mixtures were done by Phil Irving, Hans-Kasper Wipf, Malcolm McCamish, Babu Venkataraghavan, and Karsten Levsen. I am particularly indebted to Tim Wachs and Paul Bente for reversing the geometry and computerizing the Hitachi RMU-7 used in the bulk of our MS/MS research in the last decade. The design of the new tandem double-focusing MS was done largely by Peter Todd with the construction by him, Mike Baldwin, Don McGilvery, Mike Barbalas, Greg Wendel, and Mike Wixom, and with important contributions from Henk Boerboom, Peter Derrick, and Richard Porter. Frank Bockhoff performed the extensive recent MS/MS studies including those on the gasoline mixture and phosphate chirality. Myung Kim greatly improved our basic understanding of the collision process. Finally, none of this research would have been possible without the generous financial support of the National Institutes of Health and the Army Research Office, Durham.

Intramolecular Iminium Ion–Sulfide Charge-Transfer Association: A Recurring Theme in the Study of Thiaspirane Alkaloids

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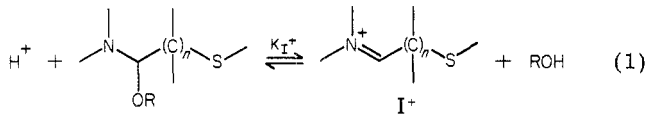
The aquatic macrophyte *Nuphar luteum*, commonly known as the yellow pond lily or spatterdock, produces piperidine and quinolizidine alkaloids having a regular sesquiterpenic carbon skeleton.[1] The quinolizidine structure is also incorporated, along with a sulfur atom, in a C_{30} dimer alkaloid, referred to as a thiaspirane. Through configurational change at C-7 and C-7′, four stereoisomeric types are possible (see Figure 1). Indeed three, **1**–**3**, of the four types have been isolated and the fourth, **4**, has been prepared from **1**.[2] The three natural thiaspiranes occur as diamines (R_1, R_2, R_3, R_4 = H), monohemiaminals (R_1, R_2 = H, OH; R_3 = R_4 = H or R_1 = R_2 = H; R_3, R_4 = H, OH) and bishemiaminals (R_1, R_2 = R_3, R_4 = H, OH). However in comparison to the diamines, the thiaspirane hemiaminals proved the more interesting since these possessed exceptional properties attributed to the intramolecular charge-transfer association of sulfur with iminium ion, the latter being in equilibrium with the hemiaminal as shown in eq 1.



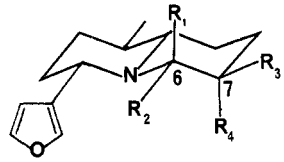
I-OR

Thus this Account is concerned with α- (I^+, n = 1) and β-thioiminium ions (I^+, n = 2), the corresponding thiohemiaminals (I-OR, R = H), and the manifestation of the charge-transfer association whose character is supported by additional observations disclosed herein. However for the most part the observations discussed here are those made in the course of structure studies carried out in my laboratory and others over the course of recent years.

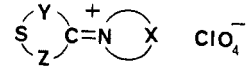
Robert T. LaLonde received his B.A. degree from St. John's University, MN, in 1953 and the Ph.D. from the University of Colorado, Boulder, CO, in 1957. After being employed by the Jet Propulsion Laboratories in Pasadena, CA, he engaged in postdoctoral research at the University of Illinois, Urbana, and joined the SUNY College of Environmental Science and Forestry in 1959. He is now Professor of Chemistry. Among his current research interests are natural products of significance to aquatic ecology.

Optical Properties Consistent with an Intramolecular Charge-Transfer Association

An early indication of sulfur–iminium ion interaction came from the UV spectra of hemiaminals. Thus spectra of thiohemiaminals such as **3** (R_1 = R_2 = H; R_3, R_4 = H, OH), **3** (R_1, R_2 = R_3, R_4 = H, OH) and the synthesized epimeric pair **5** and **6** in neutral 95% eth-



5, R_1, R_2 = H, OH; R_3 = SCH_3; R_4 = CH_3
6, R_1, R_2 = H, OH; R_3 = CH_3; R_4 = SCH_3
7, R_1 = R_2 = H; R_3 = SCH_3; R_4 = CH_3
8, R_1 = R_2 = H; R_3 = CH_3; R_4 = SCH_3
9, R_1, R_2 = H, OH; R_3 = CH_3; R_4 = OH
17, R_1 = R_2 = R_3 = H; R_4 = CH_3
18, R_1 = H; R_2 = D; R_3 = SCH_3; R_4 = CH_3
19, R_1 = D; R_2 = H; R_3 = CH_3; R_4 = SCH_3
21, R_1 = D; R_2 = H; R_3 = OH; R_4 = CH_3
22, R_1 = H; R_2 = D; R_3 = OH; R_4 = CH_3
23, R_1, R_2 = H, OH; R_3 = p-$SC_6H_4CH_3$; R_4 = CH_3
24, R_1 = D; R_2 = H; R_3 = p-$SC_6H_4CH_3$; R_4 = CH_3
25, R_1 = H; R_2 = D; R_3 = p-$SC_6H_4CH_3$; R_4 = CH_3



