinetic analysis shall be presented elsewhere.

Scheme I

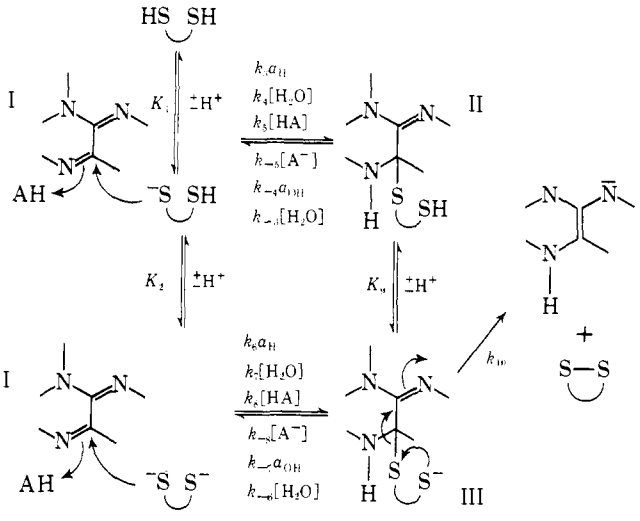

Table I. Correspondence between Curves of Figure 1 and Rate Constants of Scheme I

Curve, Figure 1	Rate law	Definition of rate constants with respect to Scheme I
a0	k_{a_0}[HS–SH] [I]	$k_{a_0} = k_3K_1$
a1	K_{a_1}[HS–S$^-$] [I]	$k_{a_1} = (k_4[H_2O] + k_6K_2)$
a2	k_{a_2}[$^-$S–S$^-$] [I]	$k_{a_2} = k_7[H_2O]$
b	k_b[HS–S$^-$] [I]	$k_b = \dfrac{k_{10}(k_5a_H + k_4[H_2O] + k_6K_2 + k_7K_2[H_2O]/a_H)}{\dfrac{k_{-5}a_H[H_2O]}{K_9} + \dfrac{k_{-4}K_W}{K_9} + k_{-6}[H_2O] + k_{-7}a_{OH}}$

We propose that the reaction does not involve hydride transfer, that a covalent intermediate is formed, that the site of attack by sulfur is C(4a), and that general acid catalysis occurs at N(5).[5] We observe buffer rate terms of the form, k_{B_2} [$^-$S–S$^-$][HA][I]. For hydride transfer one sulfur atom must be protonated, so the kinetically equivalent expression, k_{B_2}' [$^-$S–SH][A$^-$][I], must be considered. This term requires general base catalyzed hydride transfer from sulfur to flavin for which we are unable to draw a reasonable mechanism.

Below pH 7 and above pH 11, where no ionizations occur among reactants, another rate parameter (curve b in Figure 1) must be included in the overall rate expression to explain the results. This suggests a change from rate determining attack to rate determining breakdown of an intermediate and argues against any one-step mechanism, including hydride ion transfer. When breakdown (curve b) is *not* rate determining (ca. pH 7–11) buffer catalysis is observed (rate terms: k_{B_1} [HS–S$^-$][HA][I] and k_{B_2} [$^-$S–S$^-$][HA][I]). As breakdown becomes rate determining at pH greater than 11 buffer catalysis is lost, while at pH less than 7 a new buffer term is observed.[6]

Buffer catalysis probably does not involve the general base catalyzed removal of a proton from un-ionized thiol in a concerted rate determining attack on I. If this were the mechanism of buffer catalysis, the observed rate that might be reached by adding buffer would never exceed the rate of the fully ionized sulfur, because HS–S$^-$ would always be a better nucleophile than HS–SH ··· A$^-$. We observe, however, that buffers can increase the rate at least 50% above the calculated rate for HS–S$^-$ (data not presented). The view that catalysis does not involve the removal of a sulfur proton is consistent with the reaction of thiols with carbonyls.[7] Formation of hemithioacetals by weakly basic thiols proceeds with thiol anion attack at carbon and general acid catalysis at oxygen.[7a,b] The corresponding reaction of strongly basic thiols does not show buffer catalysis.[7c]

