General Procedure for Second Cycloaddition. The appropriate monocycloaddition product was dissolved in enough toluene to make the solution ~0.10 M. The solution was degassed by bubbling argon through for ~5 min. The solution was heated in a sealed tube at 240 °C for 3-5 h. The solution was concentrated and the residue chromatographed on silica gel using ether-hexane as the solvent.

1,2,4a,4b,7,8,8a,9a-Octahydro-7,8-dimethyl-3,9*H*-fluorene-3,9-dione (11a): yield 0.16 g (35% overall); IR (film) 1720, 1745, 1450 cm^{-1}; NMR ($CDCl_3$) δ 1.1-1.35 (m, 6 H), 2.0-3.1 (broad m, 12 H), 5.6-5.9 (bs, 2 H).

1,2,4a,4b,7,8,8a,9a-Octahydro-7-methyl-8-phenyl-3-*tert*-butyldimethylsilyloxy-9*H*-fluoren-9-one (11b): yield 0.26 g (32% overall); NMR (CCl_4) δ 0.20 (s, 6 H), 0.70 (d, 3 H, J = 7 Hz), 1.0 (s, 9 H), 5.05 (m, 1 H), 6.20 (m, 2 H), 7.5 (m, 5 H); IR (film) cm^{-1} 1735, 1648, 1250, 1190, 835, 780; high-resolution mass spectrum $C_{26}H_{36}O_2Si$ requires 408.248 47, measured 408.248 56.

1,2,4a,4b,7,9a-Hexahydro-7-methyl-8-phenyl-3-*tert*-butyldimethylsilyloxy-9*H*-fluoren-9-one (13a): yield 0.24 g (30% overall); NMR (CCl_4) δ 0.2 (s, 6 H), 1.0 (s, 9 H), 5.1 (m, 1 H), 5.85 (m, 1 H), 6.0 (m, 1 H), 7.4 (m, 5 H); IR (film) cm^{-1} 1720, 1660, 1250, 1190, 832; high-resolution mass spectrum $C_{26}H_{34}O_2Si$ requires 406.232 81, measured 406.232 70.

1,2,4a,4b,7,9a-Hexahydro-7,9a-dimethyl-8-phenyl-3-*tert*-butyldimethylsilyloxy-9*H*-fluoren-9-one (13b): yield 0.235 g (28% overall); NMR (CCl_4) δ 0.20 (s, 6 H), 1.0 (s, 9 H), 5.0 (m, 1 H), 5.90 (m, 1 H), 6.05 (m, 1 H), 7.50 (m, 5 H); IR (film) cm^{-1} 1720, 1640, 1460, 1190, 830; high-resolution mass spectrum $C_{27}H_{36}O_2Si$ requires 420.248 46, measured 420.248 38.

7-Methyl-3-*tert*-butyldimethylsilyloxy-9*H*-fluoren-9-one (16). To a stirred solution of 22 mg of **15** in 2 mL of toluene was added 30 mg of DDQ. The reaction mixture was refluxed for 24 h. The solution was diluted with ether, filtered, and concentrated: yield 0.21 g (100%); NMR ($CDCl_3$) δ 0.28 (s, 6 H), 1.02 (s, 9 H), 2.36 (s, 3 H), 7.45 (m, 6 H); IR ($CHCl_3$) cm^{-1} 1700, 1600, 1255, 1215, 833, 791; high-resolution mass spectrum $C_{20}H_{24}O_2Si$ requires 324.154 56, measured 324.151 14; UV (MeOH) 256, 278 nm.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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Production of a Fluorescent Conjugate Acid of 8-Methoxypsoralen and an Unusual Mechanism for Its Nonradiative Decay

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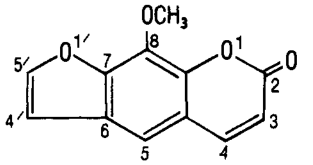
Abstract: The protonation constant (pK_{BH^+}) of 8-methoxypsoralen was determined from measurements of its absorption in various concentrations of sulfuric and perchloric acids using Hammett acidity functions. Proton nuclear magnetic resonance spectra of highly acidic solutions indicated protonation of the exocyclic oxygen atom. With D_2SO_4, proton exchange with the furan side of the molecule (4′,5′ positions) was observed. The intensity of fluorescence of the conjugated acid increases markedly with increasing acid concentration in solutions where absorption measurements indicate that protonation is nearly complete. This unexpected behavior is discussed and a mechanism is proposed.

Introduction

Initially, our interest in 8-methoxypsoralen (8-MOP) was sparked by the use of that compound in a novel and experimental treatment of psoriasis. In the treatment, the compound is ingested or applied topically, and after a suitable time interval the patient is irradiated with ultraviolet radiation of wavelengths longer than 300 nm. While the mechanism by which the photochemotherapy alleviates the symptoms is not fully understood, it is believed to involve the photoaddition of 8-MOP to epidermal DNA.



8-methoxypsoralen (8-MOP)

We were examining the fluorescence quenching of 8-MOP with various quenchers with the intent of using this data to help elucidate the distribution of the compound in tissue samples. One of the first quenchers we studied was H$^+$, provided by different strong acids. The quenching followed Stern-Volmer kinetics[1] but, much to our surprise, we observed no new fluorescence, attributable to the conjugate acid of 8-MOP. We had reasoned by analogy to the related compounds, the 7-amino-

