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Registry No. (L)-(SAH) analogue (base = adenine), 979-92-0; (D)-(SAH) analogue (base = adenine), 53276-26-9; (DL)-(SAH) analogue (base = adenine), 58976-18-4; (SAH) analogue (base = N^6-methyladenine), 53228-06-1; (SAH) analogue (base = N^6,N^6-dimethyladenine), 58936-13-3; (SAH) analogue (base = cytidine), 50615-58-2; 5′-chloro-5′-deoxyadenosine, 892-48-8; 5′-chloro-5′-deoxy-N^6-methyladenosine, 19254-36-5; 5′-chloro-5′-deoxy-N^6,N^6-dimethyladenosine, 59987-43-8; 5′-chloro-5′-deoxycytidine, 31652-78-5; L-homocysteine monosodium salt, 82695-92-9; D-homocysteine monosodium salt, 88945-99-7; DL-homocysteine monosodium salt, 28223-71-4; homocystine, 462-10-2.

Solvent Effects on Fluorescence Properties of Sodium Lasalocid (Ionophore X-537A)

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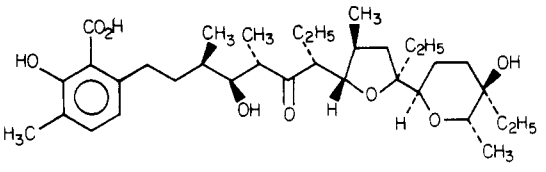
Recent interest in lasalocid has been focused on its ability to transport metal ions and biogenic amines across lipoidal membranes.[1-4] This transporting ability may be utilized to facilitate the in vivo absorption of polar molecules.[5,6] The strength of ion–lasalocid interactions and the physical–chemical properties of the associated species largely determine the rate and extent of ion transport. Fluorescence measurements have been used to obtain a relative measure of the ion–ionophore interactions.[7] Complexation of lasalocid with metal ions leads to an increase or decrease of the fluorescence intensity depending on the quantum yield of the resulting complex.[3] The compound lasalocid (I) belongs to the group of carboxylic



I

acid ionophores. It is an open-chain compound with one tetrahydrofuran ring, one tetrahydropyranic ring, and a salicylate moiety containing the carboxylate head group.

The molecule assumes an open-chain configuration in a polar environment, but in an apolar environment or upon complexation with metal ions or protonated amines, its configuration is that of a pseudocyclic ring structure characterized by a hydrophobic exterior.[8-11]

Table I. Solvent Effects on Sodium Lasalocid Fluorescence

solvent	ϵ [a]	ϕ^{rel}_f [b]	λ_{max}, [c] nm
CH_3OH	32.63	1.00	405
$CHCl_3$	4.81	1.58	407
C_2H_5OH	24.30	3.63	409
i-C_3H_7OH	18.90	3.88	410
$CH_3CO_2CH_3$	6.68	5.50	412
CH_3CN	37.50	6.25	414
C_6H_6	2.28	8.75	416

[a] Dielectric constants at 25 °C, obtained from: CRC Handbook of Chemistry and Physics, 10th ed., p 62. [b] Quantum yield of lasalocid fluorescence measured relative to its fluorescence in methanol at 25 ± 0.5 °C with λ_{ex} = 310 nm by using a Aminco-Bowman spectrofluorometer and are not corrected for changes in solvent refractive index. Error is ± 5%. [c] Wavelength of maximum fluorescence intensity ± 1 nm.

The aromatic hydroxyl and carboxyl groups collectively constitute a fluorophore exciting at 313 nm and emitting at 420 nm.[12] Large solvent effects have been observed relative to the amplitude of the circular dichroism (CD) spectra of lasalocid.[4] Since fluorescence techniques have been used to obtain information about stoichiometries and association constants of cation–lasalocid interactions, the present studies have been conducted to investigate the solvent effects on fluorescence properties of lasalocid. Solvents of different polarities and hydrogen-bonding capabilities are expected to have strong effects on the conformation and in turn, on the fluorescence properties of the molecule.

The relative fluorescence quantum yield (ϕ^{rel}_f) and the wavelength of the fluorescence maximum (λ_{max}^{fl}) are strongly dependent on the solvent character as shown in Table I. The data clearly suggests that a decrease in hydrogen-bonding ability and/or polarity of the solvent causes an increase in ϕ^{rel}_f and a red shift in the λ_{max}^{fl}. Examining the effects of alcohols, it can be observed that both ϕ^{rel}_f and λ^{fl}_{max} increase in the order of isopropanol > ethanol > methanol. Although, these results along with the fact that acetonitrile > methanol clearly indicate that the hydrogen-bonding ability of the solvent is the prime factor, the observation that benzene > methyl acetate, suggests that solvent polarity, as measured by dielectric constant, has some effect on ϕ^{rel}_f and λ^{fl}_{max}.

