Trapping of the Oxocarbonium Ion Intermediate in the Hydrolysis of Acetophenone Dimethyl Ketals[1]

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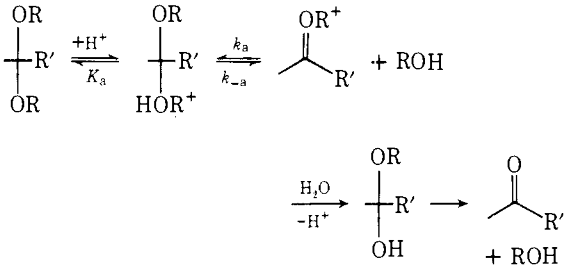
Abstract: Dilute sulfite dianion traps the oxocarbonium ion intermediate in the hydrolysis of acetophenone dimethyl ketals, but does not affect the rate of hydrolysis. Protonation of the corresponding enol ether generates the same intermediate, which shows identical trapping behavior. This establishes that the oxocarbonium ion is a free, solvent-equilibrated intermediate. It is concluded that reaction of the intermediate with sulfite is diffusion limited because (1) the ratios of the rate constants for sulfite and water attack, k_S/k_{H_2O}, are 10^1–10^3 M^{-1}, rather than the value of approximately 10^8 M^{-1} that is expected for activation-limited reactions, and (2) this ratio exhibits a ρ^+ value of -1.6, rather than a value close to zero that is expected for activation-limited reactions. The diffusion-limited trapping provides a "clock" from which the lifetimes of the intermediates are estimated to be in the range of approximately 10^{-5}–10^{-8} s. The reaction with water to give ketone is general base catalyzed; sulfite may also give ketone by attack of an oxygen atom followed by elimination to give SO_2. The rate of ketal hydrolysis follows σ with $\rho = -2.2$ and K_{eq} for oxocarbonium ion formation gives $\rho = -3.6$ with a Yukawa–Tsuno parameter of $r = 0.5$. The r values for rate and equilibrium constants are not additive and a modified Yukawa–Tsuno equation is proposed. Extrapolation of structure–reactivity relationships gives lifetimes for the oxocarbonium "intermediates" formed from glycosides and aliphatic acetals in the range 10^{-11}–10^{-15} s or less. It is concluded that lysozyme must stabilize the oxocarbonium ion "intermediate" by at least 5–7 kcal/mol.

There is a large body of evidence that is consistent with a mechanism for the hydrolysis of acetals, ketals, and ortho esters in which protonation of the reactant occurs in a rapid equilibrium step, followed by rate-determining formation of an oxocarbonium ion and rapid hydration to give a hemiacetal and the carbonyl product (eq 1).[2-4] However, some reactions of this class undergo hydrolysis through a mechanism that involves general acid catalysis and it has been suggested that in certain cases reactions of glycosides involve nucleophilic attack at the reacting carbon atom without the formation of an oxocarbonium ion intermediate.[2,3,5-7] In order to improve our understanding of the mechanism of these reactions it would be helpful to obtain direct evidence for the formation of a free oxocarbonium ion intermediate and to be able to estimate its lifetime as a function of reactant structure.



(1)

Cordes and co-workers have obtained evidence for the trapping of an oxocarbonium ion intermediate by aqueous hydroxylamine, semicarbazide, and methoxyamine during the acid-catalyzed cleavage of ortho esters.[8] The facts that (1) trapping can be observed in the presence of a large molar excess of water, (2) the effectiveness of the amine nucleophiles increases with increasing basicity (β_{nuc} ~0.4), and (3) the relative reactivities of water and the amine nucleophile are independent of reactant structure ($\rho = 0$) demonstrate that the oxocarbonium intermediate has a sufficient lifetime to show selectivity toward nucleophiles and that neither water nor the amine react with the intermediate at a diffusion-controlled rate.

In the course of attempts to synthesize α-methoxysulfonic acids we noted that sulfite ion was able to compete successfully with water as a nucleophile in the acid-catalyzed cleavage of certain acetophenone ketals. This observation led to the work reported here, which provides evidence for the trapping of an oxocarbonium ion intermediate in ketal hydrolysis and permits an estimation of its lifetime.

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Organic compounds were purified by recrystallization or distillation. Glass distilled water was used throughout.

Acetophenone dimethyl ketals were prepared by the reaction of trimethyl orthoformate in methanol with the parent ketone.[9] **1-(1-Methoxyethenyl)-4-methylbenzene** was prepared from p-methylacetophenone dimethyl ketal by the "cracking" method described by Loudon[9] with the following minor changes. The ketal (7.25 g, 0.04 mol) was added to 150 mL of azeotropically dried, refluxing chlorobenzene containing 50 mg of p-toluenesulfonic acid. The solution instantly turned bright red and was allowed to reflux for 30 min. Triethanolamine (100 mg) was added to stop the reaction and the chlorobenzene was removed by distillation at reduced pressure. The desired enol ether (2.9 g, 50%) was distilled at 120 °C (9 mm); the NMR spectrum agreed with that described previously.[9]

Stock solutions of the substrates were prepared in methanol at ~0.04 M. Aliquots (5–10 μL) were diluted into thermostated spectrophotometer cells containing 3.0 mL of the desired aqueous buffer solution. All stock solutions were thoroughly degassed with argon prior to use. In some runs, particularly those involving slow reactions and small absorbance changes, 1 mM ethylenediaminetetraacetic acid was added to retard oxidation of the sulfite. Stock solutions of bisulfite/sulfite buffers were prepared daily from the solids and were titrated with starch–iodine immediately after use. The apparent pK_a of bisulfite at a total concentration of 0.033 M 25 °C, ionic strength 1.0 (KCl), was determined from the pH of solutions prepared at five different buffer ratios to be 6.61 ± 0.01.

Kinetic Measurements. The rates of appearance of carbonyl compounds were followed by measuring the increase in absorbance at the following wavelengths: p-methoxyacetophenone, 285 nm; p-methylacetophenone, 258, 262, or 290 nm; acetophenone, 246 nm; p-chloroacetophenone, 255 nm; p-bromoacetophenone, 258 nm; m-bromoacetophenone, 250 nm. Reaction rates were followed using a Zeiss PM-6KS spectrophotometer equipped with an automatic cell changer and a digital printout. Constant temperature was maintained at 25 °C by the use of a thermostated cell compartment; ionic strength was maintained at 1.0 with potassium chloride. First-order rate constants were determined from semilogarithmic plots of $(A_\infty - A_t)$ against time and were typically linear for over 3 half-times. Good end points were obtained for the first phase in all cases except for the p-methoxy compound where slow breakdown of the α-methoxysulfonic acid was significant. For this compound, end points were estimated by adding 3% of the observed absorbance change to the absorbance after 5 half-times. The pH of each solution was determined at the completion of the experiment using a Radiometer PHM-26 pH meter equipped with a combined glass electrode.

The fraction of the cleavage products trapped as α-methoxysulfonic acid was calculated from $1 - (A_\infty - A_0)_{\text{obsd}}/(A_\infty - A_0)_{\max}$, in which A_0 is the absorbance extrapolated to zero time (equal to the absorbance of the ketal and a small amount of ketone impurity) and $(A_\infty - A_0)_{\max}$ is the absorbance change observed in the absence of bisulfite buffer at a comparable pH value. Corrections for the formation of bisulfite addition compounds from the ketone product were calculated from equilibrium constants for this reaction (K_{add}), the concentration of bisulfite ion, and the observed absorbance change due to the ketone, $(A_\infty - A_0)_{\text{obsd}}$. Such corrections are generally small; however, for ketones containing strong electron-withdrawing groups the corrections become significant and limit the range of buffer concentrations that can be examined. For the enol ether, 1-(1-methoxyethenyl)-4-methylbenzene, A_0 was taken to be the same as for *p*-methylacetophenone dimethyl ketal under identical conditions. The final absorbance that would be observed if all the products were trapped as α-methoxysulfonic acid could not be obtained directly from A_0 in this reaction because the enol ether has significant absorbance at the wavelength of the experiment. It was shown that the absorbance of *p*-methylacetophenone ketal and of *p*-methylacetophenone bisulfite, extrapolated to infinite bisulfite concentration, are both about 5% of the absorbance of the parent ketone at comparable concentrations. Careful examination of the NMR spectrum of the ketal and of the enol ether showed each to contain ≤5% ketone impurity. Uncertainties in A_0 for the enol ether result in only small uncertainties in the calculation of the fraction of ketone trapped at low concentrations of sulfite ion; however, at higher concentrations these uncertainties become significant as shown by the error limits in Figure 4.

Determination of K_{add}. Stock solutions of the parent ketones were diluted into thermostated spectrophotometer cells containing appropriate concentrations of potassium bisulfite and 0.002 M acetate buffer (pH ~4.6) at ionic strength 1.0 (KCl). Absorbance decreases relative to solutions containing no bisulfite were measured and values of $-K_{\text{add}}$ were determined from the abscissa intercepts of plots of $1/\Delta$ absorbance against $1/[\mathrm{HSO_3^-}]$.

