destabilized by two gauche O–O interactions. Two conformers are consistent with $^3J_{C3,H1}$ ($\theta \simeq 90°$) and neither can be distinguished by $^3J_{H1,H2}$. The data, therefore, are insufficient to assign a preferred C1–C2 bond conformation in this isomer.

Hydrates and dimethyl acetals appear to adopt similar conformations. Orientation of the methyl groups of dimethyl acetals (C1–O1 bond torsions) was not examined.

Conclusions

The uncertainties that arise in the conformational analysis of furanosyl rings have been discussed in this and other reports. The assignment of conformations of these structures based on only three ^3J coupling values is tenuous at best, although, as shown here, additional information is available from ^{13}C–^1H couplings.

Unequivocal chemical shift assignment is a prerequisite for conformational analysis. Assignment of the individual methylene (C4) protons of the tetrofuranosyl ring is particularly important because their coupling to C1 is a sensitive indicator of the conformation in the region of the anomeric center. Assignment of the resonances to individual C4 protons based on substituent effects, magnitudes of $^2J_{CH}$ and $^3J_{CH}$, and selective [^{2}H] substitution, all demonstrate that H4*S* is the more shielded methylene proton in tetrofuranosyl rings. The "syn–upfield" rule for 1,2-interactions is upheld in these systems.

Three ^{13}C–^1H couplings across the ring oxygen reflect the preferred orientation of O1. Conformations with O1 quasi-axial (or near quasi-axial) are preferred for all ring configurations, a manifestation of the anomeric effect which appears to dominate all other factors in determining ring conformation.

Ring flexibility appears to increase as 1,2- and 1,3-interactions increase, such that, in the tetroses, the α-threo isomer appears to be most stable and the β-erythro isomer least. We are currently testing this conclusion with the use of ab initio molecular orbital calculations.

While this study has shown that a first-order analysis of ^1H–^1H and ^{13}C–^1H coupling constants and ^{13}C relaxation times does not provide a complete understanding of tetrofuranosyl ring conformation, it has produced an extensive body of data that must be accommodated in future models. The use of ^{13}C–^1H coupling data in conformational studies of five-membered rings provides a better basis upon which conformational inferences can be made. Internuclear ^1H–^1H distances, determined in solution by DESERT[50] and/or dynamic NOE methods,[51] as well as more recent two-dimensional NMR approaches, may provide complementary information on the conformational properties of these ring systems.

Acknowledgment. We thank J. Dadok and A. Bothner-By of the NMR Facility for Biomedical Research at Carnegie-Mellon University for their assistance in obtaining the 600-MHz ^1H NMR spectra and for helpful discussions. A.S. thanks the Notre Dame J. Jones Faculty Research Development Fund and the Research Corporation for financial support.

Registry No. D-[4-^{13}C]Erythrose, 90913-08-9; L-[4-^{13}C]threose, 90913-09-0; D-[6-^{13}C]glucose, 70491-70-2; L-[6-^{13}C]idose, 90913-10-3; potassium [^{13}C]cyanide, 25909-68-6; 1,2-*O*-isopropylidene-D-*xylo*-dialdopentofuranose, 53167-11-6; α-D-erythrofuranose, 72599-80-5; methyl α-D-erythrofuranoside, 52613-15-7; β-D-erythrofuranose, 72599-81-6; methyl β-D-erythrofuranoside, 53109-84-5; α-D-threofuranose, 80877-72-1; methyl α-D-threofuranoside, 64609-20-7; β-D-threofuranose, 80877-73-2; methyl β-D-threofuranoside, 25158-74-1; methyl α-D-arabinofuranoside, 56607-40-0; methyl β-D-arabinofuranoside, 25129-51-5; methyl α-D-lyxofuranoside, 22416-73-5; methyl β-D-lyxofuranoside, 22861-09-2; methyl α-D-ribofuranoside, 52485-92-4; methyl β-D-ribofuranoside, 7473-45-2; methyl α-D-xylofuranoside, 1824-96-0; methyl β-D-xylofuranoside, 1824-97-1; D-erythrose dimethyl acetal, 74761-31-2; D-threose dimethyl acetal, 90913-11-4.

Supplementary Material Available: ^1H NMR spectra of D-threose in D_2O at 180, 300, and 600 MHz (Figure 3); 300 MHz ^1H NMR spectrum of D-erythrose in D_2O (Figure 4); 600 MHz ^1H NMR spectra of methyl β-D-[1-^{13}C]-, [2-^{13}C]-, and [4-^{13}C]-erythrofuranosides (Figure 5) (3 pages). Ordering information is given on any current masthead page.