10, X = $(CH_2)_4$; Y = CH_2; Z = $(CH_2)_2$
11, X = $(CH_2)_5$; Y = CH_2; Z = $(CH_2)_2$
12, X = $(CH_2)_4$; Y = Z = $(CH_2)_2$
13, X = $(CH_2)_4$; Y—S = $CH_2SCH_2CH_3$; Z = CH_3
14, X = $(CH_2)_5$; Y—S = $CH_2SCH_2CH_3$; Z = CH_3

15, X = $(CH_2)_4$; Y = $(CH_2)_5$
16, X = $(CH_2)_5$; Y = $(CH_2)_5$

anol were transparent beyond 250 nm. But in acidic

(1) J. T. Wróbel, *Alkaloids*, **16**, 181 (1977).
(2) R. T. LaLonde and C. F. Wong, *Can. J. Chem.*, **56**, 56 (1978).

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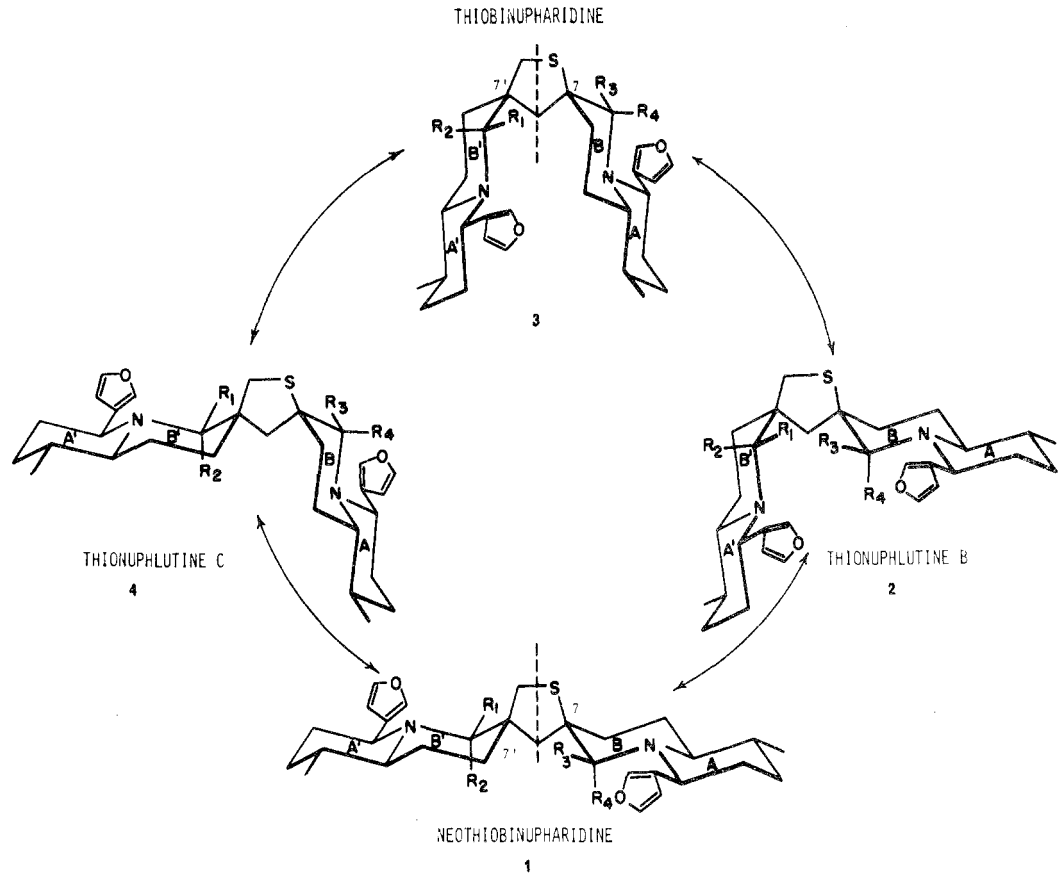


Figure 1. The four stereochemical classes of Nuphar thiaspirane alkaloids showing conceptual interconversion achieved through rotating AB and A′B′ quinolizindine ring systems about C-7 and C-7′, respectively. Dashed vertical lines represent "pseudo-C_2" axes which distinguish the "pseudosymmetrical" types.