Product Identification. Hydrolysis of the acetophenone dimethyl ketals and of 1-(1-methoxyethenyl)-4-methylbenzene gave absorbance spectra identical with those of the corresponding ketones, within experimental error. The structure of the α-methoxysulfonic acids was inferred from the method of preparation and from the NMR spectrum of a sample obtained from hydrolysis of *p*-methylacetophenone dimethyl ketal in a 1 M solution of potassium bisulfite buffer, 50% dianion, in D_2O (chemical shifts relative to DSS in δ: 1.96 (s, 3 H) $\mathrm{ArC(SO_3^-)(OCH_3)C}H_3$; 2.38 (s, 3 H) *p*-$CH_3$; 3.31 (s, 3 H) -$OCH_3$; ~7.4 (m, 4 H) ArH). A portion of the NMR sample was hydrolyzed in dilute hydrochloric acid giving an acid-catalyzed rate constant identical with that obtained on acidification of samples of *p*-methylacetophenone dimethyl ketal or 1-(1-methoxyethenyl)-4-methylbenzene, which had been hydrolyzed in the presence of 16 mM sulfite dianion, giving approximately 50% trapping (Figure 1).

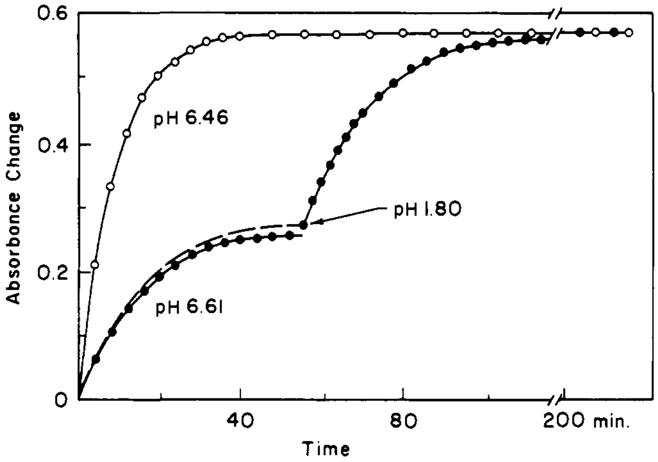


Figure 1. Plot of the change in absorbance at 262 nm as a function of time for the hydrolysis of *p*-methylacetophenone dimethyl ketal in the absence of bisulfite buffers (open circles) and in the presence of 0.033 M bisulfite buffer, 50% ionized (closed circles), at 25 °C and ionic strength 1.0 with KCl. After 60 min, 15 μL of 31% H_2O_2 was added to the cell containing the bisulfite buffer, oxidizing the excess sulfite and dropping the pH to 1.80. The dashed line in the figure represents the total concentration of ketone corrected for the equilibrium formation of the bisulfite addition compound.

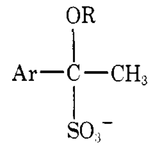
Table I. Hydrolysis of *p*-Methylacetophenone Dimethyl Ketal in the Presence of Bisulfite Buffers[a]

$[\mathrm{HSO_3^-}]$, M	pH[b]	$10^4 k_{\text{obsd}}$, s^{-1} [c]	$(k_{\text{obsd}}/a_{\mathrm{H^+}})$, $M^{-1}\,s^{-1}$ [d]
0[e]	6.21	24.0	3.9×10^3
0.0073	6.52	10.8	3.6×10^3
0.0146	6.57	9.82	3.7×10^3
0.0291	6.60	9.62	3.8×10^3
0.0364	6.59	9.32	3.6×10^3
0.0437	6.60	9.63	3.8×10^3
0.0510	6.61	8.92	3.6×10^3

[a] At 25 °C, ionic strength 1.0 with KCl, potassium bisulfite buffers, 50% monoanion. [b] Determined at the end of the experiment. [c] Observed first-order rate constant for the appearance of *p*-methylacetophenone. [d] Second-order rate constant for the appearance of *p*-methylacetophenone, based on hydrogen ion activity. Average value $3.7 \pm 0.2 \times 10^3\ M^{-1}\,s^{-1}$. [e] External buffer 0.002 M cacodylate.

Results

The hydrolysis of substituted acetophenone dimethyl ketals in the presence of bisulfite buffers is biphasic (Figure 1). The first phase follows pseudo-first-order kinetics with a rate constant identical with that for hydrolysis of the ketal at the same pH value and the second phase represents a much slower reaction that is also acid catalyzed. Figure 1 shows data for the hydrolysis of *p*-methylacetophenone dimethyl ketal in the presence of 16 mM sulfite dianion at pH 6.61 (lower curve) and at a comparable pH value in the absence of sulfite (upper curve). The addition of bisulfite to the product ketone causes only a small change in absorbance under these conditions; the absorbance after correction for this addition is shown by the dashed line in Figure 1. After completion of the first phase of the reaction, 15 μL of 31% H_2O_2 was added to oxidize the excess sulfite and decrease the pH to 1.80. The second phase then results in a quantitative formation of the ketone with an acid-catalyzed rate constant of approximately 0.07 $M^{-1}\,s^{-1}$. These results suggest that a fraction of the ketal is trapped as the sulfite addition compound, an α-methoxysulfonic acid (**1**), which undergoes slow further hydrolysis to the ketone product.



$$\mathrm{Ar{-}\overset{\displaystyle OR}{\underset{\displaystyle SO_3^-}{C}}{-}CH_3}$$

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The rate constants for acid-catalyzed cleavage of the ketal are independent of the concentration of sulfite buffer in the range 0-0.1 M total buffer concentration (Table I). It has been reported previously that the hydrolysis of acetophenone diethyl ketals is not subject to general acid catalysis.[5] The observed rate constants for the acid-catalyzed cleavage of substituted dimethyl acetophenone ketals, $k_{\mathrm{H^+}}$, and the equilibrium constants, K_{add}, for addition of bisulfite to the ketone product under the conditions of these experiments are summarized in Table II. A Hammett plot of K_{add} against σ^+ was found to be linear with a slope of $\rho^+ = 1.1$, which is similar to the ρ^+ value of 1.25 for the equilibrium addition of bisulfite to substituted benzaldehydes.[10]

The fraction of ketal that is trapped as the sulfite addition compound increases with increasing concentration of sulfite

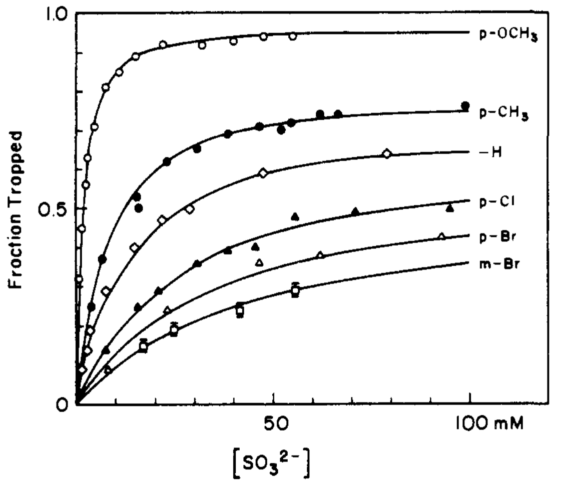


Figure 2. The fraction of cleavage products trapped as the α-methoxysulfonic acid is shown as a function of the concentration of sulfite dianion for p-OCH$_3$ (○), p-CH$_3$ (●), H (◇), p-Cl (▲), p-Br (△), and m-Br (□) acetophenone dimethyl ketals in potassium bisulfite buffers, pH 6.6, at 25 °C and ionic strength 1.0 with KCl.

Table II. Partitioning of Substituted Acetophenone Dimethyl Ketals between SO_3^{2-} and H_2O[a]

Substituent	k_{H^+}, M^{-1} s^{-1} [b]	K_{add}, M^{-1} [c]	$[SO_3^{2-}]_{1/2}$, mM[d]	f_{max}[e]
p-OCH$_3$	9.2×10^3	<1	1.4	0.97
p-CH$_3$	3.7×10^3	3	8.6	0.84
H	1.6×10^3	5.5	14	0.75
p-Cl	7.0×10^2	8	27	0.66
p-Br	5.8×10^2	9	35	0.58
m-Br	2.5×10^2	16	~40	~0.5

[a] At 25 °C, ionic strength 1.0 with KCl, using sulfite/bisulfite buffers, 50% ionized, pH 6.61. [b] Approximate rate constant for ketal hydrolysis, based on average of two determinations in the pH range 6.1-6.3. [c] Equilibrium constant for the formation of the ketone bisulfite. [d] Concentration of sulfite dianion required to give half-maximum trapping. [e] Fraction of hydrolysis products trapped as the α-methoxysulfonic acid extrapolated to infinite sulfite concentration.

dianion and decreases with electron-withdrawing substituents on the acetophenone ketal (Figure 2). The fraction trapped approaches a limiting value, f_{max}, with increasing sulfite concentration and this limiting value also decreases with electron-withdrawing substituents on the ketal. Plots of $1/f$ against $1/[SO_3^{2-}]$ were found to be linear and gave values of $1/f_{max}$ and $-1/[SO_3^{2-}]_{1/2}$ as the intercepts on the ordinate and abscissa, respectively; the values of $[SO_3^{2-}]_{1/2}$, the concentration of sulfite dianion giving half-maximal trapping, and of f_{max} are summarized in Table II. The data were corrected for the equilibrium formation of α-hydroxysulfonic acid from the ketone product using the values of K_{add} in Table II. The correction is small for most ketones but becomes large for m-bromoacetophenone, so that trapping of the coresponding ketal could be measured accurately only in dilute sulfite buffers. The partitioning ratio between sulfite dianion and water was found to be the same at pH 5.66 (sulfite-bisulfite buffers up to 0.1 M, 10% dianion) as at pH 6.6 for acetophenone dimethyl ketal, indicating that the sulfite dianion is the reactive species.