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Spectral Properties and Basicity of Stilbazolium Betaines Containing Bulky Substituents on the Quinoid Ring

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Several derivatives of 4-[(4-oxocyclohexa-2,5-dienylidene)ethylidene]-1,4-dihydropyridine were synthesized. The effect of bulky substituents in the immediate vicinity of carbonyl on the basicity and visible spectra of these compounds is described. The basicity was established spectroscopically in 52% methanol–water. A phenol-like effect of substituents on the basicity was observed. Since this effect was much less pronounced than that in the phenolate ion, it may be concluded that the contribution of quinoid resonance structure is important in this kind of compound. A fine structure pattern was observed in the visible spectra of the studied compounds. Variation in the fine structure was investigated in a number of protic and aprotic solvents and solvent mixtures. When the relative absorption intensities at 540, 585, and 625 nm were expressed as peak ratios, a sensitive indicator of solvent polarity was obtained for some regions of the E_T polarity scale.

Spectral properties of merocyanine dyes are known to be strongly affected by the medium. Among the merocyanines, dyes of the stilbazolium betaine type (Scheme I) have aroused much interest because of their extreme solvatochromic properties.[1,2] Recently, Donchi and coworkers have observed drastic changes in the UV–vis absorption spectra of a surfactant merocyanine, 1-hexa-

(1) Brooker, L. G. S.; Keyes, G. H.; Heseltine, D. W. *J. Am. Chem. Soc.* **1951**, *73*, 5350–5356.

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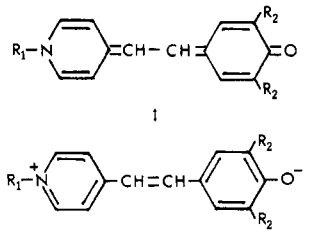
Scheme I



Ia, $R_1 = C_{16}H_{33}$; $R_2 = H$
b, $R_1 = HO(CH_2)_2$; $R_2 = t$-Bu
c, $R_1 = HO(CH_2)_6$; $R_2 = H$
d, $R_1 = HO(CH_2)_6$; $R_2 = CH_3$
e, $R_1 = HO(CH_2)_6$; $R_2 = t$-Bu

decyl-4-[(4-oxocyclohexa-2,5-dienylidene)ethylidene]-1,4-dihydropyridine (Ia), in micellar solutions.[3] According to the authors, the merocyanine chromophore was in fact responding to the polarity and hydrogen ion concentration in the vicinity of the surfactant head groups in micelles.

These kinds of compounds seem promising as molecular probes of polarity and hydrogen ion permeability of membrane bilayers. The main disadvantage of using these compounds is their location in the bilayer; rather than becoming completely incorporated into the bilayer, these probes will localize at interfaces where the measured properties may not be quite representative for the membrane.

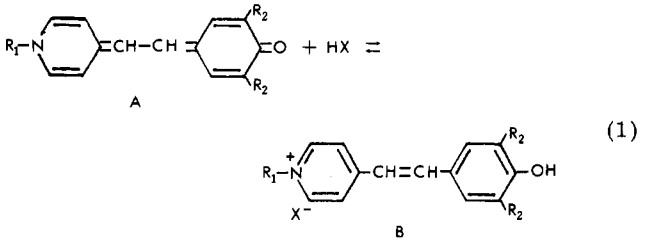
In order to study the less polar regions of the bilayers, we made two modifications: (i) the introduction of two strongly hydrophobic radicals, *tert*-butyls, to the immediate vicinity of the polar carbonyl group and (ii) the introduction of a hydroxyalkyl substituent at the nitrogen atom. It was hoped that these two modifications might make it possible to locate the merocyanine chromophore at varying depths in the membrane.

Surprisingly, these modifications seriously affected the chemical and spectral properties of the molecule.

In this paper we describe the synthesis and characterization of some 1-(hydroxyalkyl)-4-[(4-oxo-3,5-dialkylcyclohexa-2,5-dienylidene)ethylidene]-1,4-dihydropyridines.

Results and Discussion

Syntheses. All compounds were synthesized according to literature procedures.[1,2] Only the di-*tert*-butyl-substituted merocyanines (Scheme I, b and e) were easily obtained in the form of a pure free base (eq 1, A). The



(1)

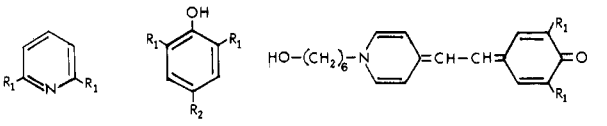
synthesis of less crowded compounds (R_2 = H or Me) gave mixtures of the free base (A) with the protonated merocyanine (B). In some cases, only after repetitive treatments with concentrated ammonia and NaOH, it was possible to isolate the free base with elemental analyses and spectra consistant with the structure.