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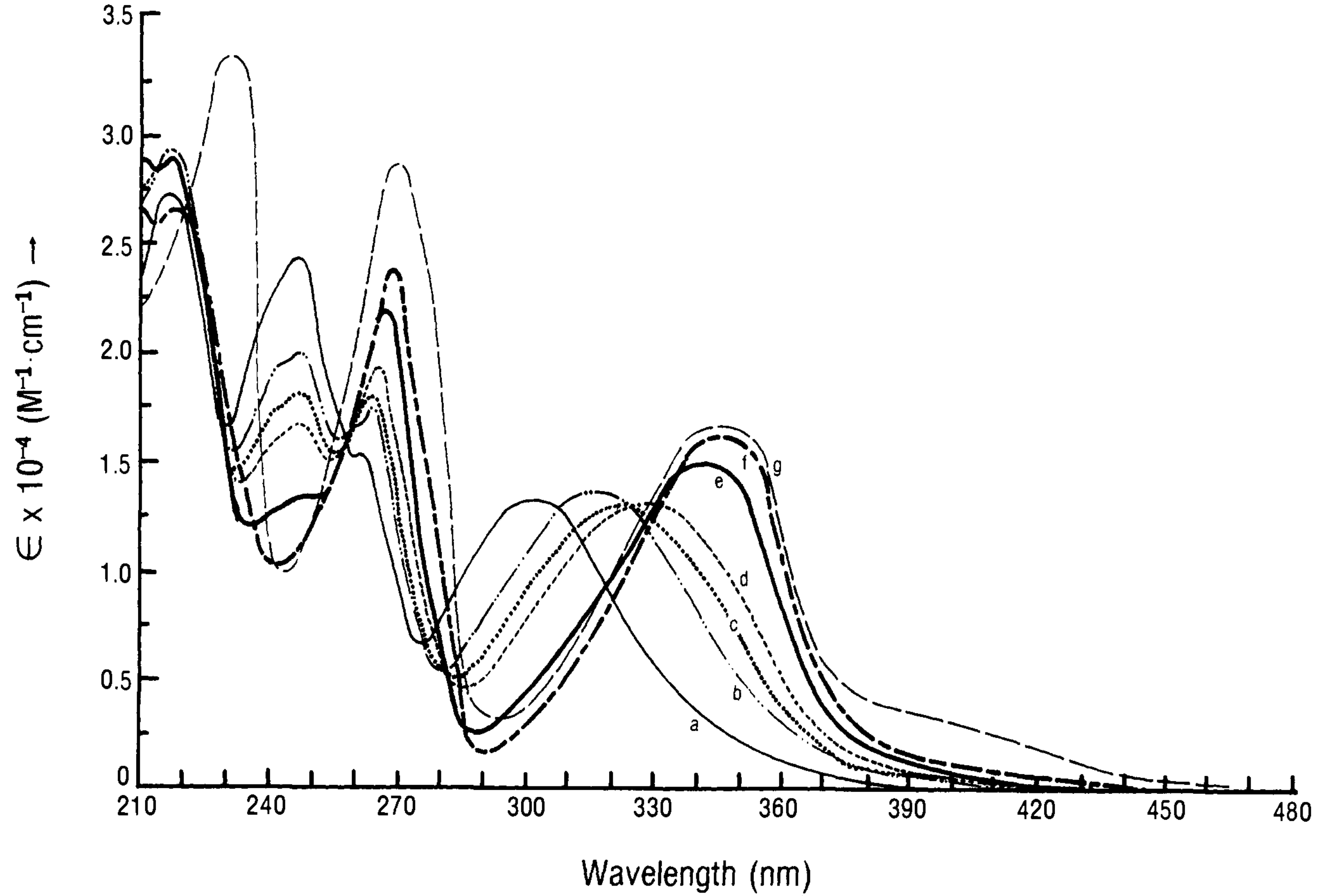
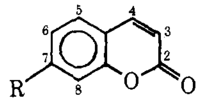


Figure 1. Absorption spectra of 8-MOP: (a) —, in water; (b) —••—••, in 60% H_2SO_4; (c) ·····, in 65% H_2SO_4; (d) ------, in 67.5% H_2SO_4; (e) —, in 75% H_2SO_4; (f) — — —, in 88% H_2SO_4; (g) — — —, in 95% (concentrated) H_2SO_4.

or 7-hydroxycoumarins, in which fluorescence can be observed from both the parent compounds and their conjugate acids.[2]



$R = NR_2$ or —OH

The present study extended our earlier work and, in particular, probed the regime of very high acid concentrations. At the highest acidities studied, we observed a new fluorescence, red shifted from that of 8-MOP. We conclude that a protonated form of 8-MOP is responsible for the new emission. This result we reconcile with our earlier observations by an explanation which invokes a new mechanism for nonradiative decay of excited states which undergo proton-transfer reactions.

Experimental Section

Materials. 8-Methoxypsoralen (8-MOP), pfs grade, was obtained from Sigma Chemical Co. and was used as received after checking its purity by thin layer chromatography and determining that it was free from fluorescent impurities. The sulfuric acid solutions were prepared by dilution of Allied Chemical Electronic Reagent sulfuric acid (95% minimum) and the concentrations were determined by titrating with standard sodium hydroxide. Molarity vs. weight percent conversions were made using tabulated data for aqueous H_2SO_4.[3] Sulfuric acid from Matheson Coleman and Bell was also used to test the reproducibility of some of the results. Perchloric acid reagent grade (72%) was purchased from Matheson Coleman and Bell and dilutions were done using standard molarity vs. weight percent data.[4] For spectral measurements the solutions of 8-MOP in various concentrations of acid were prepared by pipetting 6-μL aliquots of an almost saturated solution of 8-MOP in methanol into 10-mL volumetric flasks containing known concentrations of acid. The concentration of 8-MOP in each case was 2×10^{-5} M. It was found that the presence of the very small quantity of methanol in no way affected the absorption spectra.

Absorption and Emission Spectra. The absorption spectra of 8-MOP in concentrated acid (45–95% H_2SO_4 and 55–72% $HClO_4$) were recorded with a Cary-219 spectrophotometer at room temperature. Deoxygenation of the samples by bubbling nitrogen gas did not affect the shape or intensity of the absorption spectrum in 95% H_2SO_4. The fluorescence spectra were scanned at room temperature using a Perkin-Elmer MPF-44A fluorescence spectrophotometer. All emission readings were taken using the same 1-cm quartz cell to maintain consistency between the measurements. It was not necessary to apply a correction for the photomultiplier response because the spectra to be compared showed no shift in λ_{max}. The excitation monochromator was set at 350 nm with a slit width chosen to produce a 6-nm spectral bandwidth. The emission was recorded with a 4-nm bandwidth. No change in fluorescence intensity was observed after the solution was flushed with nitrogen gas. Reported results were obtained with fresh solutions since the spectra slowly changed on standing.