Considerable information on the conformation of a molecule can be obtained from the study of its fluorescence properties. The fluorescence process occuring from singlet excited state (S_1) normally competes with other photophysical processes of intersystem crossing and internal conversion to the ground state for deactivation of the excited singlet states. An increase in interaction of lasalocid with the solvent molecules may result in a change in both the excited singlet-state lifetime (τ_f) (eq 1) and the

$$\tau_f = \frac{1}{k_f + k_{st} + k_s} \quad (1)$$

fluorescence quantum yield (ϕ_f). This is clearly suggested by eq 2 and 3, which provide expressions for τ_f and ϕ_f,

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Table II. Solvent Effects on ϕ^{rel}_f, k_f, and τ^{rel}_f

solvent	ϕ^{rel}_f	$k_f \times 10^{-3}$, s^{-1}	τ^{rel}_f [a]
CH_3OH	1.00	2.38	1.00
$CHCl_3$	1.58	1.66	2.26
C_2H_5OH	3.63	1.73	4.98
i-C_3H_7OH	3.88	1.58	5.85
$CH_3CO_2CH_3$	5.50	1.66	7.87
CH_3CN	6.25	1.73	8.62
C_6H_6	8.75	1.73	12.00

[a] τ_f calculated according to eq 3 and expressed relative to the value in methanol.

respectively. where k_f is the unimolecular rate constant for fluorescence, k_{st} is the unimolecular rate constant for intersystem crossing to the T_1 state, and k_s is the unimolecular rate constant for internal conversion to the ground state (S_0). But internal conversion to the ground state is usually an insignificant pathway for radiationless deactivation of the carbonyl excited singlet state.[13] Therefore, the eq 1 can be rewritten as

$$\tau_f = \frac{1}{k_f + k_{st}} \tag{2}$$

and the expression for ϕ_f can be given by

$$\phi_f = \frac{k_f}{k_f + k_{st}} = k_f \tau_f \tag{3}$$

In the absence of any direct measurement of the excited singlet-state lifetime, an approximate value for τ_f can be calculated from eq 3 by knowing the relative fluorescence quantum yield (ϕ^{rel}_f) and the unimolecular rate constant for fluorescence (k_f). If a compound exhibits a symmetrical band in the ultraviolet absorption spectrum, the value of k_f can be estimated by utilizing eq 4[14,15] where ν_m^2 is the

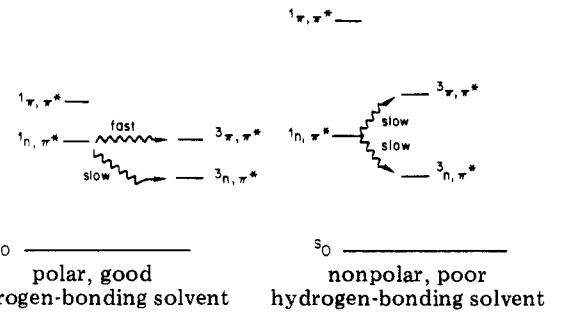
$$k_f = \nu_m^2 \epsilon_{max} \Delta\nu^{1/2} / (3.5 \times 10^8) \tag{4}$$

mean frequency for the absorption band (cm^{-1}), ϵ_{max} is the maximum molar absorptivity for the absorption band, and $\Delta\nu^{1/2}$ is the half-width of the absorption band (cm^{-1}). Spectroscopic experiments[14] clearly demonstrated the utility and validity of eq 4 in relating the rate constant for fluorescence with the integrated intensity of the ultraviolet absorption band.

The solvent effects on the k_f values derived from the electronic absorption spectrum of lasalocid are shown in Table II. It can be observed from the data presented in Table II that the solvent effect on k_f is only minimal. In fact, an increase in ϕ^{rel}_f is not associated with a corresponding increase in k_f values. This observation suggests that the fact that changes in the intersystem crossing rates are probably the primary reasons for the observed solvent effect on ϕ^{rel}_f.