ethanol, a band ($\epsilon \simeq 2000$) at 295 nm appeared. The band's appearance was reversible; it disappeared on basification but reappeared on reacidification. The diamine alkaloids **1** and **3** ($R_1 = R_2 = R_3 = R_4 = H$) in acid revealed no such band nor did the β-thio tertiary amines **7** and **8**.[3] The α-hydroxy hemiaminal **9**, as its iminium perchlorate in 95% ethanol, produced only short-wavelength end absorption (ϵ_{220} 8000) in the region (220–235 nm) characteristic of simple iminium ions.[4] Subsequently, Dr. Richard Hammer, working in my laboratory, observed that α- and β-thioiminium perchlorates (**10**–**14**) in acetonitrile gave weak bands (ϵ 170–1000) in the 275–295-nm region where the spectra of **15** and **16** were transparent.[5] All these UV observations were consistent with charge-transfer (CT) behavior,[6] which had been demonstrated earlier in a similar case—the intramolecular interaction of divalent sulfur with carbonyl in thiacyclic ketones.[7-9] However in the present instance, the ground-state association involves redistribution of charge which is distinguished from separation of charge involved in previous CT cases. Consequently a solvent change is unlikely to influence significantly the position of the absorption maximum. Full redistribution of charge to sulfur, generating a thiiranium ion, seems to be an unsatisfactory representation of ground-state association in α-thioiminium ions in view of the following consideration. Neutral thiiranes absorb weakly in the range 259–262 nm (ϵ <50).[10,11] But while there is well-known kinetic, stereochemical, and spectral evidence for thiiranium ions,[12] there has never been a report that these ions absorb in the UV. Moreover, the observation of the CT bands is not limited to cases of α-thioiminium ions but includes β-thioiminium ions where formation of thietanium ions in thiaspiranes is precluded for steric reasons.

The investigation of thiohemiaminal circular dichroism (CD), an obvious extension of the UV studies, was intended to find a facile method for distinguishing stereochemical types of thiaspiranes. This goal was achieved, but the studies also demonstrated the chiroptical dependence of the 295-nm CT band. As shown in Figure 2, the pseudoenantiomeric pair **5** and **6**, as iminium perchlorates in 95% ethanol, gave positive ($[\theta]^{25}_{298}$ 22 000 (*c* 1.5 mg/10 mL)) and negative ($[\theta]^{25}_{300}$ −14 000 (*c* 0.8 mg/5 mL)) CD bands, respectively.[13] Since the relative configuration of C-7 was known and **5** and **6** were prepared from (*R*,*S*,*S*,*S*)-(−)-1,4,7,10-deoxynupharidine (**17**), the correlation of the C-7 configuration with the sign of the CD band for α-thio-

(3) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Am. Chem. Soc.*, **95**, 6342 (1973).
(4) G. Opitz, H. Hellmann, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 117 (1959).
(5) Satisfactory elemental analyses and spectra consistent with the structures of all iminium salts were obtained.
(6) N. J. Turro, "Modern Molecular Photochemistry", Benjamin/Cummings, Menlo Park, CA, 1978, pp 135–7.
(7) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Am. Chem. Soc.*, **82**, 4075 (1960).
(8) L. A. Paquette and L. D. Wise, *J. Am. Chem. Soc.*, **89**, 6659 (1967).
(9) A. Padwa and A. Battisti, *J. Am. Chem. Soc.*, **94**, 521 (1972).
(10) R. E. Davis, *J. Org. Chem.*, **23**, 216 (1958).
(11) D. J. Pettitt and G. K. Helmkamp, *J. Am. Chem. Soc.*, **28**, 2932 (1963).
(12) W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, **8**, 482 (1969).
(13) R. T. LaLonde and C. F. Wong, *J. Org. Chem.*, **38**, 3225 (1973).

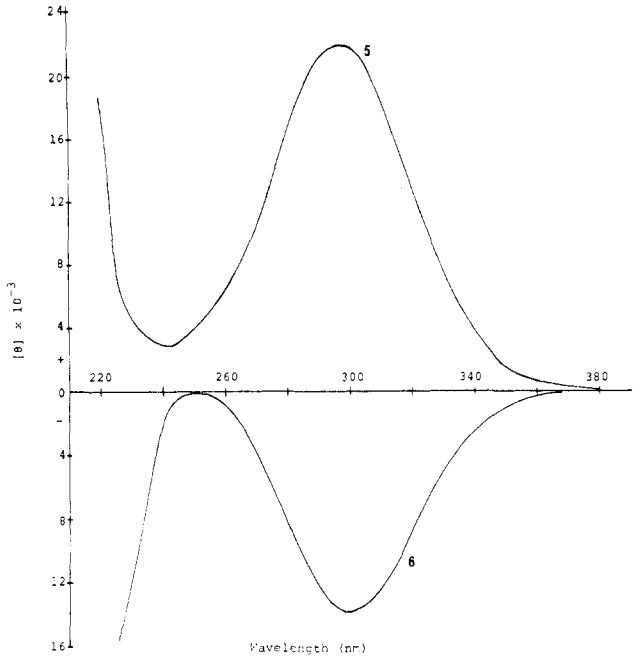


Figure 2. The circular dichroism of **5** and **6**, as iminium perchlorates, in 95% ethanol.