Obtaining pure free bases in the stilbazolium betaine series appears a common synthesis problem. This may be seen by comparison of the analytical results, melting points, and H_2O contents reported for the same betaine in different papers.[1,2,4,6] Some authors[4] used only the C/N ratio to characterize the compounds. Since the deprotonation of synthesized merocyanines seemed to be much easier in the case of the di-*tert*-butyl-substituted compounds as compared to the unsubstituted ones, it was thought that the bulky substituents may decrease the basicity in this series. Similar effects have been observed in the pyridine series[7] and seem to be a general feature where the acid form carries more charge than its conjugated base. This was observed, for instance, by Cohen and Jones in the series of 4-substituted phenols.[8] Determination of the dissociation constants in our series (see next section) has shown that the *tert*-butyl substituents have an opposite effect, that is, increasing the basicity of the compounds. Therefore the more difficult deprotonation observed in the case of the unsubstituted merocyanine may not be explained by its higher basicity. It may be rationalized by a formation of a complex between the protonated molecule and the free base. This kind of complex was proposed by Gibson and Bailey for 5-substituted-2-hydroxy-4-stilbazole derivatives.[9] Being less soluble than the free base, the complex hinders the purification process. We demonstrated the existence of such a complex by mixing equimolar amounts of Ic (mp 175–177 °C) with Ic·HCl (mp 165–167 °C) dissolved in ethanol and by isolating a red solid, mp 200–202 °C. This product was less soluble than both components and its melting point was higher. Several recrystallizations from ethanol–ammonia did not substantially change either the melting point or the analytical results (% Cl).

Basicity Studies. The apparent dissociation constants of conjugated acids of compounds Ic, Id, and Ie were determined spectroscopically in 52% methanol–water.

The obtained results are recorded in Table I, which includes for comparison the literature results for some phenols and pyridines. It may be seen that in pyridine series bulky *tert*-butyls ortho to nitrogen increase the acidity of the pyridinium ion with $\Delta pK_a = -0.80$. In the

Table I. Values of pK_a for 2,6-Disubstituted Pyridines (A), Phenols (B), and Stilbazolium Betaines (C)



compd	R_1	R_2	pK_a	solvent	ref
CH^+	H		9.34 ± 0.05	52% methanol	
CH^+	CH_3		9.56 ± 0.04	52% methanol	
CH^+	t-C_4H_9		9.98 ± 0.05[a]	52% methanol	
AH^+	H		4.38	50% ethanol	7
AH^+	CH_3		5.77	50% ethanol	7
AH^+	t-C_4H_9		3.58	50% ethanol	7
B	H	H	11.16	50% ethanol	8
B	t-C_4H_9	H	14.22	50% ethanol	8
B	H	CHO	8.40	50% ethanol	8
B	t-C_4H_9	CHO	9.33	50% ethanol	8
B	H	NO_2	7.89	50% ethanol	8
B	t-C_4H_9	NO_2	7.49	50% ethanol	8

[a] The stilbazolium betaine and its perchlorate salt were used for this determination.

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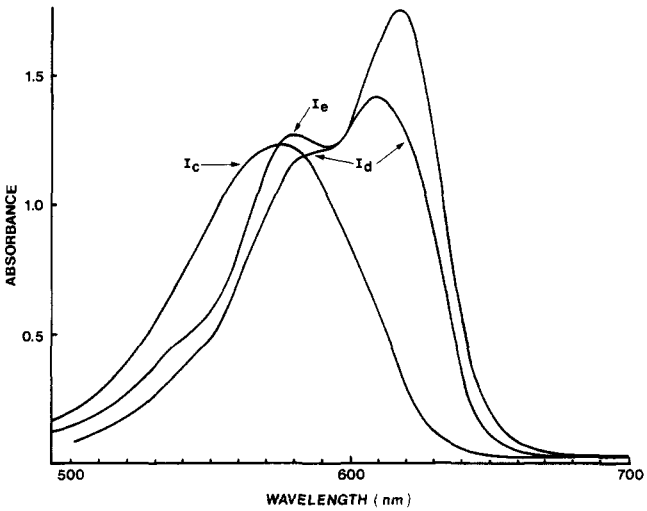

Figure 1. Visible spectra of Ic, Id, and Ie in acetonitrile.

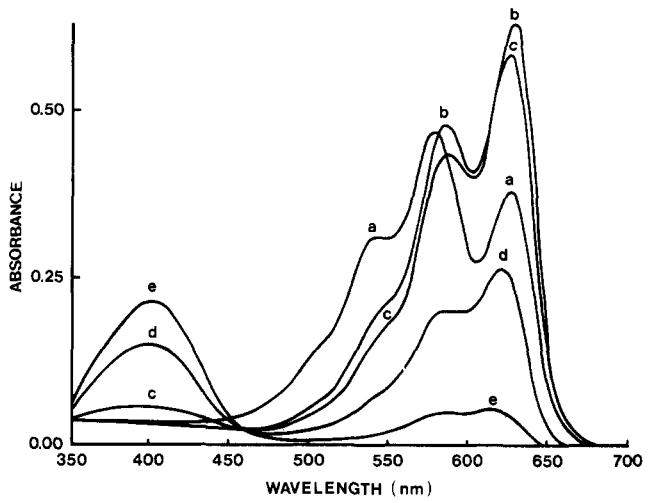

Figure 2. Visible spectra of Ie in 1,4-dioxane–H_2O: (a) 0% H_2O; (b) 10% H_2O; (c) 15% H_2O; (d) 20% H_2O; (e) 30% H_2O.