The effect of acetate anion on the fraction of product trapped at different concentrations of sulfite is shown in Figure 3. As the concentration of acetate anion is increased, the concentration of sulfite ion necessary to give half-maximal trapping also increases. However, the limiting fraction trapped at high sulfite concentrations, f_{max}, remains essentially constant, as shown by the constant ordinate intercept of the reciprocal plots in the inset. Values of $[SO_3^{2-}]_{1/2}$ for a series of acetate ions, cacodylate ion, and phosphate dianion are given in Table III.

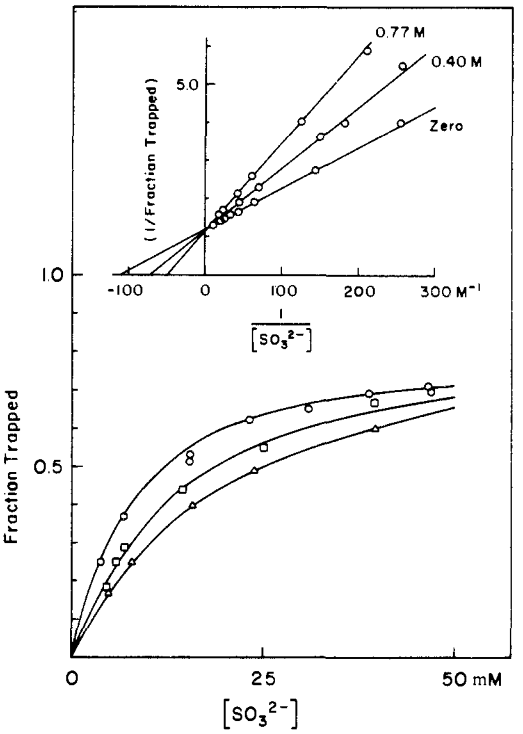


Figure 3. The fraction of p-methylacetophenone dimethyl ketal trapped as the α-methoxysulfonic acid as a function of the concentration of sulfite dianion in the presence of 0 (○), 0.4 (□), and 0.77 M (△) added potassium acetate at 25 °C, ionic strength 1.0 with KCl, in potassium bisulfite buffers, 50% monoanion, pH 6.61. Double reciprocal plots of these data are shown in the inset.

Table III. Effect of Buffers on the Partitioning of p-Methylacetophenone Dimethyl Ketal between SO_3^{2-} and H_2O[a]

Buffer	pK_a	pH	Buffer concn, M	$[SO_3^{2-}]_{1/2}$, mM[b]	k_B, M^{-1} s^{-1} [c]
None		6.6		8.6	
Phosphate	6.49[d]	6.58	0.45	14	1.3×10^8
		6.55	0.30	13	1.7×10^8
		6.59	0.15	10	1.2×10^8
Cacodylate	6.16[d]	6.53	0.77	20.5	1.3×10^8
		6.45	0.30	13	1.4×10^8
Acetate	4.60	6.61	0.77	21	9.8×10^7
		6.56	0.40	15	9.9×10^7
Cyanoacetate	2.23	6.68	0.77	14	4.3×10^7
Trifluoroacetate	0.25[e]	6.65	0.77	14	4.3×10^7
		6.66	0.52	12	4.1×10^7
Water			55.5		9.1×10^5

[a] At 25 °C, ionic strength 1.0 with KCl. [b] Concentration of sulfite dianion required to give half-maximal trapping. [c] Second-order rate constant for buffer catalysis calculated assuming the buffer free base to be the catalytically active species. [d] J. P. Fox and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 1436 (1974). [e] At zero ionic strength; A. L. Henne and C. J. Fox, *ibid.*, **73**, 2323 (1951).

The hydrolysis of 1-(1-methoxyethenyl)-4-methylbenzene in the presence of sulfite/bisulfite buffers was also found to be biphasic and to exhibit a hyperbolic increase in the fraction of product trapped with increasing concentration of sulfite dianion. As shown in Figure 4, the fraction of product trapped as the α-methoxysulfonic acid at a given concentration of sulfite is identical, within experimental error, for the enol ether and for the corresponding ketal. The data in this "Eadie plot"[11] are fit by a common intercept of 0.84 = $f_{\max}$ and slope of -0.0089 M = $-[SO_3^{2-}]_{1/2}$.

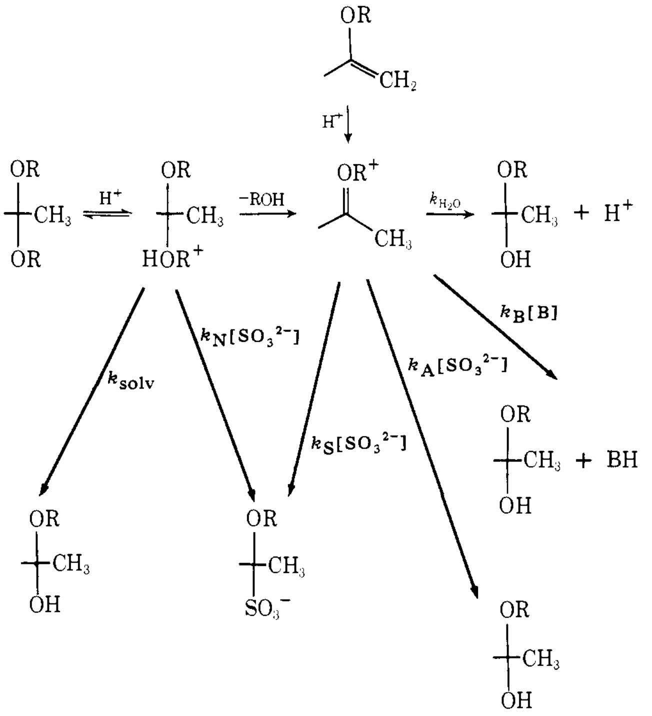
The observed rate constants for cleavage of the enol ether were found to increase linearly with increasing concentration of bisulfite buffers from 0 to 0.16 M, giving a value of $k_{HA} = 0.07$ M^{-1} s^{-1} and $k_{H^+} = 410$ M^{-1} s^{-1}. A value of $k_{H^+} = 370$ M^{-1} s^{-1} for this compound has been reported previously and the hydrolysis of substituted acetophenone vinyl ethers has been shown to be catalyzed by general acids with a Brønsted slope α of approximately 0.5.[9]

The predominant product from the cleavage of *p*-methylacetophenone dimethyl ketal in the presence of 0.15 M aqueous hydroxylamine, 50% base, was found to be the oxime after 1 half-time (ketone, $\lambda_{\max} = 256$ nm, $A(248/260) = 0.88$; oxime, $\lambda_{\max} = 245$ nm, $A(248/260) = 1.43$; observed, $\lambda_{\max} = 249$ nm, $A(248/260) = 1.24$). Under the same conditions there was no detectable formation of oxime from the free ketone. Similar experiments in the presence of a series of hydroxylamine concentrations in the range 0.008–0.080 M free base gave half-maximal trapping at 0.03 ± 0.01 M hydroxylamine, based on the 23% difference in the extinction coefficients of oxime and ketone at 256 nm. The reason that the oxocarbonium ion can be trapped to give oxime under conditions in which the ketone does not react is presumably that the initial product of hydroxylamine addition to the oxocarbonium ion, ROCMe(Ar)NH_2OH^+, readily loses a proton and ROH to give the oxime, whereas the initial addition product from the ketone, $^-$OCMe(Ar)NH_2OH^+, usually expels hydroxylamine to regenerate ketone. No trapping by azide or thiosulfate ions was observed.

Discussion

Several pathways for the acid-catalyzed cleavage of acetals, ketals, and related compounds are shown in Scheme I. The rate constants k_{solv} and k_N refer to reactions of solvent and some nucleophile, such as sulfite, with the protonated acetal or ketal. The k_{solv} and k_N pathways would generally be expected to involve some degree of nucleophilic participation by water or sulfite, but include any reaction mechanism in which bond formation to the nucleophile occurs before the leaving alcohol has diffused away from the oxocarbonium ions. The other rate constants refer to reactions with a free oxocarbonium ion intermediate that has a lifetime sufficient for its equilibration with the solvent environment.

Scheme I



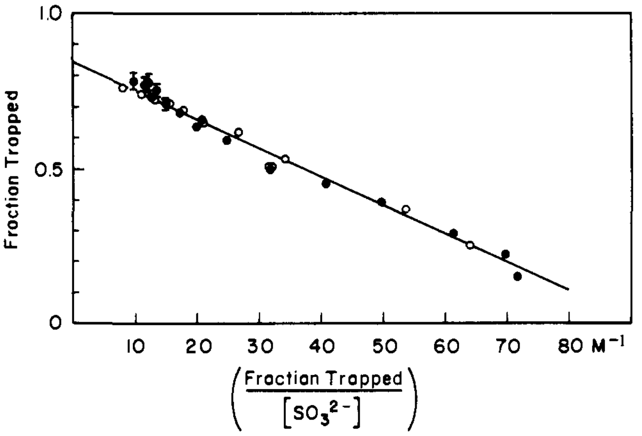


Figure 4. The dependence of the fraction of product trapped as α-methoxysulfonic acid on the concentration of sulfite dianion for *p*-methylacetophenone dimethyl ketal (open circles) and for the enol ether, 1-(1-methoxyethenyl)-4-methylbenzene (closed circles), at 25 °C, ionic strength 1.0 with KCl, in bisulfite buffers, 50% dianion, at pH 6.61. The ordinate intercept gives $f_{\max}$ and the slope is $-[SO_3^{2-}]_{1/2}$.