iminium ions was secured. The equatorial conformation of the C-7 sulfur atom in 6-hydroxythiobinupharidine (**3**, $R_1 = R_2 = H$; R_3, R_4 = H, OH) had been established independently.[14] Thus the (*S*)-7 configuration was determined by the positive CD band occurring at 295 nm, as shown in Figure 3. 6-Hydroxyneothiobinupharidine (**1**, $R_1 = R_2 = H$; R_3, R_4 = H, OH), having a C-7 axial sulfur atom, possessed the (*R*)-7 configuration since this α-thiohemiaminal in acid produced a negative CD band at 295 nm (Figure 3). The same relation is exhibited by the corresponding pair of β-thiohemiaminals, **1** (R_1, R_2 = H, OH; $R_3 = R_4 = H$) and **3** (R_1, R_2 = H, OH; $R_3 = R_4 = H$). However, as Figure 3 reveals, the CD bands resulting from β-thioiminium ions appear in the shorter 275-nm region while the α-thioiminium bands appear at the longer 295-nm region.[15,16] Thus, CT CD bands resulting from (*S*)-7, (*S*)-7′, (*R*)-7 and (*R*)-7′ configurations are unique in terms of the combination of their sign and wavelength.

As might be expected from the foregoing, the acidic solution CD of 6,6′-bishemiaminals produced bands both at the short- and long-wavelength regions as revealed by the bisiminium perchlorate of (*R*,*S*)-6,6′-dihydroxy-7,7′-thionuphlutine B, **2** (R_1, $R_2 = R_3$, R_4 = H, OH), which gave a negative band at 308 nm but a positive band at 277 nm.[13] Similarly, the bisiminium perchlorate of (*S*,*S*)-6,6′-dihydroxy-7,7′-thiobinupharidine, **3** (R_1, $R_2 = R_3$, R_4 = H, OH), produced two positive bands, as shown in Figure 4. However, from the study carried out by Dr. Chunfook Wong, it appears that the β-thioiminium ion, located at C-6′, is much more sensitive to solvolysis than the α-thioiminium ion, located at C-6, since upon stepwise dilution from a 1 mM to a 0.17 mM 95% ethanol solution (roughly a 5-fold dilution) the shorter wavelength band disappeared while the longer one was unchanged. Addition

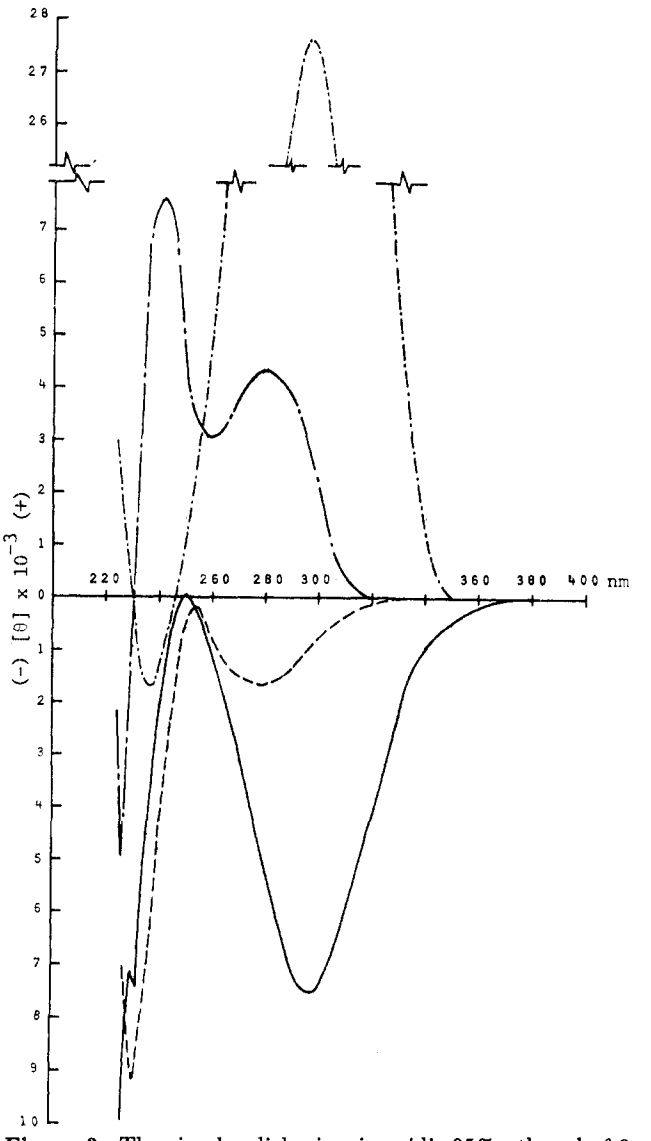


Figure 3. The circular dichroism in acidic 95% ethanol of 6-hydroxythiobinupharidine (**3**, $R_1 = R_2 = H$; R_3, R_4 = H, OH) (-·-·), 6′-hydroxythiobinupharidine (**3**, R_1, R_2 = H, OH; $R_3 = R_4$ = H) (—··—), 6-hydroxyneothiobinupharidine (**1**, $R_1 = R_2 = H$; R_3, R_4 = H, OH) (—), and 6′-hydroxyneothiobinupharidine (**1**, R_1, R_2 = H, OH; $R_3 = R_4 = H$) (- - -).

of perchloric acid to the 0.17 mM solution resulted in the reemergence of the shorter wavelength band.