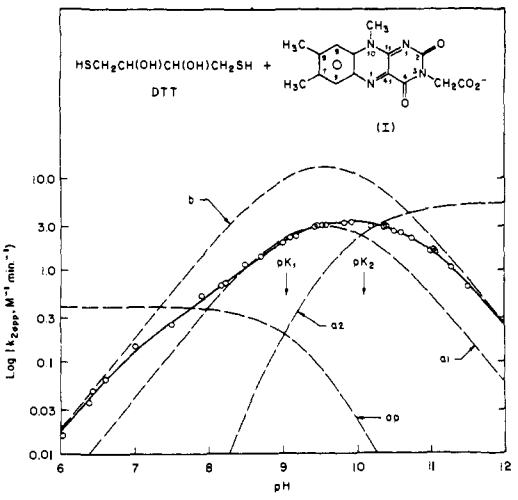

Figure 1. pH–rate profile of the reaction of dithiothreitol (DTT) with 3-carboxymethyllumiflavin (I) in water. Reactions were carried out anaerobically under argon at 25°, μ = 1.0 (KCl) by following reduction of I at 448 nm. Pseudo-first-order plots with excess DTT were obtained with a variety of buffers and extrapolated to zero buffer concentrations. Curves a0, a1, and a2 represent individual contributions from the kinetically distinguishable attack terms, respectively, k_{a0} [HS–SH][I], k_{a1} [HS–S$^-$][I], and k_{a2} [$^-$S–S$^-$][I]. Curve b represents the breakdown term, k_b [HS–S$^-$][I]. Solid curve, log (k_{2app}), is based on best fit values for k_{a0}, k_{a1}, k_{a2}, and k_b: 0.40, 4.8, 5.3, and 21 M^{-1} min^{-1}, respectively. Open circles are data.

A reaction to form a covalent flavin–thiol adduct followed by SN2 displacement at the sulfur bound to flavin by a second thiol anion must generate a formal negative charge at the N(5) and N(1) positions in the two steps of the reaction. A comparison of the acidities of the conjugate acids of these N-anions indicates their relative stabilities. Because the pK_a of N(5) in II, III or reduced I should be high (pK aniline ~27,[8] p$K_{N(5)H}$ in II ~ 24[9]) compared to the pK_a of N(1) in reduced I (pK_a = 6.6),[10] the step which develops charge on N(5) may exhibit buffer (i.e., general acid) catalysis.[11,12] The step which develops charge on N(1) can not be general acid catalyzed (at least at pH values above the pK_a of N(1) in reduced I), because N(1) protonation would lead to a thermodynamically less stable product.[15]

Adduct formation at C(4a) would develop negative charge at N(5) in attack and at N(1) in breakdown. If the reaction occurred by this mechanism, then curves a0, a1, and a2 would represent attack steps, because they are rate determining between pH 7 and 11 where buffer catalysis is observed. Curve b would represent breakdown, because when it is rate determining at high pH[6] there is loss of buffer catalysis. This is consistent with the results. Adduct formation at N(5) would develop negative charge at N(1) in attack and at N(5) in breakdown. By this mechanism curves a0, a1, and a2 would represent breakdown steps and curve b would represent the attack of HS–S$^-$ on I with rate term, k_b[HS–S$^-$][I]. This mechanism is unreasonable by the following argument. Up to pH 11.5 we find no contribution from a rate term of the form, $k_{b'}$ [$^-$S–S$^-$][I]. This requires that the rate constant ($k_{b'}$) for attack of $^-$S–S$^-$ (the predominant species at high pH) at N(5) must be at least 30 times smaller than k_b, which seems unlikely. Attack at C(6) or C(8) predicts results similar to attack at N(5). Attack at C(1a) has been previously ruled out.[16]

Reaction of monothiols with flavins[17,18] also is consistent

with the proposed mechanism. This reaction shows no buffer catalysis and has the rate law, k_m [RSH][RS$^-$][flavin], consistent with a breakdown step analogous to k_{10} in Scheme I being rate determining. Breakdown from an N(5) adduct is inconsistent with these results, because the reaction should then be buffer catalyzed, as discussed above. The breakdown step with dithiols is faster because of proximity effect.[19]

The attack of a thiol anion at C(4a) is analogous to the attack of thiols on imines, a reaction for which there is chemical precedent.[20] Breakdown of adduct III is somewhat analogous to the reaction of thiols with thiocyanate,[21] and the leaving group (reduced flavin anion) is similar to an anionic enamine. Thiol attack at C(4a) with general acid catalaysis at N(5) is analogous to the general acid catalyzed attack of sulfite on C(4a).[22]

We have demonstrated that an oxidation-reduction reaction of flavins with dithiols proceeds by way of a covalent intermediate. This reaction may serve as a model for lipoic acid dehydrogenase, thioredoxin, and glutathione reductase.