Magnetic Resonance Spectra. NMR spectra of 8-MOP in $CDCl_3$ and D_2SO_4 were run using both Varian HA-100 and T-60 NMR spectrometers for ^1H and a CFT-20 NMR spectrometer for ^{13}C NMR. ESR spectra of 8-MOP/H_2SO_4 and deoxygenated 8-MOP/H_2SO_4 were run in an E-12 EPR spectrometer.

Results

Absorption and Emission. The absorption spectra of 8-MOP in various concentrations of sulfuric acid as well as in water are shown in Figure 1, while Figure 2 shows the spectra in various concentrations of perchloric acid. There were no significant spectral changes upon leaving the samples in cell compartments for 30–45 min. The absorption spectra showed gradual bathochromic solvent shifts with λ_{max} increasing from 303 nm in pure water to 327 nm in 67.5% H_2SO_4. At higher acidities, where significant amounts of $(8\text{-MOP})H^+$ were present, there was an increase in absorption intensity and λ_{max} shifted to 347 nm.

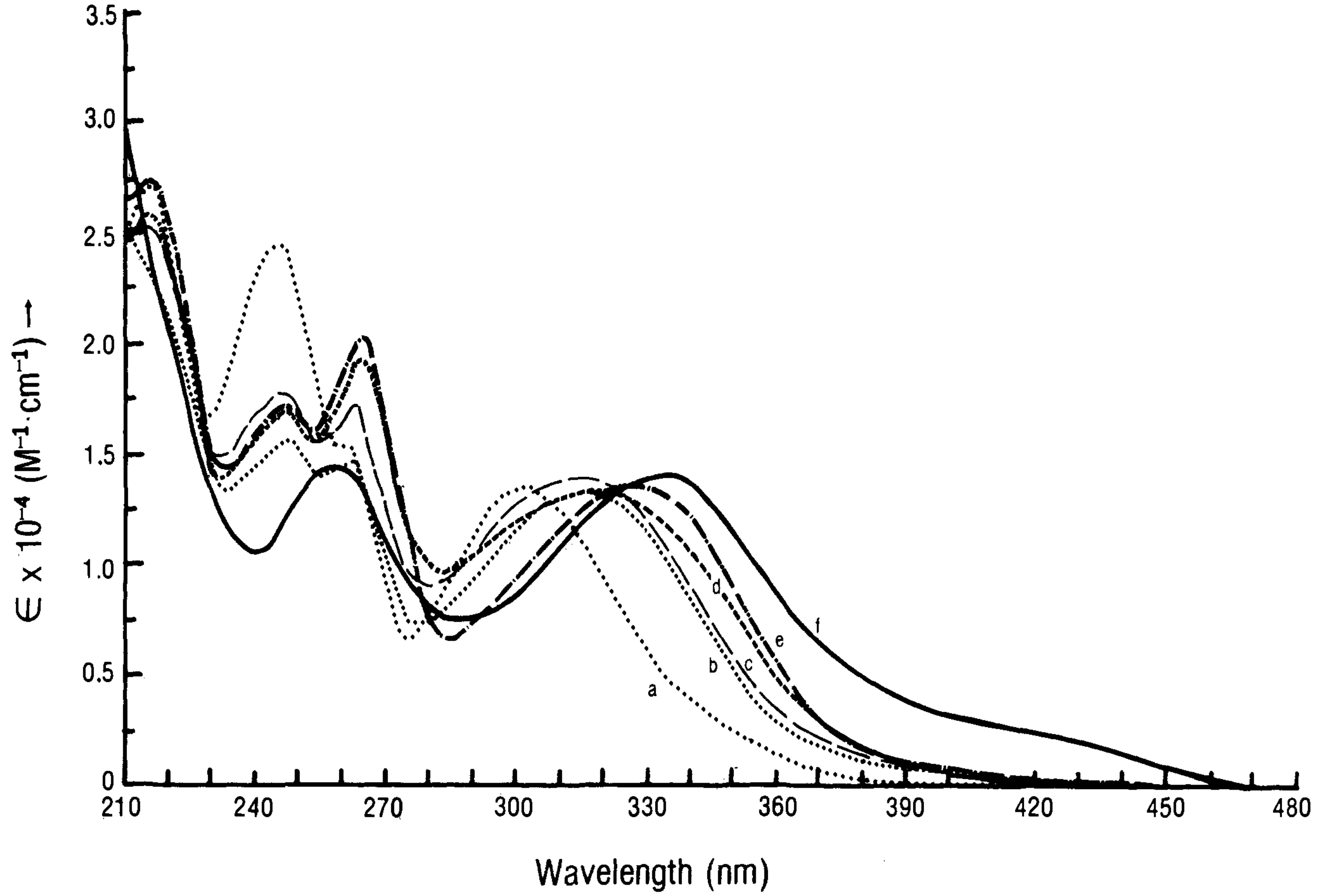


Figure 2. Absorption spectra of 8-MOP: (a) ·····, in water; (b) ------, in 55% $HClO_4$; (c) — — —, in 60% $HClO_4$; (d) ---, in 65% $HClO_4$; (e) —·—, in 67.5% $HClO_4$; (f) —, in 72% (concentrated) $HClO_4$.

The absorption λ_{max} of 8-MOP in both 95% H_2SO_4 and 72% $HClO_4$ shifts gradually to shorter wavelength with time (followed up for 7 days) evidencing the formation of new species. Increasing the temperature enhances the rate of this change. Along with the shift, the λ_{max} intensity also increases. Typically for 2×10^{-5} M 8-MOP in concentrated sulfuric acid, the shift in 5 days is from 347 to 326 nm and corresponding maximum absorbance increase is from 0.33 to 0.55. The similar nature of the spectral shift in both concentrated sulfuric acid and in concentrated perchloric acid rules out the possibility of sulfonation in the former case.