The appearance of two CD bands, one characteristic of α-thioiminium ions and the other characteristic of β-thioiminium ions, is an argument for an intramolecular CT interaction. That two distinct CD bands would arise from the intermolecular association of sulfur in one molecule with one or the other iminium ions in a second is incomprehensible in view of the near-C_2 symmetry of the thiobinupharidine ring system. Additional evidence pertinent to the question of intra- vs. intermolecular CT has been obtained by Dr. Timothy Eckert who has made observations working with α-thio hemiaminal **6** and α-hydroxy hemiaminal **9**.[17] The optical density of the 292-nm UV band was measured at several concentrations, ranging from 10^{-4} to slightly more than 10^{-3} M, for **6** in acidic 95% ethanol. A plot of the optical density against I-OR concentration gave a straight

(14) R. T. LaLonde, C. F. Wong, and H. G. Howell, *J. Org. Chem.*, **36**, 3703 (1971).
(15) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Org. Chem.*, **39**, 2892 (1974).
(16) R. T. LaLonde and C. F. Wong, *J. Org. Chem.*, **41**, 291 (1976).
(17) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Am. Chem. Soc.*, **94**, 8522 (1972).

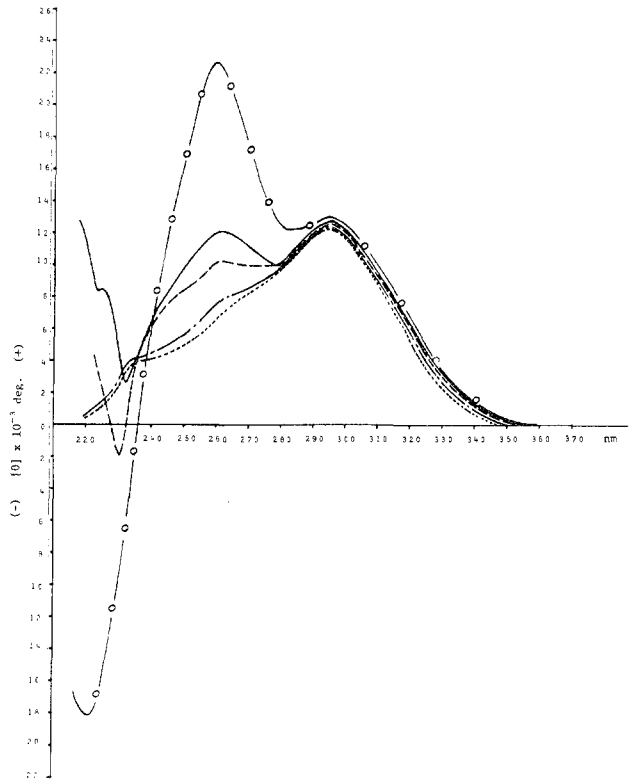


Figure 4. The circular dichroism, determined in 95% ethanol, of the bisiminium perchlorate of 6,6′-dihydroxythiobinupharidine (**3**, R_1, R_2 = H, OH; R_2, R_4 = H, OH) at concentrations: 1 mM (—), 0.5 mM (– – –), 0.25 mM (—·–), 0.17 mM (· · ·), and 0.17 mM + 2 drops of 0.2 M $HClO_4$ (—o—). Curves for the first four solutions are in fact coincidental from 280 to 360 nm but are offset slightly from one another to show the shape of each.

line. This result is consistent with the expected behavior of an intramolecular association but inconsistent with an intermolecular dimeric association since the latter requires a $[\text{I-OR}]^2$ dependency of the optical density of the absorbing species. Furthermore, the acidified α-hydroxy hemiaminal **9** at 5.8×10^{-4} M showed no band in the 250–300-nm region either in the absence or presence of an excess of thiolane.

The influence of sulfur in stabilizing the iminium ion against solvolysis has been observed by Dr. Wong by comparing log K'_{I^+} values for the α-thioiminium ions from **5** and **6** and the α-hydroxyiminium ion from **9**. Expression 2 follows from the equilibrium reaction, eq 1. Since the concentration of hydroxylic solvent

$$K_{I^+} = [\text{HOR}][I^+]/([\text{I-OR}][H^+]) \quad (2)$$

([HOR]) is large in relation to iminium ion I^+, and therefore remains essentially constant, expression 2 reduces to eq 3, where $[H^+]_{1/2}$ is the hydrogen ion

$$K'_{I^+} = [I^+]/([\text{I-OR}][H^+]_{1/2}) \quad (3)$$

concentration at the point of one-half ionization to iminium ion. At this point, [I-OR] = $[I^+]$ and therefore

$$\log K'_{I^+} = \text{pH}_{1/2} \quad (4)$$

Thus by plotting the absolute value of the molecular ellipticity $[\theta]$ against pH, the S-shape curves shown in Figure 5 were obtained. The $\text{pH}_{1/2}$ was determined from the curves as the pH at which $[\theta]$ is half the difference of the maximum $[\theta]$ at the lowest pH and the minimum $[\theta]$ at the highest pH. In this manner log K'_{I^+} values of 7.8, 7.0, and 5.9 were obtained for iminium