phenol series the effect of the steric hindrance depends also on the para substituent. When the para position is unsubstituted, R_2 = H, the ortho *tert*-butyls greatly decrease the phenol acidity with $\Delta pK_a = 3.06$; this effect is much smaller, $\Delta pK_a = 0.93$, when R_2 = CHO and with a strongly electron withdrawing $R_2 = NO_2$, *tert*-butyls increase the acidity with $\Delta pK = -0.4$. It may be concluded that the effect of bulky substituents on the acid–base equilibrium depends on charge distribution in the acid–conjugated base pair. When the acid is the charged species, *tert*-butyls in the vicinity of the charged atom will increase the acidity, probably by steric hindrance of solvation of the ion. If, on the contrary, the charge is present in the base, a bulky substituent will increase the basicity of the species by the same effect. In the stilbazolium betaine series a phenol-like effect is observed. Since this effect is much smaller than in the case of 4-unsubstituted phenols, it is logical to assume that the quinoid form plays an important role in the resonance hybrid (Scheme I) and that the negative charge on the oxygen atom is smaller than that in the phenolate ion.

A rough graphical estimation suggests that the contribution of the betaine form to the resonance hybrid in 52% methanol is about 40%. This estimation is based on the following approximations: (i) there is no negative charge on the oxygen atom in the quinoid form; (ii) the oxygen charge in the betaine form is equal to −1; and (iii) a similar situation is assumed for the pyridine–phenolate pair, the pyridine being totally uncharged and the phenolate anion a totally charged base.

A different charge distribution in stilbazolium betaine series was proposed by Benson and Murrell, who calculated net charges on all atoms using the SCF π-electron theory and have concluded that in polar solvents the charge on the oxygen atom is equal to −0.92.[10] On the other hand, Steiner and co-workers studying the cis–trans isomerization of stilbazolium betaines provided good evidence for a more important participation of the quinoid form.[11] The value (−0.92) given in ref 10 seems to overestimate the charge on oxygen. This value is even much higher than the one estimated by others[12] for the phenolate ion (−0.474) which is a stronger base than merocyanines.

Spectroscopic Data. Figure 1 shows the visible absorption spectra of Ic, Id, and Ie in acetonitrile. One may see three well-resolved absorption peaks in the long-wavelength region for Ie (peak 1 at 625 nm, peak 2 at 585 nm, and peak 3 at 540 nm), a similar pattern with poorer resolution for Id, and a simple Gaussian type large peak in the case of Ic. This long-wavelength absorption is attributed to the free base (eq 1, A) since the protonated merocyanines (eq 1, B) absorb in the 390–420-nm region.

This peculiar effect of substituents on the absorption spectra of stilbazolium betaines was, to our knowledge, never observed, and this prompted us to study the spectra of the *o*-di-*tert*-butyl-substituted compound Ie in other solvents. The absorption spectra of Ie in a less polar solvent, 1,4-dioxane, presents a better resolution in the long-wavelength region (Figure 2, spectrum a). One may also see that the amplitudes of the fine structure peaks are different in this solvent as compared to those in acetonitrile. The question arises as to whether it is a general feature of this type of compounds and if further changes in solvent properties will bring parallel variations in the relative intensities of absorption peaks. If this proves to be the case, then molecules of this type can be used as sensitive indicators of the polarity of the medium. The monitoring of peak intensity ratios is often more convenient than the usual solvatochromic study. A similar approach was recently described by Glushko and co-workers,[13] who found that vibrational fine structure of pyrene fluorescence is solvent dependent and proposed to apply this property in monitoring changes of polarity in membranes.

We studied the visible spectra of Ic and Ie in a variety of media. The results summarized in Table II show that the absorption energies of Ie as compared with Ic are less affected by the medium polarity. Instead, the relative intensities of fine structure peaks represented in Table II by $r_1 = \epsilon_2/\epsilon_1$ and $r_2 = \epsilon_3/\epsilon_1$ are sensitive to the solvent.

Figure 3 shows the effect of solvent polarity on the absorption peak ratios. It may be seen that protic solvents act in a different manner than the aprotic ones. The ratio r_1 for the aprotic solvents decreases gradually in the range of E_T = 34.5 to 40 kcal/mol and after that remains constant. Protic solvents act in the opposite direction, increasing r_1 proportionally to the solvent polarity in the range of E_T = 50–55.5 kcal/mol. In the range of E_T =