We used Hammett acidity functions, H_0, to estimate the value of pK_{BH^+} of 8-MOP from the spectrophotometric data. To do so required that we take account of the medium-dependent changes in the spectra of the absorbing species. Figures 1 and 2 indicate that the spectrum of BH^+ has maxima at 347 and 337 nm in H_2SO_4 and $HClO_4$, respectively. However, the strong bathochromic shift in the spectrum of the free base with increasing acid concentration below 60% H_2SO_4 indicates that the spectrum in water cannot be used as a reference. We used a simple form of the method of Yates, Stevens, and Katritzky[5] using the value of ϵ_{350} in 60% H_2SO_4 as the value of ϵ_B and the value of ϵ_{350} in 95% H_2SO_4 as the value of ϵ_{BH^+} in the equation

$$\frac{[B]}{[BH^+]} = \frac{\epsilon_{BH^+} - \epsilon}{\epsilon - \epsilon_B} \qquad (1)$$

Values of pK_{BH^+} were calculated using the equation

$$H_0 = -\log\left(\frac{a_{H^+}f_B}{f_{BH^+}}\right) = pK_{BH^+} + \log\frac{[B]}{[BH^+]} \qquad (2)$$

The estimate of pK_{BH^+} could probably have been improved by reiteration to correct for further bathochromic shift in the spectrum of B. Such a procedure might have been plagued by the intrusion of other species which are indicated by the increased absorption in the 370–440-nm region by solutions in 95% acid. There is also question as to which of several acidity functions are best to use in studying bases of various structural types, a subject reviewed succinctly by Noyce and Jorgenson.[6] These refinements seemed unnecessary for our purposes since we primarily wished to observe the spectroscopic and chemical behavior of BH^+ and it is rather evident that it is the principal solute species in solution containing 88% or more H_2SO_4. The data are summarized in Table I.

Table I. Molar Extinction Coefficients at 350 nm and Acidity Data for 2×10^{-5} M 8-MOP in Sulfuric Acid

acid concn, %	$-H_0$[a]	λ_{max}, nm	ϵ	pK_{BH^+}
H_2O		303	2400	
45[b]	2.85	309	3500	
60	4.46	316	5500[c]	
65	5.10	321	7000	−5.91
67.5	5.45	327	9000	−5.80
70[b]	5.80	333	10 500	−5.90
75	6.56	341	14 000	−6.07
81[b]	7.50	344	15 700	−6.52
88	8.61	346	16 400	
95	9.85	347	16 750[d]	

[a] Data from ref 4 and 7. [b] Curves not plotted in Figure 1 for the sake of clarity of other spectra. [c] Taken as value of ϵ_B in eq 1. [d] Taken as value of ϵ_{BH^+} in eq 1.

The limited number of data taken in perchloric acid solutions could not be analyzed in the same way to give consistent values of pK_{BH^+} using reported values of H_0. In $HClO_4$ the