The observed trapping and partitioning of products during the acid-catalyzed cleavage of substituted acetophenone ketals are inconsistent with any mechanism involving a significant role of the k_{solv} and k_N pathways and provide direct evidence for a reaction that proceeds through a free, solvent-equilibrated oxocarbonium ion intermediate. The observation of up to 97% trapping under conditions in which sulfite has no effect on the observed reaction rate (Tables I and II) shows that sulfite ion is not present in the transition state of the rate-determining step and that the product-determining steps are different from the rate-determining step; i.e., there must be an intermediate on the reaction pathway that can react with either solvent or sulfite. The fact that identical partitioning is observed for the acid-catalyzed cleavage of *p*-methylacetophenone dimethyl ketal and 1-(1-methoxyethenyl)-4-methylbenzene (Figure 4) provides evidence that the same intermediate is formed from the ketal and the enol ether. Any reaction through the k_{solv} or k_N pathways with the protonated ketal or any other species that contains the leaving alcohol molecule would provide a pathway for product formation from the ketal that is not available to the enol ether, so that the identical partitioning of the two compounds is evidence that neither of these pathways makes a significant contribution to the cleavage of the ketal. The fact that the limiting amount of trapping at high sulfite concentration, $f_{\max}$, as well as the partitioning at low sulfite concentrations are the same for the ketal and the enol ether makes it virtually certain that the identical trapping behavior does not represent a coincidental equality of rate constant ratios for the two compounds.

Partitioning of the intermediate according to Scheme I is described by

$$f = \frac{k_S[SO_3^{2-}]}{k_S[SO_3^{2-}] + k_{H_2O} + k_A[SO_3^{2-}] + k_B[B]} \qquad (2)$$

in which f is the fraction of ketal or enol ether that is trapped as the α-methoxysulfonic acid and k_A and k_B are rate constants for catalysis of ketone formation by sulfite dianion and by other bases, respectively. The observed leveling off of the partitioning ratio at high sulfite concentrations (Figure 2) requires that there be a sulfite-catalyzed reaction of the intermediate that leads to ketone formation with the rate constant k_A as well as a nucleophilic reaction with sulfite that gives trapping with the rate constant k_S. The partitioning ratio at high sulfite con-

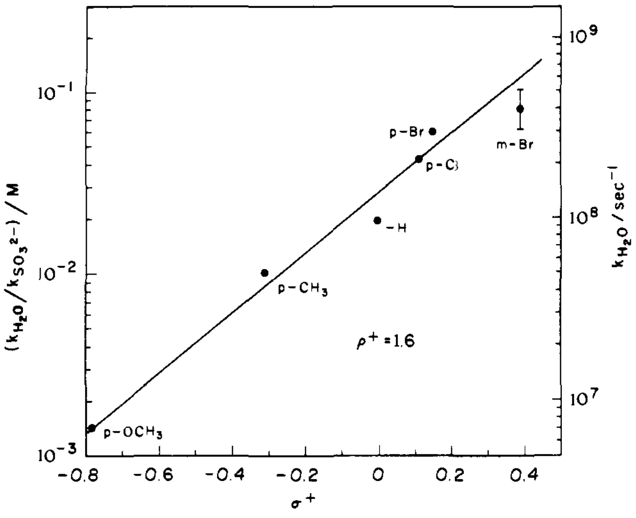


Figure 5. Dependence on σ^+ of the partitioning between water and sulfite of the intermediate oxocarbonium ion formed from substituted acetophenone dimethyl ketals. The left scale shows the observed partitioning ratio and the right scale shows the absolute values of the rate constants for reaction with water, assuming a constant value of $k_{SO_3^{2-}} = 5 \times 10^9$ M^{-1} s^{-1}.

centrations approaches a constant value that is equal to the ratio of these rate constants, k_S/k_A. The limiting fraction of trapped product, $f_{max} = k_S/(k_S + k_A)$, may be obtained from the ordinate intercept of a linear plot of the experimental data according to

$$\frac{1}{f} = \left(\frac{k_{H_2O} + k_B[B]}{k_S}\right)\frac{1}{[SO_3^{2-}]} + \frac{k_S + k_A}{k_S} \qquad (3)$$

and the concentration of sulfite ion giving half-maximum trapping, $[SO_3^{2-}]_{1/2} = f_{max}(k_{H_2O} + k_B[B])/k_S$, may be obtained from the negative reciprocal of the abscissa intercept of the plot (Table II).

The lifetime and rate constant for reaction of the intermediate carbonium ion with water can be obtained from the partitioning ratio, k_S/k_{H_2O}, if k_S is known. The following evidence supports the conclusion that the rate constant k_S represents a diffusion-controlled reaction of sulfite dianion with the oxocarbonium ion.

The observed ratios of the rate constants for reaction of the carbonium ion with 1 M sulfite dianion and with water are in the range 1.3×10^1 to 7×10^2 (Table IV). These ratios are inconsistent with the ratios close to $10^{7.9}$ that have been observed for activation-controlled reactions of sulfite and water with carbonium ions and other electrophilic reagents.[12] The small ratios for trapping of the intermediate formed in ketal and enol ether hydrolysis can be explained if the reaction of sulfite, but not water, with the intermediate is diffusion controlled. The small ratios do not represent simply a decrease in selectivity with increasing reactivity from a "Hammond-type" effect because the ratios of approximately $10^{7.9}$ (from the N^+ scale of nucleophilic reactivity) are independent of the reactivity of the electrophilic reagent over a large range of rate constants that includes rate constants for sulfite of 4.5×10^8 M^{-1} s^{-1} in hydroxylic solvents; there is a sharp break in the N^+ correlation just above this value as the diffusion-controlled limit is reached.[13]

Further evidence for a diffusion-limited reaction with sulfite ion is provided by the dependence of the partitioning ratio between water and sulfite on the structure of the oxocarbonium ion, with a value of $\rho^+ = 1.6$ for the ratio k_{H_2O}/k_S (Figure 5). If both water and sulfite ion reacted with the oxocarbonium ion in activation-limited reactions, the substituent effects on the rate constants should largely cancel and there should be little or no effect of substituents on the rate constant ratio. In fact, the partitioning ratio for the reaction of water and "α-effect" amines with the oxocarbonium ion formed from an ortho ester of benzoic acid shows essentially no effect of substituents ($\rho = 0$); this reaction is not diffusion limited because the oxocarbonium ion displays selectivity toward different nucleophiles with a value of $\beta_{nuc} = 0.4$.[8] If the reaction with sulfite ion is diffusion controlled ($\rho = 0$) the value of $\rho^+ = 1.6$ for the rate constant ratio is the value of ρ^+ for the attack of water on the oxocarbonium ion. The absolute values of k_{H_2O} can then be calculated assuming a diffusion-controlled rate constant of $k_S = 5 \times 10^9$ M^{-1} s^{-1}.[14] These values of k_{H_2O} are given in Table IV and are plotted on the right-hand ordinate of Figure 5. The value of $\rho^+ = 1.6$ (correlation coefficient = 0.987) for the reaction of water with oxocarbonium ions is similar to the values of $\rho^+ = 1.71$ and 1.4 for the addition of water and hydroxide ion, respectively, to benzaldehydeimmonium ions.[15]

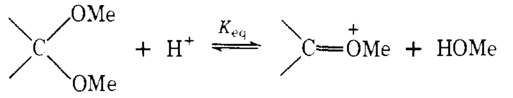
Table IV. Calculated Rate Constants for the Addition of Water to Oxocarbonium Ions Derived from Substituted Acetophenone Dimethyl Ketals[a]

Substituent	k_{H_2O}/k_S, M[b]	k_{H_2O}, s^{-1} [c]	K_{eq}[d]
p-OCH$_3$	1.4×10^{-3}	7.0×10^6	7.2×10^{-2}
p-CH$_3$	1.0×10^{-2}	5.0×10^7	4.1×10^{-3}
H	1.9×10^{-2}	9.5×10^7	9.3×10^{-4}
p-Cl	4.1×10^{-2}	2.1×10^8	1.8×10^{-4}
p-Br	5.9×10^{-2}	3.0×10^8	1.1×10^{-4}
m-Br	$\sim 8 \times 10^{-2}$	$\sim 4 \times 10^8$	3.4×10^{-5}

[a] At 25 °C, ionic strength 1.0 with KCl. [b] $[SO_3^{2-}]_{1/2}/f_{max}$; see Table II. [c] Calculated assuming $k_S = 5 \times 10^9$ M^{-1} s^{-1}. [d] K_{eq} = $[ArMeC{=}OMe^+][MeOH]/[ArMeC(OMe)_2][H^+]$.

Finally, trapping of the oxocarbonium ion is also observed in dilute hydroxylamine, with half-maximal formation of oxime at 0.03 ± 0.01 M hydroxylamine. Assuming $k_S = 5 \times 10^9$ M^{-1} s^{-1} for sulfite dianion, the rate constant for reaction with hydroxylamine is then $\sim 2 \times 10^9$ M^{-1} s^{-1}. If the reactions were activation limited, the rate constant for reaction with hydroxylamine would be expected to be some 700-fold smaller than that for sulfite, based on the N^+ values of 7.9 and 5.05 for the reactions of sulfite and hydroxylamine, respectively, with carbonium ions.[31]

Structure-Reactivity Relationships. The absolute values of the equilibrium constants for oxocarbonium ion formation from substituted acetophenone dimethyl ketals may be calculated from the ratio of the rate constants for the reactions in the two directions if it is assumed that the second-order rate constants for the addition of water ($k_2 = k_{H_2O}/55.5$ M) and methanol are the same.