(10) Benson, H. G.; Murrell, J. N. *J. Chem. Soc., Faraday Trans. 2*, **1972**, *68*, 137–143.
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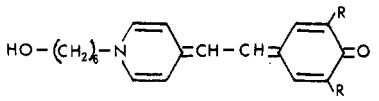
Table II. Visible Absorption Maxima of Ic (R = H) and Ie (R = *t*-Bu) in Different Solvents



solvent	E_T, kcal/mol	R = H λ_{max}, nm	R = *t*-Bu λ_{max}, nm peak 1	peak 2	peak 3	r_1[a]	r_2[b]
methanol	55.5	490	600	585	540	0.98	0.39
ethanol	51.9	520	615	585	540	0.75	0.24
n-butanol	50.2	537	622	583	540	0.69	0.20
n-pentanol	49.1	540	623	585	540	0.68	0.21
dodecanol		560	630	585	540	0.69	0.23
acetonitrile	46.0	575	616	579	540	0.71	0.26
DMF	43.8	577	617	580	540	0.71	0.24
acetone	42.2	582	620	577	540	0.73	0.31
pyridine	40.2		631	585	540	0.69	0.24
THF	37.4		627	580	540	0.91	0.47
1,4-dioxane	36.0		625	577	540	1.22	0.77
benzene	34.5		627	580	540	1.34	0.93

[a] Peak 2/peak 1 absorption ratio. [b] Peak 3/peak 1 absorption ratio.

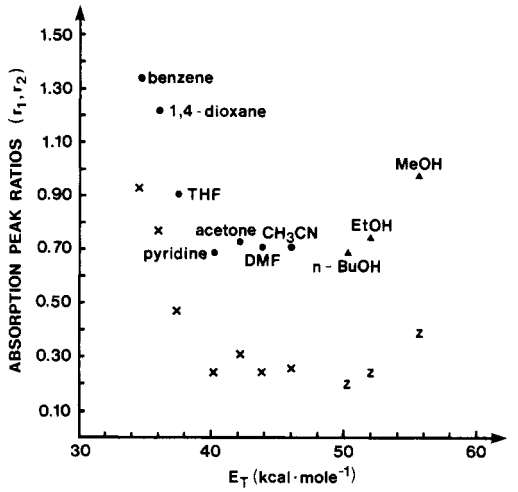


Figure 3. Plot of absorption peak ratios r_1 and r_2 vs solvent polarity (E_T). Values for compound Ie in different solvents: (●) r_1 for aprotic solvents; (▲) r_1 for alcohols; (X) r_2 for aprotic solvents; (Z) r_2 for alcohols.

40–50 kcal/mol there is no effect of solvent polarity on the peak ratio. The absorbance ratio r_2 behaves similarly.

The E_T values exhibit in general a good, mostly linear correlation with a large number of other solvent-sensitive processes. Solvents, according to E_T values may be divided into three groups: protic, dipolar aprotic, and aprotic solvents. The absorbance ratios r_1 and r_2 behave very differently in each of these three groups of solvents. The range of E_T = 40–50 kcal/mol covers roughly the group of aprotic dipolar solvents and some higher alcohols. One may think that different degrees of solvation are responsible for these results. Aprotic solvents probably interact with the solute, stabilizing the nitrogen positive charge. Maximal stabilization of this type is probably reached at E_T = 40 kcal/mol. Protic solvents act principally, but not exclusively, by hydrogen bonding of the negatively charged oxygen. It is possible that in the case of the sterically hindered betaines, higher alcohols cannot play this role.

A more accurate polarity gradient may be obtained by using binary solvent mixtures.

Figures 2 and 4 show variations of the long-wavelength spectra of Ie in 1,4-dioxane–water as a function of water contents.

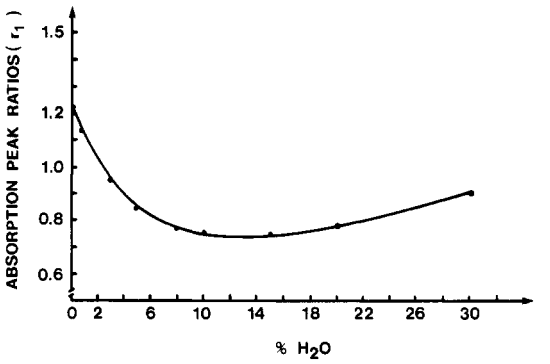


Figure 4. Plot of absorption peak ratio r_1 vs. % H_2O. Compound Ie (5.88×10^{-6} M) in 1,4-dioxane–H_2O.