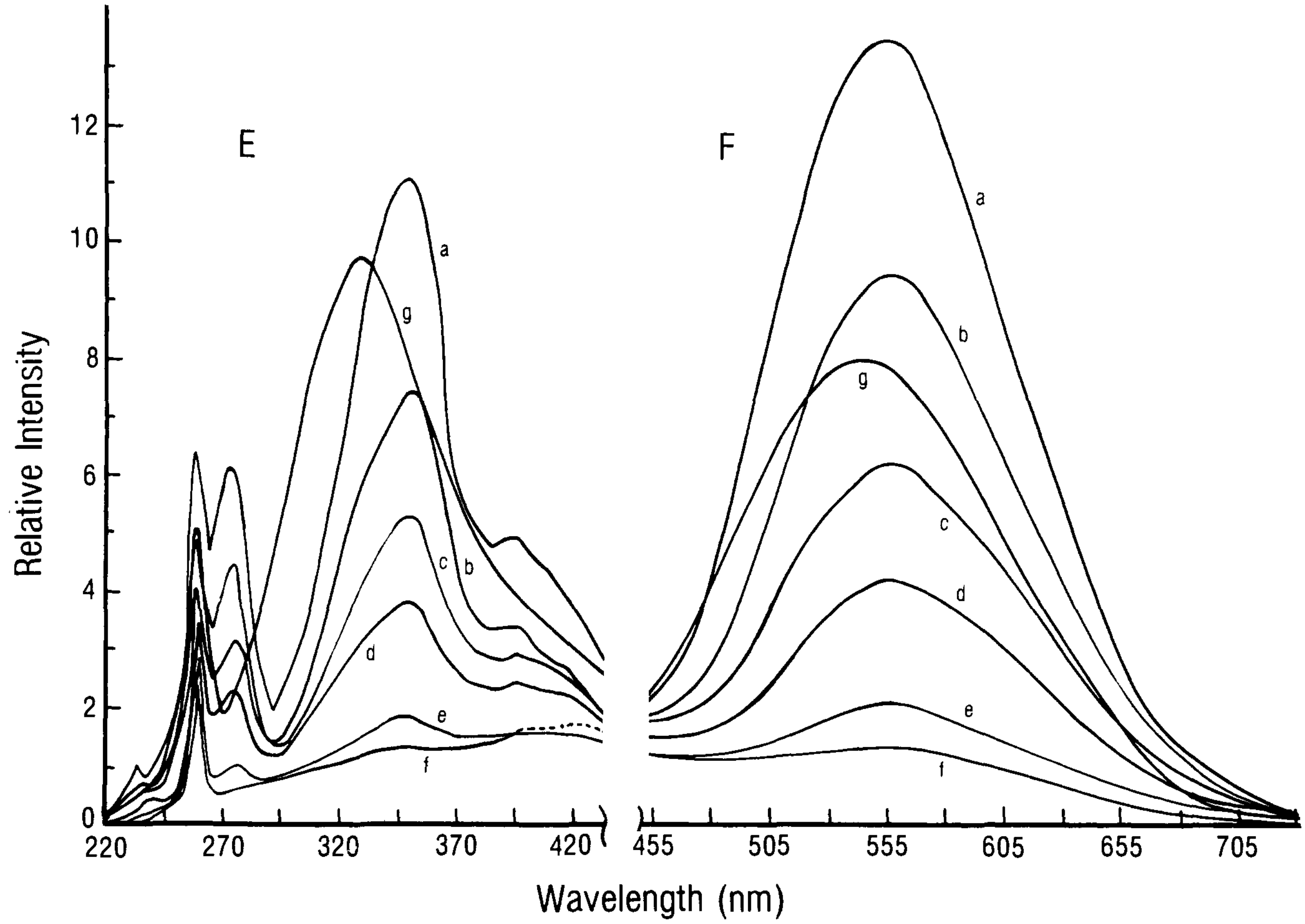


Figure 3. Fluroescence (F) and excitation spectra (E) of conjugate acids of 8-MOP in H_2SO_4 and $HClO_4$: (a) in 95% H_2SO_4; (b) in 93% H_2SO_4; (c) in 91% H_2SO_4; (d) in 88.5% H_2SO_4; (e) in 85% H_2SO_4; (f) in 81% H_2SO_4; (g) in 72% $HClO_4$. Excitation spectra are measured with λ_{em} 520 nm and fluorescence spectra are measured with λ_{ex} 350 nm. Spectra a-f are at gain = 3; spectra g's are at gain = 10.

Table II. NMR Spectral Data for 8-MOP

	chemical shifts[a]		
type of proton	$CDCl_3$	D_2SO_4 + D_2O (50:50)	98% D_2SO_4
H_3[b]	6.35	6.62	7.45
H_4[b]	7.78	8.94	9.76
H_5	7.36	7.88	8.15
$H_{4'}$[c]	6.82	7.30	7.53
$H_{5'}$[c]	7.68	7.88	8.15
OCH_3	4.30	4.33	4.62

[a] Units of δ with Me_4Si as internal standard. [b] $J_{3,4}$ = 9.7 Hz in all solvents. [c] $J_{4',5'}$ = 2.5 Hz in all solvents.

bathochromic shifts due to medium effects on absorption of 8-MOP and to protonation to form $(8\text{-MOP})H^+$ are compressed into a much smaller spectral region than in H_2SO_4 solutions. Consequently we could not make an easy assignment of a value of ϵ_B to be used in eq 1. However, there is a substantial red shift in absorption in the region around 65% $HClO_4$ ($H_0 = -6.43$). This is consistent with the value of pK_{BH^+} of -6 estimated in sulfuric acid solutions.

The conjugated acid of 8-MOP is found to fluoresce at room temperature in solutions containing the highest acid concentrations of both H_2SO_4 and $HClO_4$ as shown in Figure 3. The fluorescence intensity decreases with decreasing sulfuric acid concentration and at 81% H_2SO_4 the fluorescence is nearly indiscernible. The excitation spectra are also represented in Figure 3. They were measured by keeping the fluorescence monochromator at 520 nm. The excitation spectra reproduce the absorption spectra of protonated 8-MOP. Quantitative comparison was not attempted because no correction for the instrumental response was made. The apparent 260-nm peak is an artifact appearing at half the monitoring wavelength. The excitation spectra appeared to be the same qualitatively with the fluorescence monochromator set at 500 and 554 nm and in sulfuric acids from different sources. The fluorescence and excitation spectra of 8-MOP in concentrated $HClO_4$ only are also represented in Figure 3. (Note the difference in gain.)

Magnetic Resonance. The spectrum of 8-MOP in $CDCl_3$ is essentially identical with that reported by Krauch, Farid, and Schenck.[8] We were able to separate the H_4 and $H_{5'}$ protons at 100 MHz as is shown by the insert in Figure 4A. The assigned chemical shifts are included in Table II for comparison with the spectra in acid solution.

8-MOP dissolves readily in 95% sulfuric acid but only very slowly in solutions in which protonation is expected to be incomplete. Because of the irreversible chemical changes noted in the measurements of absorption spectra (vide supra), we did not attempt to prepare 8-MOP solutions for NMR study by direct dissolution in solvents containing intermediate amounts of H_2SO_4. Instead, solutions in 95 or 98% acid were diluted to 50% acid concentration after standing for varying periods of time. We carried out extensive study in H_2SO_4 solutions which is not reported in detail because all of the solvent features of those results, along with others, are also shown by experiments in which solutions were prepared in 98% D_2SO_4 and subsequently diluted to 50% with D_2O.

Figures 4 and 5 show that there are considerable changes in chemical shifts on going from $CDCl_3$ to 50% acid and still more extensive changes in 98% D_2SO_4. In both solutions the H_3 and H_4 signals stand out strongly because of the coupling

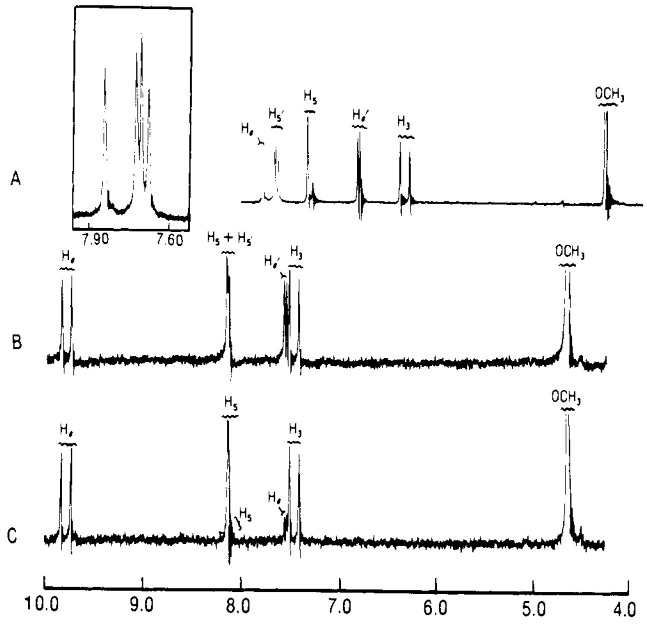


Figure 4. ^1H NMR spectra of 8-MOP and protonated product: (A) spectrum of 8-MOP in chloroform-*d* containing 1% Me_4Si (signal at 7.30 ppm arises from $CHCl_3$ in solvent, insert shows signals from H_4 and $H_{5'}$ on expanded scale); (B) freshly prepared solution of 8-MOP in 98% D_2SO_4 run within 10 min; (C) same solution as in B run after 60 min.