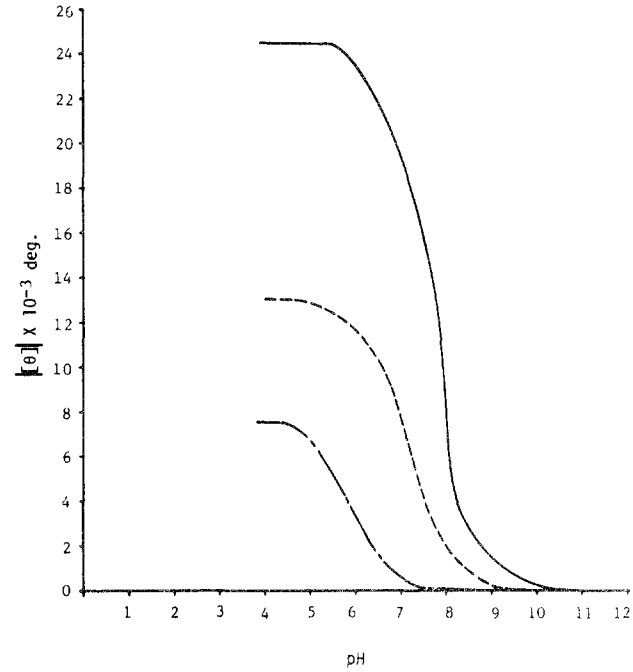


Figure 5. Plots of the absolute value of $[\theta]$ vs. pH for **5** (—), **6** (– – –), and **9** (—··–). CD for values of $[\theta]$ were determined in methanol–water solution (70:30) which was adjusted to an initial pH of about four with acetic acid. Subsequent pH adjustments were made by adding aqueous sodium hydroxide solution.

ions from **5**, **6**, and **9**,[18] respectively. The meaning of these log K'_{I^+} values is the following. The α (used in the usual steric sense) methylthio group in **6** stabilizes the iminium ion against solvolysis ($K_{sol} = 1/K_{I^+}$) by a factor of slightly more than 10 compared to the α hydroxyl group in **9**. This factor of stabilization reflects, at least in part, a contribution of the sulfur–iminium ion CT complex against solvolysis in relation to the α-hydroxy iminium ion, an ion for which no evidence of CT interaction is manifest. The difference in the log K'_{I^+} values for the epimeric thioiminium ions **5** and **6** would seem to reflect the greater resistance to solvolysis of **5** from the α surface than **6** from the β surface. This interpretation will be echoed by results obtained in the studies reviewed in the next section.

Stereoselectivity of Metal Hydride Reductions

In connection with mass spectral examinations performed in the course of structure elucidation, deuterium-labeled thiaspiranes were prepared by reducing the hemiaminal forms with sodium borodeuteride in alcoholic solvents.[3,19] 6,6′-Dihydroxythionuphlutine B (**2**, R_1, R_2 = R_3, R_4 = H, OH) underwent reduction with the incorporation of two atoms of deuterium, which were axial at both C-6 and C-6′ as determined by ^{1}H NMR. Under the same conditions, which involved the use of methanol[20] as solvent, 6,6′-dihydroxythiobinupharidine (**3**, R_1, R_2 = R_3, R_4 = H, OH) incorporated one axial and one equatorial deuterium. Since evidence pointed to the same configuration at C-7′ in both thiaspiranes, it was reasoned that the same steric mode of reduction occurred at C-6′, but the variable steric mode of re-

(18) The positive iminium ion CD band of **9** in acidic methanol–water (70:30) solution was observed at 234 nm.

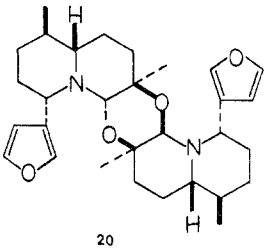
(19) R. T. LaLonde, C. F. Wong, and W. P. Cullen, *Tetrahedron Lett.*, 4477 (1970).