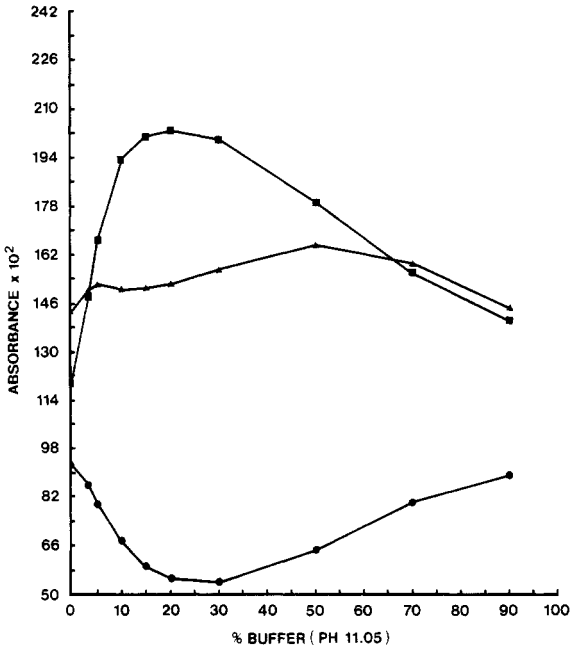


Figure 5. Plot of optical densities of peak 1 (■), peak 2 (▲), and peak 3 (●) vs. % buffer pH 11.05. Compound Ie (2×10^{-5} M) in 1,4-dioxane–buffer.

By gradual addition of water to a 5.88×10^{-6}M solution of the merocyanine Ie in 1,4-dioxane, the optical density of peak 1 sharply increases without shifting until about 15% H_2O. After this critical point, the absorption intensity of this peak decreases gradually with a slight blue shift. Changes in the absorption values of peak 1 are accompanied by parallel changes in peak 3 while the optical density of the peak 2 remains almost unaffected (Figure 2). Beginning at about 15% of water, a large peak corresponding to the protonated form appears at λ_{max} = 400 nm.

In order to eliminate the eventual interference of the protonated form on the long-wavelength peak ratios, the series of measurements was repeated using a carbonate buffer of pH 11.05 instead of water. A plot of absorbances of the three peaks vs. buffer concentration is given in Figure 5. In these conditions the protonated form does not appear and the other peak ratios are not significantly modified as compared with the previous experiment. The longest wavelength band (peak 1) behaves in the same manner, the "critical" point occuring in this case at 20% buffer solution (Figures 4 and 5). The behavior of peak 1 of the di-*tert*-butyl-substituted stilbazolium betaine Ie (Figure 6) is similar to that described by Brooker and co-workers for the absorption maximum of benzothiazolium betaines in pyridine–water mixtures.[1] According to the authors the point of the highest ϵ_{max}, so

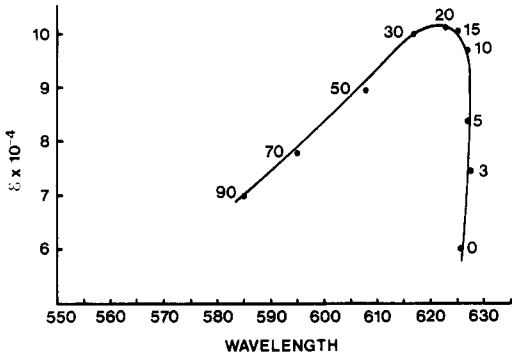


Figure 6. Absorption peak 1 maximum of Ie (λ_{max} and ϵ_{max}) in 1,4-dioxane–buffer (pH 11.05). The numbers against the points denote % of buffer.

called "isoenergetic point", corresponds to a situation when the quinoid and zwitterrionic resonance structures have an equal energy. Under such a condition the two structures contribute equally to the ground and the excited state, resulting in a high maximum molar extinction coefficient.

One may speculate on the origin of the two other peaks in the long-wavelength absorption of the merocyanine Ie. The aggregation phenomena are often responsible for the fine structure of polymethine dye spectra.[14,15] Formation of dimers and higher polymers of dyes is observed mostly in aqueous solutions, but deviations from Beer's law have also been observed for certain dyes in organic solvents of low polarity and were attributed to the appearence of contact ion pairs.[16] The aggregation phenomena have been eliminated in this work by studing the absorption spectra of Ie in 1,4-dioxane as a function of the merocyanine concentration. Beer's law was strictly observed in the range of 0.4×10^{-6} to 0.25×10^{-3} M for all three peaks.

The hypothesis of a conformational isomerism seems doubtful. Indeed, *tert*-butyl groups at ortho positions to the carbonyl do not create a particular, if any, steric hindrance, and methyl groups even less. Whereas, only in the alkyl-substituted stilbazolium betaines, the fine structure was observed. Moreover, the steric hindrance to planarity of a conjugated system usually induces a loss of the fine structure.

Also, cis–trans isomerism would be difficult to rationalize, especially because in similar systems both isomers absorb at the same wavelength and may be distinguished only by the values of molar extinction coefficients.[11] Another kind of isomerism, so-called allopolar isomerism, was mentioned in early work on the merocyanine series,[17,18] but this phenomenon is also related to a severe steric hindrance to planarity and hence cannot be the cause of the absorption fine structure in the present case.

Vibrational levels, other transitions, or some very special solvation phenomena related to the inherent hydrophobic environment of the chromophore should be taken into account (Further investigations are in progress).