between the two (J = 9.7 Hz), so their assignment was easy. Resolution of signals of $H_{4'}$ and $H_{5'}$ was not as simple. In 98% acid there is a clearly resolved doublet on the low-field side of the H_3 signal. There is also an excess integral associated with the signal at δ 8.15 assigned to H_5. This part of the spectrum can be resolved to show that it consisted of three peaks (not shown). These were, therefore, assigned to an H_5 singlet at δ 8.15 and a doublet with J = 2.5 Hz centered at 8.15 ppm. The doublet is obviously paired with the one centered at 7.53 ppm. On dilution to 50% acid the H_3 doublet moves much more to high field than the other nearby doublet. The changes in H_5 and its companion doublet are nearly the same so they are again difficult to resolve. Since $H_{4'}$ is at much higher field than $H_{5'}$ in $CDCl_3$ we presume that the same relationship obtains in 50% D_2SO_4. In the spectra of solutions in 98% acid the weakly coupled doublet centered at δ 7.53 is assigned to $H_{4'}$ and that at δ 8.15 to $H_{5'}$. All of the assignments are given in Table II.

As solutions in 98% D_2SO_4 were allowed to stand at room temperature the signals attributed to $H_{4'}$ and $H_{5'}$ decreased in intensity and were nearly gone in 1 h. The solutions allowed to stand before dilution to 50% concentration showed corresponding decreases in the signals assigned to those two protons. Obviously slow exchange of D for H is occurring. The rates of exchange at the two positions are similar, although careful monitoring shows that $H_{5'}$ is exchanged slightly more rapidly than $H_{4'}$. The consistency in qualitative kinetic observations made on diluted and undiluted solutions assures that there has been no inversion of the relative positions of the chemical shifts between the protonated and unprotonated forms.

When samples were allowed to stand overnight inside the NMR cavity (~32 °C), additional peaks appeared. There was also a significant increase in a sharp signal that had been observed at δ 0.12 upfield from the methoxy peak. Warming the solutions to higher temperatures further accelerated these changes.

We also looked briefly at ^{13}C spectra. In $CDCl_3$ containing tris(acetylacetonato)chromium(III) as a shift reagent we observed separated resonances for all 12 carbon atoms. We had hoped to use ^{13}C spectra in H_2SO_4 to further identify the exchange reactions. However, coupled and decoupled spectra were ambiguous, probably because chemical changes of significant magnitude occur during the acquisition time normally required to produce spectra with good resolution.

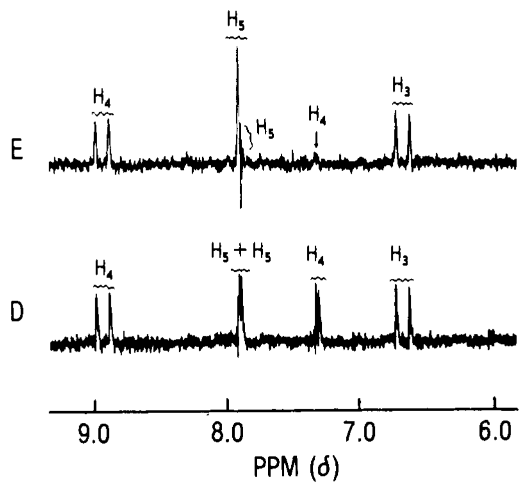


Figure 5. (D) NMR spectrum of 8-MOP in 98% D_2SO_4 after diluting the solution with D_2O (50:50) within 10 min of preparation; (E) dilution in D_2O was made after 90 min of solution preparation.

The ESR spectra of both degassed and undegassed samples of 8-MOP in 95% H_2SO_4 showed no evidence for production of cation radicals, a process that might conceivably have been involved in the irreversible changes.

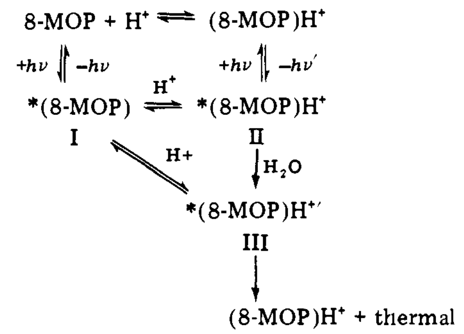
Discussion

The results shown in Table I and in Figure 1 indicate that 8-MOP is a base and that pK_{BH^+} is between −5.5 and −6.5. The uncertainty derives from the semiempirical character of acidity functions as well as from the uncertainties arising from the variation of the absorption characteristics of neutral and protonated species in different media. However, there can be little doubt that a conjugate acid of 8-MOP is the principal solute species in sulfuric acid solutions containing more than 81% H_2SO_4 (H_0 = 7.5) and in 72% perchloric acid (H_0 = 7.7). In the very concentrated acid solutions, H_2SO_4 = 95% or $HClO_4$ = 72%, absorption due to species other than B or BH^+ appears in the wavelength region 370–440 nm and all the solutions with H_2SO_4 > 60% undergo chemical changes on standing.