If ϕ^{rel}_f increases with decreasing polarity and hydrogen-bonding ability of the solvent, because the rate constant for intersystem crossing (k_{st}) decreases, then the fluorescence decay time τ_f, as defined by eq 2, must increase as ϕ^{rel}_f increases. On the other hand, if the increase in ϕ^{rel}_f is due to an increase in k_f, then τ^{rel}_f will decrease as ϕ^{rel}_f increases. The relative fluorescence quantum yields and relative fluorescence lifetimes of lasalocid in the solvents studied have also been summarized in Table II. The increase in both ϕ^{rel}_f and τ^{rel}_f with decreasing solvent polarity and hydrogen-bonding ability tend to indicate that the observed changes in fluorescence intensity of sodium lasalocid in these solvents are primarily due to the changes in the intersystem crossing rate constant, k_{st}.

Scheme I



It is very likely that the large solvent effect on the intersystem crossing rate constant is due to the fact that the solvent is changing the states that are involved in the intersystem crossing processes.[16] Theoretical calculations on azaaromatic[17] and carbonyl compounds[18] indicate that intersystem crossing will be as much as 10^3 times faster when there is a change in configuration, e.g., $^1\pi,\pi^* \rightarrow {}^3n,\pi^*$ or $^1n,\pi^* \rightarrow {}^3\pi,\pi^*$, than when the singlet and the triplet states are of the same configuration, e.g., $^1n,\pi^* \rightarrow {}^3n,\pi^*$ or $^1\pi,\pi^* \rightarrow {}^3\pi,\pi^*$.[19] Moreover, it is a well-documented fact that decreasing solvent polarity or hydrogen-bonding ability stabilizes n,π^* states and destabilizes π,π^* states.[20] Based on all these facts and observations, it can be proposed that, as shown in Scheme I, the intersystem crossing in lasalocid probably occurs from $^1n,\pi^*$ (S_1) state to $^3\pi,\pi^*$ (T_2) state in polar, good hydrogen-bonding solvents, e.g., methanol, and therefore is very fast. But with the decrease in polarity or hydrogen-bonding capability of the solvent, the vibrational energy of the $^3\pi,\pi^*$ (T_2) state will become much greater than that of $^1n,\pi^*$ (S_1), resulting in a much higher activation energy barrier for the intersystem crossing from S_1 to T_2, and the process will be much slower. The lesser the solvent polarity and the hydrogen-bonding ability, the larger the activation energy and the higher the rate constant for intersystem crossing from S_1 to T_2 will be. Based on Scheme I, it can be predicted that intersystem crossing rate will continue to decrease as a function of decreased solvent polarity and hydrogen-bonding capability, until only the slow intersystem crossing from S_1 (n,π^*) to T_1 (n,π^*) remains.

The explanation already given for the enormous solvent effect on the ϕ^{rel}_f values also accounts for the solvent effect on λ^{fl}_{max}.

If the lowest singlet state of sodium lasalocid in nonpolar, poor hydrogen-bonding solvent is a n,π^* singlet, then increasing solvent polarity or hydrogen-bonding ability would be expected to cause an initial blue shift in λ^{fl}_{max}. An examination of the λ^{fl}_{max} values in Table I suggests that going from 2-propanol to methanol causes a blue shift in λ^{fl}_{max} of lasalocid. The presence of this blue shift clearly indicates that S_1 is n,π^* in all solvents.

Based on all the facts and observations, it can be said that substantial solvent effects on the lasalocid fluorescence intensity, lifetime, and the position of fluorescence

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maxima have been observed. The ϕ^{rel}_f and τ^{rel}_f changes can be attributed to the solvent effects on the rate of intersystem crossing caused by changes in relative energies of the $^1n,\pi^*$ (S_1) and $^3\pi,\pi^*$ (T_2) states. The dependency of λ^{fl}_{max} and ϕ^{rel}_f on the solvent character may make the fluorescence technique a useful probe for molecular environment of lasalocid and can be used conveniently for complexation, ionization, and other physicochemical studies that bring about a change in the molecular environment.

Experimental Section

Lasalocid sodium salt was obtained in a 99+% purity from Aldrich Chemical Co., Milwaukee, WI, and was used without further purification. All solvents were reagent grade and stored over molecular sieves prior to use.

Relative quantum yields of fluorescence for lasalocid were obtained by using an Aminco-Bowman spectrofluorometer. Ultraviolet spectra were recorded in a Bausch and Lomb Spectronic 2000 spectrophotometer.

A stock solution of 1×10^{-2} M lasalocid sodium was prepared in methanol. Appropriate dilutions were made in various solvents to give a final lasalocid concentration of 2 μM. In the final solutions, the concentration of methanol never exceeded 1% v/v. The fluorescence intensity–concentration relationship for lasalocid was linear at the final concentration in all of the solvents used.