(4)

This assumption is supported by the closely similar rate constants for the reactions of deuterium oxide and deuteriomethanol with other oxocarbonium ions.[16] The equilibrium constants are in the range 5×10^{-2} to 3.6×10^{-5} (Table IV). The equilibrium constants show deviations for the *p*-methoxy- and *p*-methylacetophenone ketals in correlations with σ or σ^+, but give a satisfactory correlation, with $\rho = -3.6$, when an intermediate amount of resonance stabilization of the product is assumed according to the treatment of Yukawa and Tsuno,[17] using a value of $r = 0.5$ (Figure 6, lower line). This is similar to the ρ^+ value of $-10.05/3 = -3.35$ for the equilibrium formation of triarylcarbonium ions from the corresponding triarylcarbinols.[18] The ρ^+ value for the equilibrium dehydration of diarylcarbinols to diarylcarbonium ions is $-11.2/2 = -5.6$.[18]

The rate constants for hydrolysis of acetophenone dimethyl ketals in water at ionic strength 1.0 follow a Hammett correlation with $\rho = -2.2$ (correlation coefficient = 0.992) but give a slightly better fit if allowance is made for a small amount of electron donation by resonance, corresponding to a Yukawa-Tsuno parameter of $r = 0.18$ ($\rho = -2.0$, correlation coefficient = 0.998, open and closed circles, respectively, in Figure 6). These results are in agreement with a previously reported value of $\rho = -2.29$ ($r = 0.13$) for the same reaction in 5% dioxane at 30 °C.[19] At ionic strength 0.2 (maintained with potassium chloride) the value of ρ was found to be -2.2 and in 50% dioxane $\rho = -2.9$. In both cases the data give a good fit to σ with $r = 0.18$ (Figure 6). The ρ value of -2.0 is smaller than the value of $\rho = -3.3$ for the hydrolysis of substituted benzaldehyde diethyl acetals in water to give a less stable oxocarbonium ion[20] and larger than the value of $\rho = -1.16$ for the hydrolysis of methyl 4-substituted orthobenzoates.[21] The hydrolysis of benzaldehyde diethyl acetals, in contrast to that of the acetophenone ketals, exhibits no change in ρ in 50% dioxane ($\rho = -3.35$) but shows significant deviations for substituents that donate electrons by resonance, so that the data are fitted best with a Yukawa-Tsuno parameter of $r = 0.5$.[20,22]

At first glance there appears to be an anomaly in the facts that the hydrolysis reaction follows ρ, the attack of ROH on the oxocarbonium ion to form the same transition state follows ρ^+, but the equilibrium constants follow an intermediate correlation with a Yukawa-Tsuno r parameter[17] of 0.5. This might be interpreted as evidence for the unreasonable conclusion that, starting with the oxocarbonium ion, there is nearly twice as much loss of resonance stabilization in going to the transition state for the attack of ROH ($r = 1.0$) as in going to the ketal product ($r = 0.5$). Although the ρ values for the equilibrium constants and the rate constants in the two directions are additive according to the relation $\rho_{eq} = \rho_f - \rho_r$ for this or any other reaction, it is apparent that no such relationship holds for r values. The same conclusion holds for r^+ values based on σ^n according to[23]

$$\log (k/k_0) = \rho(\sigma^n + r^+(\sigma^+ - \sigma^n)) \qquad (5)$$

which are 0.6, 0.35, and 1.0 for the equilibrium, forward rate, and reverse rate constants of the reaction of eq 4 (the correlation coefficients are 0.996, 0.999, and 0.987, respectively). In general, the relationship between the structure-reactivity correlations for equilibrium and rate constants of a reaction is given by

$$\log (K/K_0) = (\rho - \rho')\sigma + (\rho r - \rho' r')(\sigma^+ - \sigma) \qquad (6)$$

in which the unprimed and primed parameters refer to the rate constants in the forward and reverse directions, respectively. This reduces to the form of a simple Yukawa-Tsuno equation, such as eq 5, when $r = r'$. This requires, for example, that if a reaction proceeds through an early transition state and $r = 0.1$ in the forward direction, the same value of $r = 0.1$ holds for the equilibrium reaction and for the late transition state in the reverse direction.

These apparent anomalies arise because $r^+(\sigma^+ - \sigma^n)$ values are not measures of Gibbs free energy changes and, as emphasized by Wepster and co-workers,[24] the contributions of different factors to linear free energy relationships should be described in terms of free energies. The problem can be avoided by using correlations that have entirely separate terms for polar and resonance terms that contribute to the observed free energy change such as those proposed by Taft, Ehrenson, Swain, and co-workers.[25] We propose the equation

$$\log (k/k_0) = \rho\sigma^n + \rho^r(\sigma^+ - \sigma^n) \qquad (7)$$

which serves the same purpose and preserves the simplicity of the original Yukawa-Tsuno approach. For hydrolysis of acetophenone dimethyl ketals the rate constants are satisfactorily correlated by $\rho = -2.0$ and $\rho^r = -0.7$, by $\rho = 1.6$ and $\rho^r = 1.6$ for the reverse rate constants, and by $\rho = -3.6$ and $\rho^r = -2.2$ for the equilibrium constants. Both the polar and the resonance parameters are additive, within experimental error, according to the relationship $\rho_{eq} = \rho_f - \rho_r$.

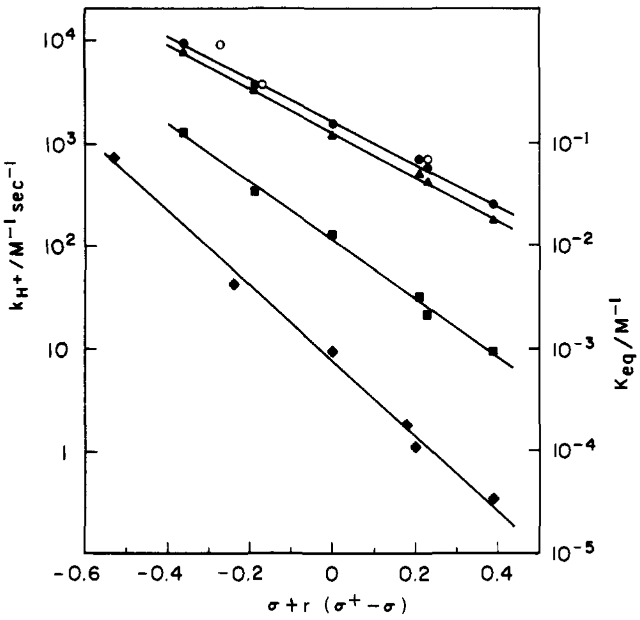


Figure 6. Dependence upon $(\sigma + r(\sigma^+ - \sigma))$ of the hydrolysis of acetophenone dimethyl ketals (left ordinate), at ionic strength 1.0 (KCl) with $r = 0$ (○) and $r = 0.18$ (●); at ionic strength 0.2 (KCl) and $r = 0.18$ (▲); and at ionic strength 0.1 (KCl) in 50% aqueous dioxane with $r = 0.18$ (■). The right ordinate (◆) is $K_{eq} = [>C{=}OR^+][ROH]/[>C(OR)_2][H^+]$ with $r = 0.5$.

The polar and resonance parameters are simply related according to $\rho^r/\rho = r^+$. This helps to explain why there is generally a poor correlation between r^+ and electron demand in a transition state or product, as measured by ρ.[23,26] There will be a closer correlation between ρ and ρ^r, because both parameters are related to the free energy change in the same way and $\rho^r = \rho r^+$. The parameter ρ^r is a measure of the *amount* that resonance contributes to the stabilization of the transition state or product of a reaction; the parameter r^+ is not a measure of the *amount* of resonance stabilization, but of the *relative* importance of polar and resonance contributions to the free energy relationship under consideration.

The balance between the development of polar and resonance effects in going from a reactant to a transition state is best evaluated from a comparison of the ρ and ρ^r values for a rate constant with those for the equilibrium constant of the reaction. Comparison of the rate and equilibrium parameters for the attack of ROH on the oxocarbonium ion gives $\rho/-\rho_{eq} = 0.44$ for the polar contribution and $\rho^r/-\rho_{eq}{}^r = 0.73$ for the resonance contribution, suggesting that there is a relatively larger contribution of the resonance than of the polar substituent effect in reaching the transition state. However, this apparent imbalance is caused largely by the inclusion of the equilibrium constant for protonation of the acetal ($1/K_a$, eq 1) in the overall equilibrium constant; this protonation does not involve resonance interaction with the developing carbonium ion. After correction for this protonation step, based on a value of $\rho = 1.1$ for the dissociation of substituted benzylammonium ions,[27] the values of $\rho/-\rho_{eq}$ and $\rho^r/-\rho_{eq}{}^r$ are 0.64 and 0.73, respectively; for the hydrolysis reaction the corrected values of ρ/ρ_{eq} and $\rho^r/\rho_{eq}{}^r$ are 0.36 and 0.32, respectively. These values indicate that there is only a small or no tendency for the loss of resonance to be greater than the polar contribution upon reaching the transition state for ROH attack.