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(5) Steps k_3 and k_6 in Scheme I could represent specific acid catalysis if the pK for protonated N(5) in I were greater than about −2. Steps k_4 and k_7 could represent stepwise thiol addition at C(4a) followed by diffusion controlled protonation by water at N(5) if pK of N(5) in II or III were less than about 24. These possibilities are under investigation.
(6) Below pH 7 in a range where breakdown is 50% or more rate determining there is a transition from one buffer term to another. This new term could represent either general acid catalysis at N(1) in breakdown (below the pK_a of N(1) in reduced I) or general base catalyzed removal of a sulfur proton from II.
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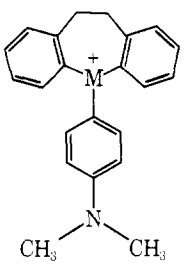
Edward L. Loechler, Thomas C. Hollocher*
Department of Biochemistry, Brandeis University
Waltham, Massachusetts 02154
Received February 10, 1975

Generation of a Silicenium Ion in Solution[1]

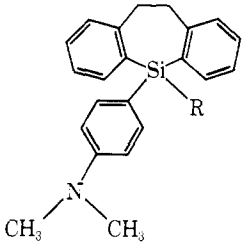
Sir:

Five-coordinate siliconium ions have been reported in salts such as $[(C_6H_5)_3Si(2,2'\text{-bipy})]I$[2] and $[SiH_3(2,2'\text{-bipy})]Co(CO)_4$[3] but no definitive examples of the generation of a trivalent silicenium ion in solution or in the solid state have yet been reported. Although carbenium ions have been studied by physicochemical methods, have been prepared as salts, and are widely accepted intermediates in organic chemistry, the literature contains a number of reports describing unsuccessful attempts to demonstrate the formation of R_3Si^+ in solution by methods that have proved useful in carbenium ion chemistry.[4,5]

The carbenium ion model chosen for the present study was the moisture and air stable carbocation **1b**.[7] The value of pK_{R^+} for **1b** is at least 11 orders of magnitude greater than that of triphenylcarbenium ion (pK_{R^+} = −6.6), which is a commonly used and convenient hydride abstraction reagent.[8]



1a, M = Si
b, M = C



2a, R = H
b, R = D
c, R = OH

The silane precursor **2a** of the silicenium ion **1a** was readily prepared in 54% yield by the reaction of *o,o'*-dilithiobibenzyl with *p*-dimethylaminophenyldichlorosilane.[9] The silane **2a** was purified by recrystallization from heptane to give a solid: mp 100–101.5°; NMR (CCl_4, δ relative to TMS) 7.7–6.55 (m, 11.8, aromatics), 5.5 (s, 0.87, SiH), 3.17 (s, 4.12, $-CH_2CH_2-$), 2.87 (s, 6.17, NMe_2); ir (CCl_4) 2118 cm^{-1} (SiH); *m/e* (70 eV) 329.

Reaction of 0.71 g (2.16×10^{-3} mol) of silepin **2a** with 0.74 g (2.16×10^{-3} mol) of triphenylcarbenium perchlorate in methylene chloride (25 ml)[10] at −40 to −50° generates a yellow-green solution. Rapid addition of this solution to a cold solution of $NaBD_4$ in dry diglyme resulted in an instantaneous discharge of color. After removal of the solvents at 30° under vacuum, the residue was dissolved in CH_2Cl_2 and filtered to remove excess $NaBD_4$, and the organic layer was hydrolyzed with water. The products were separated by column chromatography (silica gel) using hexanes–benzene as eluant. Triphenylmethane was obtained in 83% yield and the silepin **2b** was obtained in 70% yield: mp 101–102°; NMR ($CDCl_3$, δ relative to TMS), 7.8–6.6 (multiplet, 11.9, aromatics), 3.2 (s, 4.28, $-CH_2CH_2-$), 2.87 (s, 5.80, NMe_2); *m/e* (70 eV) 330. The deuterated silepin **2b** may contain a trace of starting silepin **2a** as indicated by a very weak residual ir absorption at 2118 cm^{-1}.[12] A similar trapping experiment with a slurry of $NaBH_4$ in wet dioxane afforded triphenylmethane, silepin **2a**, and silanol **2c**, in 81, 36, and 62% yields, respectively.

When the cold yellow-green reaction mixture was allowed to warm to room temperature, brilliant blue-green solutions were produced. Although triphenylmethane can be isolated in 75–88% yields from the room-temperature reactions, treatment of the remaining blue, solid, silicon-containing materials with either $NaBH_4$, $NaBD_4$, or H_2O did not afford products identifiable with the starting silepin skeleton.