Conclusion

The visible absorption spectrum of 3,5-dialkylbetaines show a fine structure pattern sensitive to solvent polarity particularly if the substituents are bulky *tert*-butyls. This peak-ratio–solvent polarity relationship is linear in the regions of E_T = 50–55.5 kcal/mol and E_T = 34.5–40 kcal/mol or in the region corresponding to 0–15% H_2O in 1,4-dioxane. It is proposed that this kind of compound may be useful as probes in detecting changes in bilayer polarity and hydrogen ion concentration. Preliminary results indicate that these compounds readily incorporate into phospholipid vesicles.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in Me_2SO-d_6 at 60 MHz on a Varian EM360L spectrometer. Chemical shifts are reported in parts per million downfield from internal Me_4Si with a multiplet (m), quartet (q), triplet (t), doublet (d), or singlet (s) designation. UV–vis spectra were taken on a Cary Model 17D spectrometer and IR spectra on a Perkin-Elmer Model 597 spectrometer, with KBr disk. Only selected IR absorptions are given.

Solvents for synthesis were reagent grade and those for UV–vis measurements were spectrophotometric grade (Fisher) and were used without further purification, except for 1,4-dioxane (Aldrich), which was percolated through a column filled with basic alumina (Brockman Activity I) and distilled from metallic sodium.

Elemental analyses were performed by Schwarskopf Microanalytical Laboratory, Inc. Woodside, NY.

Synthesis. 4-Hydroxy-3,5-dimethylbenzaldehyde was synthesized according to literature procedure[19] 70% yield; mp 111–112 °C (lit.[19] mp 111–112 °C).

Stilbazolium Betaines. The pyridinium salts were prepared by refluxing 4-picoline with the corresponding alkyl or hydroxyalkyl halide.

The pyridinium salts were condensed with the corresponding *p*-hydroxybenzaldehyde according to literature procedures.[1-6]

1-(2-Hydroxyethyl)-4-[(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)ethylidene]-1,4-dihydropyridine (Ib): recrystallized from ethanol–ammonia, 40% yield, dark green solid with a metallic lustre, mp 210–212 °C; IR (KBr) 3400, 1650, 1510, 1480, 1160, 1060, 1020, 960 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.30 (s, 18), 1.70 (m, 2), 3.33 (s, 1), 3.97 (t, 2), 6.17 (d, 1), 7.13 (s, 2), 7.16 (d, 2), 7.29 (d, 1), 7.74 (d, 2). Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96. Found: C, 78.22; H, 8.93; N, 4.02.

1-(6-Hydroxyhexyl)-4-[(4-oxocyclohexa-2,5-dienylidene)-ethylidene]-1,4-dihydropyridine (Ic): recrystallized from ethanol–ammonia, twice treated with concentrated NaOH, washed several times with ammonia; 40% yield, dark red solid, mp 175–177 °C; IR (KBr) 3425, 1650, 1510, 1480, 1160, 1060, 1035, 840, 550 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.30 (m, 8), 1.73 (m, 2), 3.36 (s, 1), 4.10 (t, 2), 6.05 (d, 2), 6.38 (d, 1), 7.26 (d, 2), 7.43 (d, 2), 7.66 (d, 1), 8.13 (d, 2). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.51; H, 7.94; N, 4.72.

1-(6-Hydroxyhexyl)-4-[(3,5-dimethyl-4-oxocyclohexa-2,5-dienylidene)ethylidene]-1,4-dihydropyridine (Id): recrystallized from ethanol–ammonia and pyridine; 71% yield; dark blue solid, mp 174–176 °C; IR (KBr) 3400, 1650, 1510, 1480, 1160, 1020 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.30 (m, 8), 1.73 (m, 2), 1.92 (s, 6), 3.33 (s, 1), 4.12 (t, 2), 6.30 (d, 1), 7.18 (s, 2), 7.27 (d, 2), 7.50 (d, 1), 7.96 (d, 2). Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.37; N, 4.30. Found: C, 76.77; H, 8.44; N, 3.87.

1-(6-Hydroxyhexyl)-4-[(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)ethylidene]-1,4-dihydropyridine (Ie): recrystallized from ethanol–ammonia; 60% yield; dark violet solid, mp 130–132 °C; IR (KBr) 3350, 1650, 1510, 1480, 1160, 1020, 960, 940 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.33 (m, 8), 1.40 (s, 18), 1.72 (m, 2), 3.36 (s, 1), 3.93 (t, 2), 6.15 (t, 2), 6.15 (d, 1), 7.16 (s, 2), 7.18 (d, 2) 7.28 (d, 1), 7.77 (d, 2). Anal. Calcd for $C_{27}H_{39}NO_2$: C, 79.17; H, 9.60; N, 3.42. Found: C, 78.49; H, 9.68; N, 3.32.

Spectroscopic Determination of Basicity. pH measurements were performed with a Fisher Accumet (Model 320) pH meter with a Graphic Controls combined electrode without correction for the difference of electrode solvent and the measured medium.