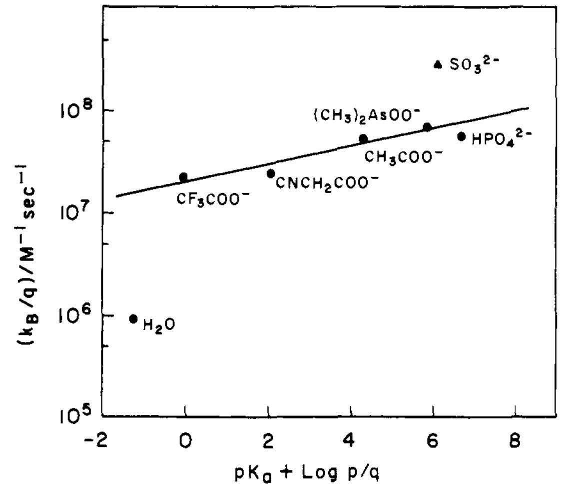


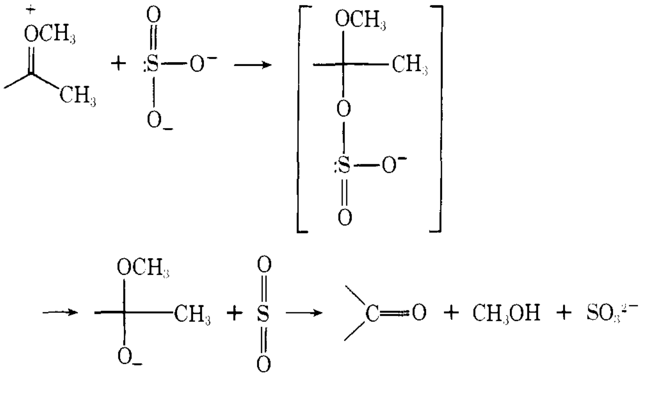
Figure 7. Brønsted plot for buffer-catalyzed addition of water to the oxocarbonium ion derived from *p*-methylacetophenone dimethyl ketal, 25 °C, ionic strength 1.0 with KCl. The point for sulfite dianion is the catalytic constant required to give f_{max} = 0.84 (see text).

The trend of ρ values for the hydrolysis of substituted benzaldehyde acetals ($\rho = -3.3$), acetophenone ketals ($\rho = -2.0$), and benzoate ortho esters ($\rho = -1.2$) in water suggests that there is a progressively earlier transition state in these reactions; this conclusion is supported by the smaller secondary α-deuterium isotope effects for the hydrolysis of ortho esters (k_H/k_D = 1.05 for ethyl orthoformate) than of acetals (k_H/k_D = 1.17 for propionaldehyde diethyl acetal).[2,20,21,28] The changes are correlated with increasing resonance stabilization of the product by electron donation from an additional oxygen atom or by hyperconjugation and are in the direction expected from a "Hammond-type" effect with increasing stabilization of the product that shifts the position of the transition state toward reactants along the reaction coordinate. The oxocarbonium ion formed during the hydrolysis of 2-(4-methoxyphenyl)-2-methoxy-1,3-dioxolane is stable enough to be observed directly,[29] as is also the intermediate formed during the hydrolysis of addition compounds of a phthalimidium ion, a related series of compounds at the acyl level of oxidation;[30] attempts to observe the formation of an oxocarbonium ion from *p*-methylacetophenone dimethyl ketal in aqueous perchloric acid and in acidic methanol were unsuccessful. These differences are in accord with the difference in equilibrium constants for carbonium ion formation from the ketal of 4.1×10^{-3} and from the phthalimidium adduct of 3.8; the rate constants for addition of water to the two carbonium ions are 5×10^7 and 56 s^{-1}, respectively.[30] However, the rate constant for acid-catalyzed hydrolysis of the methanol addition compound of the phthalimide is 20 $M^{-1}\ s^{-1}$, 180 times slower than that for the ketal, 3700 $M^{-1}\ s^{-1}$. Thus, comparison of these two systems provides direct evidence that cleavage of the compound at the acyl level of oxidation proceeds through a higher energy transition state to form a lower energy product, compared with the reaction at the carbonyl level of oxdation. A similar or decreasing rate constant with increasing oxidation level has been noted previously for certain acetals and ortho esters.[2,21,28] The rate difference may reflect an unfavorable inductive effect of the additional electronegative atom in the transition state of the reaction for the acyl compound, in which relatively little resonance stabilization has developed, and a requirement for concerted proton transfer to the leaving group of these weakly basic compounds.[2,28,30]

Catalysis of Ketone Formation. The decrease in the amount of trapping of the oxocarbonium ion by a given concentration of sulfite with increasing buffer concentration (Figure 3) suggests that buffers increase the yield of ketone by general base catalysis of the attack of water on the oxocarbonium ion (k_B, Scheme I). The attack of water on triarylcarbonium ions is known to be subject to general base catalysis.[31] Rate constants for general base catalysis of water attack by carboxylate ions, cacodylate ion, and phosphate dianion were obtained from the linear increase in (k_{H_2O}(app) = $k_{H_2O} + k_B$[B]) with increasing buffer concentration that was observed in experiments similar to that illustrated in Figure 3, assuming that there is no effect of buffers on the rate of attack of the sulfite dianion. The values of k_B shown in Table III give a Brønsted slope of β = 0.09 (Figure 7). The negative deviation for water of 1.2 log units below the Brønsted line corresponds to the same negative deviation of 1.2 log units for the proton below the Brønsted line of α = 0.91 for general acid catalysis of the reaction in the reverse direction. This deviation is somewhat smaller than the negative deviation of 2-4 log units for the proton from Brønsted plots for general acid catalysis of the hydrolysis of methyl substituted-phenyl benzaldehyde acetals.[32] It is of interest that no general acid catalysis has been detected for the expulsion of methanol from the ketal; from the available data (Table I and ref 5 and 19) the value of α for hydrolysis of the ketal is >0.98 if the proton shows the same negative deviation for methanol as for water.[33] This suggests that either the Brønsted slope α is larger or the negative deviation for the proton is smaller for methanol than for water.

Sulfite dianion is approximately fivefold more effective as a catalyst for ketone formation from the oxocarbonium ion than expected from the Brønsted plot for other general base catalysts (Figure 7). The catalytic constant for sulfite is obtained from the limiting ratio of k_S/k_A at high sulfite concentrations. Thus, some 20% of the sulfite-mediated formation of ketone can be attributed to general base catalysis of the attack of water on the oxocarbonium ion and, unless sulfite dianion has some unusual activity as a general base catalyst that is not shared by phosphate dianion, some other mechanism is required to explain the greater part of the observed catalysis of ketone formation by sulfite. Nucleophilic catalysis of ketone formation by attack of a sulfite oxygen atom on the oxocarbonium ion, followed by the elimination of SO_2 to give the hemiketal anion[34] and elimination of methanol (Scheme II), provides an attractive mechanism for this additional formation of ketone.

Scheme II



The rate constant ratio log k_A/k_S for substituted acetophenone ketals increases linearly with σ^+ and gives a value of ρ^+ = 1.4. This is slightly smaller than the value of ρ^+ = 1.6 for the attack of water and is consistent with the interpretation that the k_A term represents activation-limited formation of ketone from sulfite by a combination of direct attack of a weakly nucleophilic oxygen atom and general base catalysis of water attack by sulfite. The existence of this sulfite-catalyzed formation of ketone means that sulfite is not an effective trapping reagent for oxocarbonium ions that are less stable than those we have examined.

Cleavage of the enol ether, 1-(1-methoxyethenyl)-4-methylbenzene, is catalyzed by the bisulfite buffer, in contrast to the buffer-independent cleavage of the corresponding ketal (Table I). The fact that this catalysis is independent of the trapping reaction confirms the conclusion that this reaction proceeds through at least two steps and a free intermediate. Under conditions in which 20% of the intermediate is trapped, for example, over 80% of the observed reaction is catalyzed by the bisulfite buffer. This result and the identical partitioning of the enol ether and ketal show that the sulfite ion that is formed when bisulfite protonates the enol ether diffuses away from the intermediate faster than it reacts with the intermediate to give trapping. This requires that translational diffusion of the sulfite ion away from the oxocarbonium ion be faster than any rotation or desolvation steps that are required for nucleophilic attack of sulfite on the oxocarbonium ion to form the α-methoxysulfonic acid. It is not known for certain whether this sulfite ion is separated from the oxocarbonium ion by an intervening water molecule. It is generally believed that protonation of carbon by general acids occurs directly,[35] but the faster ionization of monoethyl malonate monoanion than of diethyl malonate has been attributed to intramolecular catalysis of proton transfer through an intermediate water molecule.[36]

Lifetimes and Lysozyme. As the oxocarbonium ion becomes less stable a point will be reached at which the hydrolysis of acetals and ketals *cannot* proceed through the rate-determining formation of a free, solvent-equilibrated oxocarbonium ion. The rate constants for the addition of water to the oxocarbonium ions formed in the hydrolysis of acetophenone ketals are in the range 7×10^6 to 4×10^8 s^{-1} (Table IV). These rate constants are correlated with those for the attack of sulfite dianion on substituted acetophenones as shown by the solid circles in Figure 8.[37] Extrapolation of this correlation to the rate constants for other carbonyl compounds gives rate constants for the attack of water on oxocarbonium ions derived from benzaldehydes and simple aliphatic aldehydes that are close to values that might be expected for diffusion-controlled translation or rotation of a water molecule into position for reaction, on the order of 10^{11} s^{-1}. The value for the oxocarbonium ion derived from formaldehyde acetals is 10^{15} s^{-1}. The oxocarbonium ions derived from glycosides are probably even less stable, in the absence of stabilization by neighboring groups, because the cyclic oxocarbonium ion will be destabilized by electron-withdrawing substituents and by ring strain.[4,38] Some indication of the instability of these oxocarbonium ions is given by comparison of the rate constants of 1.4×10^{-8} M^{-1} s^{-1} for the hydrolysis of methyl β-D-glucopyranoside,[39] 2.2×10^{-4} M^{-1} s^{-1} for formaldehyde dimethyl acetal,[40] and 0.29 M^{-1} s^{-1} for acetaldehyde dimethyl acetal[41] at 25 °C. Salomaa has estimated from considerations based on the Hammond postulate and a series of structure-reactivity extrapolations[42] that the rate constant for hydration of the oxocarbonium ion formed from acetaldehyde diethyl acetal is on the order of 10^{10} s^{-1}. Although the correlation of Figure 8 is certainly not exact, it does suggest strongly that the hydrolysis of formaldehyde acetals, glycosides, and other compounds of this class that contain electron-withdrawing substituents on the central carbon atom cannot proceed through the rate-determining formation of a free, solvent-equilibrated oxocarbonium ion.