Emission Spectra. Concentrated sulfuric acid solutions of 8-MOP emit with maxima close to 554 nm when excited in the near ultraviolet. This emission may well be the expected mirror image of the absorption which peaks at about 350 nm in the concentrated acid solutions, although both emission and absorption are so broad and structureless that judgment as to whether or not there is real overlap at a 0–0 band is somewhat arbitrary. At least there is no significantly greater Stokes shift in the emission from the conjugate acid than from the unprotonated form of 8-MOP which in water solution has an absorption maximum at 303 nm and an emission maximum at 505 nm. The emission maximum from 72% $HClO_4$ is at 541 nm and the absorption maximum is at 337 nm, which is consistent with the view that the same species is involved in emission and absorption in all the strongly acidic solutions. It is, however, necessary to postulate that there are significant bathochromic shifts in both absorption and emission of BH^+ on going from perchloric to sulfuric acid solutions.

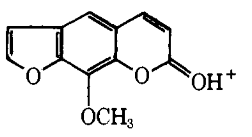
As is shown in Figure 3, the emission intensity at 554 nm increases dramatically as the concentration of sulfuric acid is increased above 81%, a medium in which 90% or more of dissolved 8-MOP exists as the conjugate acid. Since some new

Scheme I



absorption features, namely, increased absorbance in the region just below 400 nm and an intense new maximum at 230 nm, appear in the concentrated acid solutions we were initially attracted to the view that the emission originates from some second conjugate acid rather than from BH^+. However, when we measured the excitation spectra for emission at 520 nm in various acid solutions, they followed the absorption in 88% H_2SO_4 rather closely in all cases. It is clear that the excitation in the region of enhanced absorption between 370 and 400 nm is not reflected in a corresponding enhancement of emission intensity. The same is true of perchloric acid solutions where the long-wavelength absorption is even more pronounced. Unfortunately, instrumental limitations prevented investigation of the response to irradiation of the new absorption maximum at 230 nm.

The balance of evidence strongly favors the view that emission occurs from the same species in all the concentrated acid solutions and that the species is a conjugate acid of 8-MOP. Chemical intuition and NMR spectra (vide infra) indicate that the conjugate acid is protonated at the exocyclic oxygen.



We have previously reported that the fluorescence of 8-MOP in water solutions is quenched very efficiently by acid.[1] This led to speculation that the conjugate acid of electronically excited 8-MOP finds some very efficient pathway for nonradiative decay. We have now produced a fluorescent conjugate acid so our previous suggestion, at least in simple form, cannot be entirely correct.

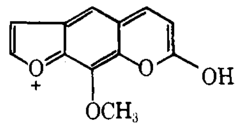
There is an interesting symmetry between the phenomena observed in dilute aqueous acid and in very concentrated acid. Addition of small amounts of acid to aqueous solutions of 8-MOP leads to efficient quenching of the fluorescence of 8-MOP and addition of water to solutions in concentrated acid leads to quenching of the fluorescence of $(8\text{-MOP})H^+$. Over a very wide range of acidities, including those where substantial amounts of the ground states of both 8-MOP and $(8\text{-MOP})H^+$ are present, there is no detectable emission from either species. The results cannot be attributed to simple proton transfer equilibrium between two excited states

$$*8\text{-MOP} + H^+ \rightleftarrows *(8\text{-MOP})H^+$$

since both *8-MOP and $*(8\text{-MOP})H^+$ emit. The results seem to indicate that the act of delivering a proton to *8-MOP or removing one from $*(8\text{-MOP})H^+$ induces rapid radiationless decay. Conceivably there is a second conjugate acid of *8-MOP which undergoes very rapid nonradiative decay.

The mechanism we propose may be written as in Scheme I. In our earlier study we observed the quenching of fluorescence of I by protons. Under those conditions of high and effectively constant water activity, we cannot determine whether III is formed directly or via II, or whether both quenching paths are operative. In the present study, at the highest acid concentrations the water activity becomes sufficiently low so that one can trap II long enough to observe its fluorescence.

NMR Spectra. The spectrum measured in $CDCl_3$ was essentially identical with that reported previously.[8] In solutions containing 95% H_2SO_4 or 98% D_2SO_4 all protons are deshielded relative to chloroform solution, as would be expected of a protonated species. The pattern of shifts is quite compatible with assignment of the structure of the conjugate acid as protonated on the carbonyl oxygen atom. The largest change in chemical shift ($\Delta\delta = 1.98$ ppm) is seen for H_4. This would be expected since C_4 should be especially depleted of electron density by ordinary conjugative interaction $-CH{=}CHC{=}O^+H \leftrightarrow -C^+H{-}CH{=}COH$. The rather large change ($\Delta\delta = 1.10$ ppm) for H_3 cannot be rationalized quite so simply but probably indicates that deshielding by an aromatic ring current in the pyrone ring is increased on protonation, a result that would also be predicted by classical resonance arguments. The pattern of changes in δ for the other protons attached to the aromatic system can be rationalized by resonance arguments which are not reproduced here. We simply note that conjugative transfer of electronic charge from the furano oxygen to the protonated carbonyl group



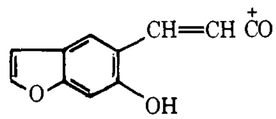
is surely significant. The interaction changes "aromaticity" relationships within the parts of the system and, in particular, decreases electron accession from the furano oxygen to C_4' and C_5'.

There are also significant changes in all values of δ, except in the methoxy group, on going from $CDCl_3$ to 50% D_2SO_4, a medium in which the concentration of the conjugate acid is very low. The changes are all in the direction of deshielding with the largest shift ($\Delta\delta = 1.16$) again being shown by H_4. We attribute this effect to solvation of the free base by the medium with the largest interactions involving hydrogen bonding by the solvent to the four oxygen atoms in 8-MOP. The strongest of those hydrogen bonds should be that to the carbonyl oxygen. This accounts for the qualitative similarity between values of $\Delta\delta$ for the "free" base in 50% acid and the conjugate acid in the most concentrated acid solutions. The result is clearly consistent with the rather large bathochromic shift in the first ultraviolet absorption maximum as aqueous solutions of 8-MOP are made increasingly acidic but at levels where extensive protonation of the solute does not occur.