(20) Methanol used for these experiments was distilled prior to use, but no precautions were taken to dry it.

duction occurred at C-6 in the two molecules. That is, both doubly labeled thiaspiranes contained axial deuterium at C-6′; likewise thionuphlutine B contained an axial deuterium at C-6, but at the same carbon thiobinupharidine contained an equatorial deuterium atom. It was reasoned further that the two bishemiaminals incorporated deuterium in a different steric mode at C-6 because the adjacent sulfur atom mediated the reduction of intermediate iminium ions by forcing the reduction to take place antiperiplanar with respect to the sulfur atom. Thus the steric mode of deuterium incorporation at C-6 indicated the configuration at C-7. That this interpretation regarding configuration was correct was shown by the X-ray study of thiobinupharidine.[21] Similarly, 6-hydroxythiobinupharidine (**3**, R_1 = R_2 = H; R_3, R_4 = H, OH) underwent reduction with the incorporation of equatorial deuterium at C-6. However, a reinvestigation of the C-6 deuterium incorporation by 300 MHz ^{1}H NMR showed that the actual amount of C-6 equatorial deuterium in the doubly and singly labeled thiobinupharidines was not 100% but 82 and 84%, respectively.[22] MacLean, Wróbel, and co-workers observed deuterium incorporation occurred with less stereospecificity. Equatorial deuterium accounted for only 40% of that introduced.[23] However, these workers employed the less acidic and polar dry ethanol as the solvent. The important point regarding the steric mode of C-6 reduction is that any equatorial incorporation occurred at all. Considering that only axial incorporation took place at C-6′ and thiobinupharidine has near-C_2 symmetry, axial incorporation at C-6 might have been expected also. Moreover to obtain C-6 equatorial reduction, the reducing agent must have approached the substrate from the direction of the more highly hindered convex surface. Thus it was on the basis of this remarkable steric result and its rationale that some sort of sulfur–iminium ion association first was recognized.

The stereospecificity of C-6 reduction in the naturally occurring thiaspirane hemiaminals was observed also in simpler synthetic analogues.[3,24] For example, when **5**, containing equatorial SCH_3, was treated with sodium borodeuteride in methanol, the tertiary amine **18** possessing 85% C-6 equatorial deuterium was obtained. But diastereomeric **6**, containing axial SCH_3, gave **19**, possessing only axial deuterium at C-6. Furthermore, the reduction of **6** occurred about 800 times faster than the reduction of **5**, a result reflecting the greater ease of β steric attack of the nucleophile.

The nature of the substrate and the reducing conditions greatly influenced the steric outcome. Once again the combination of sulfur and hemiaminal, required for the observance of the CT band, appeared necessary for stereospecific reduction as well since the oxirane dimer **20**, a hemiaminal ether, reduced with sodium borodeuteride in methanol gave the deuterium-labeled **21** and **22** in a 50:50 ratio.[17] The influence of the reducing agent can be exemplified by an observation made by Dr. Wong. The arylthio hemiaminal



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23 reduced with lithium aluminum deuteride in the much less polar ether gave tertiary amines **24** and **25** in a 50:50 ratio while a similar aryl thiohemiaminal treated with sodium borodeuteride in methanol underwent stereospecific reduction, giving a tertiary amine possessing 85% equatorial deuterium at C-6.[24]

To this point, the results reviewed in this section indicate the reduction of the α-thio hemiaminals by sodium borodeuteride in methanol is a stereospecific process dependent on the configuration of an adjacent sulfur-bearing carbon. This is not the case for the homologous β-thio hemiaminals, at least not those incorporated in the thiaspirane skeleton. The following comparison illustrates the point. As noted above, 6,6′-dihydroxythiobinupharidine (**3**, R_1, R_2 = R_3, R_4 = H, OH), having the (*S*)-7′ configuration, yielded doubly labeled thiobinupharidine possessing axial deuterium at C-6′. But reduction of 6′-hydroxyneothiobinupharidine (**1**, R_1, R_2 = H, OH; R_3 = R_4 = H), having the (*R*)-7′ configuration, gave the labeled neothiobinupharidine (**1**, R_1 = R_3 = R_4 = H, R_2 = D), also possessing axial deuterium at C-6′. Thus, the reduction of thiaspirane β-thio hemiaminals resulted in axial incorporation of deuterium regardless of C-7′ configuration.

Qualitatively, the relative rates of the two steric modes of α-thio hemiaminal reduction and the single mode of β-thio hemiaminal reduction have emerged from the reductions of bishemiaminals performed in the presence of only a single equivalent, or less, of the reducing agent. The results of these experiments, carried out in methanol, are summarized in the three reactions, eq 5–7.

6,6′-dihydroxythionuphlutine B → **2**, R_1, R_2= R_3, R_4 = H, OH

6′-hydroxythionuphlutine B[15] (5)
2, R_1, R_2 = H, OH; R_3 = R_4 = H

6,6′-dihydroxyneothiobinupharidine → **1**, R_1, R_2 = R_3, R_4 = H, OH

6′-hydroxyneothiobinupharidine[25,26] (6)
1, R_1, R_2 = H, OH; R_3 = R_4 = H)

6,6′-dihydroxythiobinupharidine → **3**, R_1, R_2= R_3, R_4 = H, OH

6-hydroxythiobinupharidine-6′-*d*[15] (7)
3, R_1 = H; R_2 = D; R_3, R_4 = H, OH

Equations 5 and 6 indicate that the reduction of C-6_{ax} > C-$6'_{ax}$, while eq 4 shows the reduction of C-$6'_{ax}$ > C-6_{eq}. It follows that C-6_{ax} > C-$6'_{ax}$ > C-6_{eq}. This relationship is consistent with the previously mentioned observation that the C-6_{ax} reduction of α-thio hemi-

(21) J. T. Wróbel, B. Bobeszko, T. I. Martin, D. B. MacLean, N. Krishnamachari, and C. Calvo, *Can. J. Chem.*, **61**, 2810 (1973).
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aminal **6** occurred 800 times faster than the C-6_{eq} reduction of diastereomeric **5**.