As the oxocarbonium ion becomes less stable the rate constant for C–O bond formation will increase until it becomes larger than the rate constant for diffusion away of water or alcohol from the oxocarbonium ion. Thus, the diffusion away of the leaving alcohol or movement into a reactive position of the attacking water molecule can become rate determining as the oxocarbonium ion becomes less stable. When this is the case the hydrolysis of methyl or ethyl acetals *must* be subject only to specific acid catalysis by the proton, unless a different mechanism intervenes. This is because the movement of water or the diffusion-controlled separation of ROH from the oxocarbonium ion is not catalyzed by buffer acids or bases.[43] Since the leaving alcohol, ROH, is fully protonated this mechanism will be manifested experimentally as specific acid catalysis.

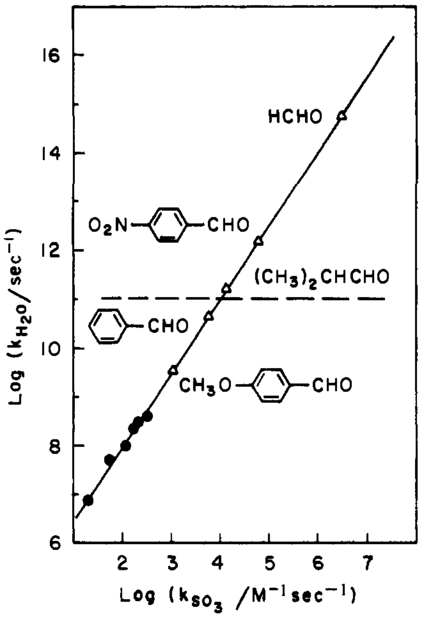
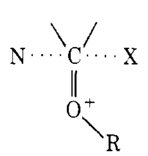


Figure 8. Correlation between the rate constants for the addition of water to oxocarbonium ions and the rate constant for addition of sulfite dianion to the corresponding carbonyl compounds, k_{SO_3}. (●) Data for acetophenones (this work); (△) estimated values of k_{H_2O} for simple aldehydes based upon values of k_{SO_3}. The dashed line represents an approximate rate constant for a diffusion-controlled reaction with water.

An alternative, "preassociation" mechanism in which the attack of water occurs before complete separation of the leaving alcohol may provide the lowest energy pathway when the oxocarbonium ion becomes sufficiently unstable. When the rate constant for the addition of alcohol to the oxocarbonium ion in the complex $H_2O{\cdot}C^+{\cdot}HOR$ (with water and alcohol correctly aligned for reaction) becomes larger than the rate constant for the rotation or translation of water out of a reactive position, the lowest energy pathway for breakdown of this complex with C–OR bond formation will have a water molecule present in a reactive position. If this is the lowest energy pathway for breakdown of the complex to reactants it is also the lowest energy pathway for formation of the complex, so that the reaction will proceed through an enforced preassociation mechanism. If the water molecule must be present in an appropriate position in a preassociation complex during C–OR bond cleavage it is likely to stabilize the developing oxocarbonium ion during C–OR bond cleavage and, as the oxocarbonium ion becomes progressively less stable and the stabilization greater, this stabilization will represent nucleophilic participation by water. The reaction will occur with inversion at the central carbon atom unless this is sterically prohibited. This sequence of mechanisms is essentially the same as that for the enforced diffusion-controlled trapping, preassociation, hydrogen-bonding and concerted mechanisms in general acid-base catalyzed carbonyl group reactions as the addition intermediate becomes progressively less stable.[43]

There is evidence that at least some reactions of glycosides do not proceed through a free oxocarbonium ion intermediate. The acid-catalyzed methanolysis of the α and β anomers of phenyl D-glucopyranoside occurs with 90 and 72% inversion, respectively, showing that the solvolysis does not proceed through a common intermediate and that the attacking methanol reacts before the phenol has completely departed from the other side of the 1-carbon atom.[44] Similarly, the methanolysis of glycosyl halides[45] and related solvolysis reactions[7] occur with predominant or complete inversion. Added chloride ion reduces the amount of inversion in both the phenyl glycoside and glycosyl halide reactions, suggesting that chloride ion can shield the 1-carbon atom on the side opposite to the leaving group through an ion pair or a species with some degree of bonding to carbon.[45] However, there can be no ion pair between a carbonium ion and a leaving uncharged phenol. The solvolysis of 2,4-dinitrophenyl glycosides in acetic acid, with which an oxocarbonium ion might be expected to react less rapidly, gives 60% inversion.[46] Nucleophilic S_N2 reactions with glycosyl halides are well known and intramolecular participation of 2-acetamido, 2-oxy anion, and possibly other substituents increases the rate of hydrolysis of glycosides.[2,7,46-48]

Structure-reactivity correlations suggest that C-O bond cleavage is essentially complete in a number of these reactions. This is consistent with a very late transition state for oxocarbonium ion formation, a rate-determining diffusional step, or a transition state with a weak interaction with both the attacking and the leaving group (**1**). The base-catalyzed solvolysis of substituted phenyl β-D-glucosides with intramolecular participation of the 2-oxygen anion, for example, exhibits a good correlation of log k and the pK of the leaving aryloxide ion with a slope of $\beta_{lg} = -1.1 \pm 0.1$.[47,49] The leaving groups include p-nitro- and p-acetylphenolates and the good fit of these compounds to the steep slope of the correlation means that the phenolate ion in the transition state is indistinguishable from a free, resonance-stabilized phenolate ion in solution; i.e., there is an extremely weak interaction with the 1-carbon atom in the transition state. Similarly, the values of β_{lg} of essentially zero (+0.23,[49] 0,[50] 0,[51] 0[52]) for the acid-catalyzed hydrolysis of alkyl and phenyl glycosides means that the leaving group closely resembles the free hydroxyl compound and has little interaction with the 1-carbon atom if, as is generally believed, these reactions involve specific acid catalysis with complete proton transfer to the leaving oxygen atom in the transition state.[2,5] The value of β_{lg} for the pH-independent solvolysis of methyl acylals of formaldehyde[53] is −0.8 and for the solvolysis of 2-aryloxytetrahydrofurans[54] the value of β_{lg} is −1.07, which implies a late transition state, possibly with rate-determining diffusion apart of the aryloxide and oxocarbonium ions. The fact that the S_N2 reaction of ethoxide ion with CH_3OCH_2Cl is 10^5 faster than with CH_3Cl means that there is considerable oxocarbonium ion character in the transition state for the former reaction.[55] These reactions are similar to the reactions of monosubstituted phosphates, which proceed through transition states that resemble the metaphosphate monoanion, with only a weak interaction with the entering nucleophile and the leaving group.[56]



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The following evidence is consistent with the speculation that the correlation of Figure 8 is more accurate than might be expected and that, as predicted by this correlation, the hydrolysis of substituted benzaldehyde acetals undergoes a transition from rate-determining formation of an oxocarbonium ion for electron-donating substituents in water to a mechanism in which the oxocarbonium ion is essentially fully developed in the transition state, such as rate-determining diffusion away of the leaving alcohol, for electron-withdrawing substituents and in aqueous organic solvents.

(1) The α-secondary deuterium isotope effect for the hydrolysis of p-methoxybenzaldehyde diethyl acetal in water is $k_H/k_D = 1.04$, consistent with a transition state with relatively little sp^2 character, whereas for p-nitrobenzaldehyde diethyl acetal the value of k_H/k_D is 1.15, suggesting a large change to a transition state with predominant sp^2 character; benzaldehyde diethyl acetal exhibits an intermediate value of $k_H/k_D = 1.09$.[2,21]

(2) The values of ρ are −2.15 for the acid-catalyzed addition of methanol to substituted benzaldehydes in 95% methanol to give acetals[57] and −1.85 for the equilibrium protonation of benzaldehydes.[58] If $XArCHOH^+$ can be taken as a model for $XArCHOR^+$, the value of ρ for the attack of methanol is $-2.15 - (-1.85) = -0.3$, which is probably not significantly different from zero. This is consistent with an oxocarbonium ion-like transition state with little or no bond formation to the attacking or departing methanol.