Registry No. Sodium lasalocid, 25999-20-6.

Micelle-Mediated Organic Synthesis: The Synthesis and Characterization of Three New Polycyclic Dioxa Cage Compounds

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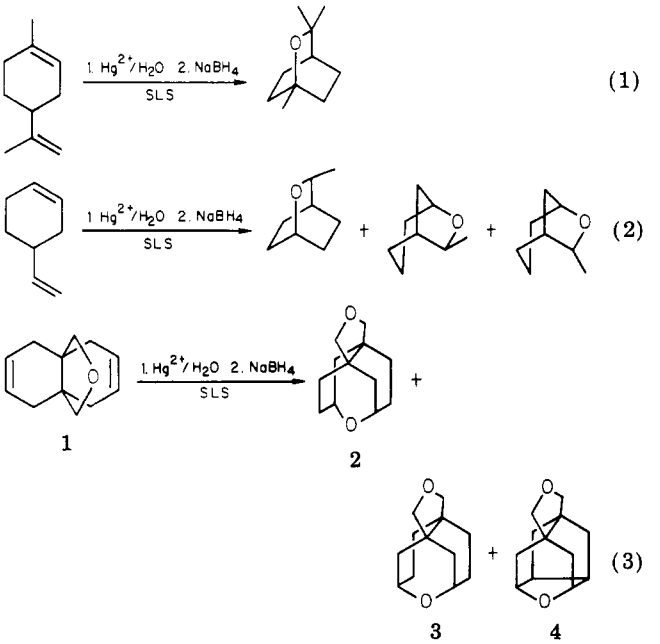
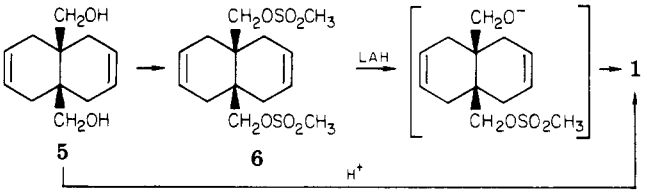
As part of our program in selective micellar catalysis of organic reactions,[2,3] we have identified a number of ways in which anionic micelles can direct the course of olefin hydroxymercuration.[2] One such perturbation is the ability of the micelle to favor the formation of cyclic ethers instead of diols in the reactions of various α,ω dienes. Examples of this cyclization are shown in eq 1 and 2.[2a] We have now applied this principle to propelladiene 1 and have succeeded in generating three new cage compounds as per eq 3. We report below a modified synthesis of 1 as well as the details of its conversion, in the presence of sodium lauryl sulfate (SLS), into cyclic ethers 2–4.[4]



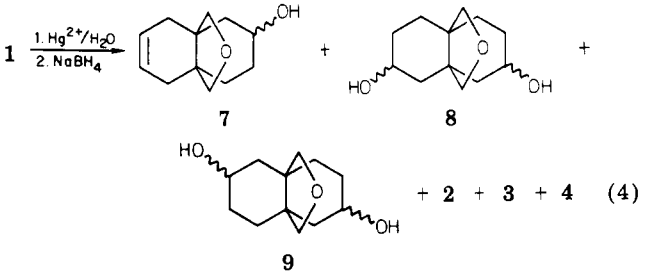
Scheme I



Results and Discussion

Synthesis of 1. The synthesis of diol 5 from butadiene and acetylenedicarboxylate, as well as its acid-catalyzed cyclization to 1 have been reported[5] (Scheme I). We have found that the conversion of 5 to its dimesylate 6 and treatment of 6 with LAH in THF gives an excellent yield of 1 via S–O bond cleavage and intramolecular trapping of the incipient alkoxide (Scheme I).

Hydroxymercuration of 1. When diene 1 is treated with aqueous $Hg(OAc)_2$, a variety of products are formed (eq 4). We have previously reported the successful con-



version of 1 to 7 by the use of 1 equiv of $Hg(OAc)_2$ in SLS solution.[2b] As expected, the use of more than 1 equiv of $Hg(OAc)_2$ leads to a mixture of diols and cyclic ethers. However, while excess $Hg(OAc)_2$ and long reaction times were used in eq 1 and 2 (to guarantee complete reaction), the preferential formation of 2–4 was adversely affected by the use of more than 3 equiv of $Hg(OAc)_2$. The best evidence for micelle-enhanced cyclization is found in reactions where a substantial amount of monoalcohol is recovered.

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