Slow Reactions. Solutions of 8-MOP in even moderately concentrated acid undergo detectable chemical changes of two kinds. First, there is fairly rapid exchange of H_4' and H_5' for deuterium in D_2SO_4. More slowly, but still at quite significant rates, especially in 72% $HClO_4$, there are irreversible changes which result in substantial changes in both the UV and NMR spectra.

Exchange of the furano protons is no surprise because both furan and benzofuran are rather reactive toward electrophilic reagents. That H_5' is exchanged more rapidly than H_4' would be expected by analogy to the behavior of furan and benzofuran in which α positions are more reactive than β positions.[9] The relative reactivities are apparently not inverted by interaction with the pyrone unit and the 8-methoxy group, nor would reversal have been expected. Semiquantitative observation indicates that the rate of exchange is about the same in 70 and 98% D_2SO_4. This is as could be expected if the mechanism involves attack of D^+ on the free base. The rate would then be proportional to $a_Ba_{D^+}$. The product of the two activities should remain essentially constant (with constant total 8-MOP concentration) in solutions where a_{D^+} is high enough to protonate most of the 8-MOP.

Although we have made no real attempt to characterize the products of the slower reactions, both UV and NMR spectra show that substantial changes in the structure occur. We suspect that ring opening occurs to give either *cis*- and/or *trans*-6-hydroxy-5-benzofuranylacrylic acid, which would exist as carboxy-protonated conjugate acids or the related acylium ions in the strongly acidic media.



The rates in sulfuric acid solutions were highest in 95% acid, the highest concentration at which the changes were monitored. However, the most rapid change of all was observed in 72% $HClO_4$. Although the rate variation in H_2SO_4 solutions could be correlated by a mechanism involving attack of a second proton on $(8\text{-MOP})H^+$, the same line of reasoning cannot account for the high rate in $HClO_4$.

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The Octant Rule. 7.[1] Deuterium as an Octant Perturber

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Abstract: (1*S*)-*exo*-2-Deuteriobicyclo[2.2.1]heptan-7-one (**1**) and (1*S*)-*endo*-2-deuteriobicyclo[2.2.1]heptan-7-one (**2**) were synthesized, and their circular dichroism spectra were measured and analyzed. Both ketones show dissignate Cotton effects near 295 nm corresponding to their n–π^* electronic transitions: **1** ($\Delta\epsilon_{296} = +0.033$) and **2** ($\Delta\epsilon_{292} = +0.132$). The nature of the isotopic perturbation on the n–π^* transitions of **1** and **2**, related β-deuterioadamantanones and cyclohexanones, and α-deuteriocyclohexanones is treated theoretically. The net contribution to the sign of the rotatory strength is determined by the relatively more consignate contribution of the C–H bond that is located in an oppositely signed octant relative to the C–D bond.

Until recently, application of the octant rule to interpret the n–π^* Cotton effects (CEs) of chiral ketones with deuterium perturbers had received very little experimental justification. During the past several years, however, an increasing interest has focused on this aspect of isotopic stereochemistry with the result that an ever-growing body of circular dichroism (CD) data is becoming available. The first attempt to study the influence of deuterium on a ketone carbonyl n–π^* Cotton effect (CE) was published by Djerassi, Closson, and Lippman in 1956.[3] No difference could be detected between the optical rotatory dispersion (ORD) spectra of 3β-acetoxy-6β-deuteriocholestan-7-one and its protio analogue. However, results derived by difference measurements of large values are not entirely satisfactory, especially since the two systems measured must be of the same concentration and optical purity, and they must have identical geometries. In an effort to overcome such shortcomings, Djerassi and Tursch[4] attempted the first direct measurement of a ketone (CE) where chirality was due to a single deuterium perturber, i.e., where the protio analogue is achiral. They prepared (3*S*)-deuteriocyclopentanone of known absolute configuration and measured its ORD spectrum but found no rotation (<42°) down to 280 nm. Subsequently, Meyer and Lobo[5] prepared (+)-camphor-*9,9,9*-d_3 which had a molecular amplitude[6] (+60.92°) 3% smaller than that of the protio compound. On the basis of this observation and the fact that the atomic refractivity of deuterium is less than hydrogen, the authors[5] concluded that deuterium, like fluorine,[7,8] makes an antioctant[6,9] contribution to the octant rule.[6,9,10]

The fruitfulness of employing a stereochemically rigid framework in detecting circular dichroism (CD) CEs due only to deuterium substitution was impressively demonstrated with (1*R*)-[1-^{2}H]-α-fenchocamphoronequinone[11] and (−)-(*S*)-4-deuterio[2.2]paracyclophane.[12] Weak but well-resolved CEs ($|\Delta\epsilon| \approx 0.02$) were observed in both examples. However, the first monoketone n–π^* CE due solely to deuterium was observed only recently in a reinvestigation of (3*R*)-deuteriocyclopentanone,[13] which gave a (−)-CD CE [$\Delta\epsilon_{304} = -0.019$ (25 °C) and $\Delta\epsilon_{302} = -0.021$ (−196 °C)]. That important observation indicated that deuterium is an "antioctant"[9] perturber. It also initiated a series of interesting and valuable papers on the CD CEs of conformationally mobile[14-16] and locked[17] cyclic deuterio ketones from the Djerassi group. In those papers, deuterium was found usually but not always[17] to exhibit an "antioctant" effect and to prefer the axial (or more hindered) configuration relative to hydrogen.[15] Other work[18] has been reported on similar systems.[17] Prior to this work[14-18] we reported on the CD CE of a conformationally immobile β-equatorial deuterioadamantanone (**5**) in which the deuterium exhibits an "antioctant" effect, in hydrocarbon solvent.[1] Subsequently, Numan and Wynberg[19] reported on their syntheses and CD spectra of **4** and **5**.

In our work on chiral perturbers we have focused on the synthesis and CD analysis of stereochemically rigid structures that are achiral when the isotope under study (e.g., deuterium) is replaced by the more abundant isotope (e.g., hydrogen). In this way the inherent effect of the isotope perturber may be

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