(3) (a) The Hammett coefficients of $\rho = -3.4$ and -4.3 for the hydrolysis of substituted benzaldehyde diethyl acetals in 50% dioxane[22] and 95% methanol,[57] respectively, are comparable to the value of $\rho = -3.6$ for the equilibrium formation of oxocarbonium ions from acetophenone acetals in water. Separating the polar and resonance parameters gives $\rho = --3.4$ and $\rho^r = -1.8 \pm 0.1$ for the benzaldehyde acetals in both mixed solvents, $\rho = -3.6$ and $\rho^r = -2.2$ for the equilibrium formation of oxocarbonium ions from acetophenone acetals, and $\rho = -2.9$, $\rho^r = -1.2$ for the rate of hydrolysis of acetophenone acetals in 50% dioxane. (b) The hydrolysis of benzaldehyde diethyl acetals in water shows less stabilization by substituents that donate electrons by resonance and has been reported[20] to follow σ with $\rho = -3.3$. Such a change in behavior would be expected if destabilization of the oxocarbonium ion and the decreased water concentration in aqueous organic solvents caused a change in rate-determining step. In contrast, the hydrolysis of acetophenone dimethyl ketals shows no change in the relative importance of polar and resonance effects and follows correlations with $r = 0.18$ ($r^+ = 0.35$) in both water and 50% dioxane (Figure 6). (c) If this same value of r is assumed to hold for benzaldehyde acetals with rate-determining C-O bond cleavage there is a slightly better fit (correlation coefficient 0.998) to a correlation with $\rho = -2.6$ for all rate constants except that for p-nitrobenzaldehyde acetal. The rate constant for p-nitrobenzaldehyde acetal shows a fourfold negative deviation from this correlation, consistent with the larger secondary isotope effect and a partial change in rate-determining step for this compound. (d) The reported value of ρ for the cleavage of methyl phenyl substituted-benzaldehyde acetals, with phenol leaving, is −2.26;[32] the data also fit $\rho = -1.95$ and $\rho^r = -0.98$, similar to the values of $\rho = -2.0$ and $\rho^r = -0.7$ for the hydrolysis of acetophenone dimethyl acetals. Phenol is a weaker nucleophile than ethanol and is less likely to attack the oxocarbonium ion to regenerate acetal, so that C-O bond breaking rather than diffusion away of the leaving alcohol is likely to be rate determining for the methyl phenyl acetals.

The fact that lysozyme catalyzes the transfer of glycosyl groups to dilute mono- and disaccharides means that an intermediate exists on the enzyme with a lifetime that is sufficient for the diffusion away of the leaving group and the diffusion of the acceptor group to the active site of the enzyme before the intermediate reacts with water.[4,59-62] This must also be the case for other enzymes that catalyze glycosyl transfer reactions and do not react by a direct displacement mechanism. If the glycosidic oxocarbonium ion is just unstable enough that its reaction with water or alcohol is diffusion controlled, the observed transferase activity makes possible an estimation of the minimum amount of stabilization of the oxocarbonium intermediate that must be brought about by interactions with the active site of the enzyme; presumably a similar stabilization exists in the oxocarbonium-like transition state of the rate-determining step.[63] The disaccharide GlcNAc-β-MurNAc is threefold more effective as an acceptor than GlcNAc which is in turn 2200-fold more effective than 1 M water,[59-60,64] giving an acceptor ratio ROH/HOH of 6.6×10^3. Chipman has estimated a ratio of k_{ROH}/k_{HOH} of 2.8×10^3 M^{-1} which upon correction to 1 M water gives a ratio of 1.5×10^5.[61] If the reaction with the acceptor is diffusion controlled, these ratios require that the intermediate be stabilized by at least 5-7 kcal mol^{-1}; if the oxocarbonium ion is less stable or the reaction with the acceptor is slower than diffusion controlled, the stabilization is correspondingly larger. This stabilization is presumably brought about by interaction of the oxocarbonium ion with the carboxylate group of Asp 52,[64-66] although there is little experimental support for such stabilization from model reactions;[67] it is conceivable that the 2-acetamido group of the substrate contributes to the stabilization.[46,48] It is unlikely that the ion pair collapses completely to an acylal because such an intermediate would be expected to be relatively unreactive toward acceptors and has not been observed to accumulate during turnover;[4,68] the intermediate may have a structure intermediate between that of the oxocarbonium ion and an acylal that gives it a short but significant lifetime.[62,63,65,69] The virtual independence on pK of the rate of reaction of small alcohols and phenol with the intermediate[60,70] means that there is essentially no charge development on the oxygen atom in the transition state for ROH attack or departure, as in the nonenzymatic acid-catalyzed hydrolysis of glycosides.

Note Added in Proof. Dr. R. A. McClelland has kindly informed us that he has calculated k_{H_2O} for the reaction of water with the oxocarbonium ion $MeOPhC(CH_3)OMe^+$ from direct measurements of the rate in concentrated acid solutions and extrapolation to zero acid concentration, using an appropriate acidity function. The resulting value of $k_{H_2O} = 10^{6.1}$ s^{-1} agrees satisfactorily with the value of $k_{H_2O} = 10^{6.8}$ s^{-1} reported here.

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Electronic Structure, Aromatic Character, and Chemical Reactivity of *o*-Quinonoidal Heterocycles

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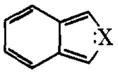
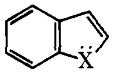
Abstract: The electronic structure of *o*-quinonoidal heterocycles is discussed in the light of NMR data which indicate (a) bond fixation in the carbocyclic ring and (b) insensitivity of the electron distribution in the carbocyclic ring to the nature of the heteroatom. A structural representation is proposed in which the π systems of *o*-quinonoidal heterocycles consist of contiguous but noninteracting butadiene and six-electron monocyclic systems. The structure reconciles their coexistent aromaticity and chemical reactivity.

Introduction

The contrast between the extreme chemical reactivity of the *o*-quinonoidal heterocycles **1** and the unreactivity of their stable Kekule counterparts **2** is intriguing, insofar as they differ only in the placement of the heteroatom, yet all contain a bicyclic 10 π electron array.[2] While it is tempting to regard them as basically *o*-xylylene derivatives, attribution of their reactivity simply to their polyenic or *o*-quinonoidal character seems inconsistent with the results of recent experimental and theoretical investigations, which indicate the heteroatom lone pairs of **1** to be strongly coupled into the π systems.[3] Moreover, isoindole (**1a**), isobenzofuran (**1b**), and isothianaphthene (**1c**) have been calculated to possess substantial resonance energies[4] (albeit less than in the corresponding Kekule compounds), a prediction verified indirectly for **1a** by our observation that isoindolenine (**3**) is converted smoothly, spontaneously, and irreversibly into **1a**, even at −40 °C.[5]

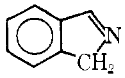


1



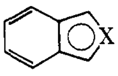
2

a, X = NH
b, X = O
c, X = S
d, X = Se



3

If the *o*-quinonoidal heterocycles are, in fact, "aromatic" in the sense of possessing substantial resonance energies, a question arises whether the aromaticity is global, extending over the entire π system, or whether it derives primarily from only one ring.[6] We posed this question for isoindole in our previous paper,[5] but were unable to choose between the alternatives using data for isoindole alone. We now return to the discussion of this point, using NMR coupling constant data and theoretical analyses for compounds **1a–d**, and propose **4** as the structural representation which best depicts their structures and reconciles their aromaticity and chemical reactivity.



4

Results and Discussion

Despite their superficial structural similarity, the heterocycles **1** display a wide range of stabilities, from the relatively stable isothianaphthene (**1c**) to the ephemeral isobenzofuran (**1b**). We sought evidence for a structural basis of these pronounced stability differences, using the NMR spectra of isoindole (**1a**), isobenzofuran (**1b**), isothianaphthene (**1c**), and benzo[*c*]selenophene (**1d**).[7] Aromatic systems generally exhibit bond length averaging, while systems which display pronounced bond length alternation invariably lack significant resonance stabilization,[8] a fact which has been employed in connection with allylic coupling constant data to establish the nonaromaticity of 2-pyrones.[9] We felt that the vicinal proton couplings in the carbocyclic rings of **1a–d** could similarly serve as an index of electron delocalization or localization, since the heteroatoms are sufficiently far removed as to influence the couplings only by their effects on the π-electron distribution.

We analyzed the NMR spectra of isoindole and benzo[*c*]selenophene using the program LAOCN3[10] and Tables I and II, respectively, summarize vicinal coupling constant data for the carbocyclic rings of **1a–d** and for several isoindoles of widely varying stabilities. The most striking feature of these data is the near constancy of the vicinal couplings J_{45} and J_{56}, with only the benzo[*c*]selenophenes deviating appreciably. Moreover, the ratio J_{56}/J_{45} ($= J_{\text{ratio}}$), proposed by Crews et al.[11] as a measure of the degree of electron delocalization in butadienic fragments, is nearly invariant, at 0.72 ± 0.02, for all members of both series, including the deviant benzo[*c*]selenophene, and shows no correlation with either reactivity or calculated indices of resonance stabilization. If J_{ratio} is indeed a valid measure of electron localization or delocalization, the data indicate the electron distributions in the carbocyclic rings to be insensitive to perturbations in the five-membered rings. The value of J_{ratio} is also significantly less than in the Kekule series (ca. 0.9),[12] indicative of at least some residual butadienic character in the carbocyclic rings. As we pointed out previously,[5] this latter observation is, in principle, consistent