An attempt to bring together the observation of CT bands, the magnitude of K_I^+ values, and the stereochemistry and rates of reduction would seem useful in reaching the underlying basis of thiohemiaminal reactivity. The key to reconciling the various observations seems to be the thioiminium ion, whose presence is required for rapid thiohemiaminal reduction and which, when internally complexed, gives rise to the CT bands. The stereospecificity of α-thiohemiaminal reduction and the comparatively greater resistance of C-6 to solvolysis, as exhibited by 6,6′-dihydroxythiobinupharidine, mean α-thio iminium ions complex internally more strongly than their β counterparts. Axial reduction of α-thio iminium ions occurs faster than axial reduction of β-thio iminium ions because at a given pH more of the former ion exists as the active intermediate whereas the β-thio iminium ion has been converted to a greater extent by solvolysis to the inert β-thio hemiaminal. However, the stereochemical approach of the reducing nucleophile is also a determinant of reduction rate when comparing α-thio iminium ions with one another. α-Thio iminium ions requiring attack at the β surface (such as **6**) undergo reduction faster than those (such as **5**) requiring attack at the α surface for the reason that the α surface is the more hindered by the 3-furyl group, a dominant shielding factor.[27] The same steric considerations account for the α-thio iminium ion of **5** being more resistant to solvolysis than the ion from **6**.

In conclusion, two primary factors influencing the kinetic and thermodynamic properties are noted: the strength of the internal complex and the stereochemistry of nucleophilic attack. This view of thio hemiaminal chemistry, pieced together from information obtained largely from studies in another context, could also play a role in understanding biological properties of thiaspirane hemiaminals and synthetic analogues.

Biological Properties

Following the observation that 6,6′-dihydroxythiobinupharidine (**3**, R_1, $R_2 = R_3$, R_4 = H, OH) was active against human pathogenic fungi,[29] an attempt was made to ascertain the structural basis for the biological activity. The study was initiated by following the activity change upon systematic structural alteration of an α-thio hemiaminal incorporated in the simpler, but similar, C_{15} deoxynupharidine skeleton. α-Thio hemiaminals, such as a mixture of **5** and **6**, were at least as active as naturally occurring **3** (R_1, $R_2 = R_3$, R_4 = H, OH). However the α-hydroxy hemiaminal **9** and tertiary amino sulfides, such as **7** and **8**, were inactive,[24] a result indicating the necessity of the α-thio hemiaminal function. Since the antifungal tests were carried out routinely in media whose pH ranged from 5.5 to 6.5, virtually all of **5** and **6** would have been in the iminium ion form. Thus the advantage of the internally complexed iminium ion may be in the preservation of the electrophilic agent against solvent nucleophiles until the agent reaches the sensitive target site in the fungal cell. However, while the α-thio hemiaminal function is necessary, its presence alone is insufficient for activity since the α-thio hemiaminal structurally equivalent to **5** and **6** but lacking the C-1 methyl and C-4 3-furyl group was devoid of activity.[24]

Prospects

We have seen that the thiohemiaminal functional group, transformed by acid to the α-thio iminium ion, is the basis not only for the unique chemical and physical properties of the thiaspirane hemiaminals and structurally simpler analogues but also is required for their biological activity. It is the apparent α-thio iminium ion link between biological activity and the sulfur stabilization of the electrophilic iminium ion that is an intriguing prospect. A future launching point in securing this link would be to ascertain if certain sulfur atom substituents which stabilize α-thio iminium ions simultaneously influence biological activity.

Considering the thio iminium ion–biological link at the ecological level, it is interesting that Nuphar rhizomes, submerged in an environment of mud and water, should contain an antibiotic which is structurally and functionally stabilized against hydrolysis. Thus one may speculate that Nuphar's chemical defense against microorganisms is finely tuned as a result of the plant's potential to produce thio iminium ions.

However, there are several questions about thio iminium ions themselves which are interesting. How much of the positive charge customarily associated with nitrogen[30] in simple iminium ions is shared by sulfur in thio iminium ions? Are interaction and noninteraction species of thio iminium ions in equilibrium with each other? How are sulfur and iminium ion juxtaposed in crystalline thio iminium salts? Future studies of thiaspirane hemiaminals and their synthetic analogues will be directed to answering these and allied questions.

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(27) The preferential shielding of the α surface of deoxynupharidine derivatives by the 3-furyl group has been discussed previously. See footnote 15 in ref 28.

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