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Methanol–water (52.1% w/w) and phosphate (pH 8.21) and carbonate (pH 11.32) buffers were made up according to procedures of standard source.[20] Phosphate buffer (pH 8.21): 0.01000 mol of KCl, 0.002752 mol of KH_2PO_4, 0.002757 mol of Na_2HPO_4 in 52.1% w/w methanol–water solvent mixture. Carbonate buffer (pH 11.32): 0.01000 mol of KCl, 0.002771 mol of $NaHCO_3$, 0.002771 mol of Na_2CO_3. Intermediate pH buffers were obtained by different mixtures of these two. Attention was made to keep a constant ionic strength.

An accurate quantity of compound was dissolved in an accurate volume of 52.1% w/w methanol–water mixture to allow a concentration of about 5×10^{-4} M. This was diluted with buffers to a concentration of 1×10^{-5} M. pH and spectra were recorded. Relative pK_a values were calculated by using the relationship

$$pK_a = pH - \log ([A^-]/[HA])$$

$[A^-]$ and [HA] were calculated from visible spectral data.

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Registry No. **1a**, 58346-32-0; **1b**, 91178-47-1; **1c**, 91178-48-2; **1d**, 91178-49-3; **1e**, 91178-50-6; **1e**·$HClO_4$, 91178-52-8; 4-picoline, 108-89-4; 4-hydroxybenzaldehyde, 123-08-0; 3,5-dimethyl-4-hydroxybenzaldehyde, 2233-18-3; 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde, 1620-98-0.

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Synthesis of (*Z*)- and (*E*)-6-Hydroxyketamine

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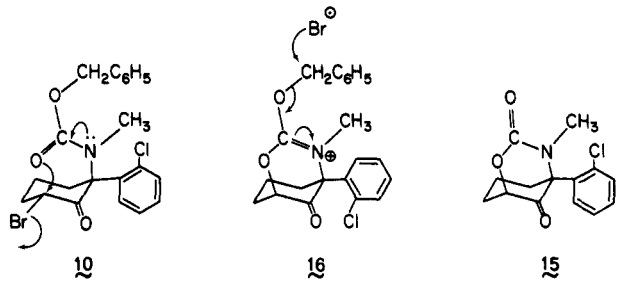
(*Z*)- and (*E*)-6-hydroxyketamine, potential metabolites of the dissociative anesthetic agent ketamine [(±)-2-(*o*-chlorophenyl)-2-(methylamino)cyclohexanone], have been prepared by oxidation of the trimethylsilyl enol ether of *N*-(methoxycarbonyl)ketamine with *m*-chloroperoxybenzoic acid. The relative stereochemistry of these diastereoisomers was established via the cyclic carbamate formed from the thermal cyclization of (*E*)-6-bromo-2-(*o*-chlorophenyl)-2-[(benzyloxycarbonyl)methylamino]cyclohexanone which, upon base hydrolysis, yielded (*Z*)-6-hydroxyketamine. Confirmation of this assignment was achieved by the selective cyclization of (*E*)-2-(*o*-chlorophenyl)-2-[(methoxycarbonyl)methylamino]-6-(tosyloxy)cyclohexanone, a reaction which the corresponding *Z* isomer did not undergo.

The anesthetic agent ketamine (**1**) is biotransformed to a variety of metabolites, some of which may have biological activity.[1,2] In order to further our knowledge of the metabolism of ketamine (Chart I), we have undertaken the synthesis of (*Z*)- and (*E*)-6-hydroxyketamine (**2** and **3**, respectively), two compounds which, on the basis of mass spectral evidence, are potential metabolites of the parent drug.[3]

Of several possible approaches to these α-hydroxy ketones[4-8] we examined first the α-bromination of *N*-benzoylketamine (**4**) with phenyltrimethylammonium tribromide.[9] A poor yield of a pure α-bromo derivative of **4** was obtained which displayed a well-defined ABX system[10] for the C_6-methine ^1H NMR signal, consistent with the 6_{eq}-bromo structures **5** and **6**. A modified pathway involving the reaction of the lithium enolate **8** of *N*-(benzyloxycarbonyl)ketamine (**7**) with bromine[11] gave a much improved yield of a pure α-bromo ketone which displayed an ^1H NMR spectrum consistent with the 6_{eq}-bromo structures **9** and **10**.

Reaction of **9**/**10** with potassium acetate in acetic acid yielded two products, neither of which proved to be the desired α-acetoxy ketones **11** and **12**. The less polar compound displayed spectral characteristics consistent with the elimination product 3-(*o*-chlorophenyl)-2-hydroxycyclohex-2-enone (**13**). Reaction of **13** with *o*-phenylenediamine gave, as expected for a potential 1,2-dione, the tetrahydrophenazine **14**.[12] Mass spectral and elemental analyses established the empirical formula of the second product as $C_{14}H_{14}NO_3Cl$, which differs from that of the starting material **9**/**10** by the elements of benzyl bromide.

Scheme I



10 **16** **15**

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