solid was filtered off and dried: 80 mg of the hydrate (87%) yield; TLC (chloroform, methanol [9:1]) R_f = 0.56; ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 7.17 and 6.75 (2 H, AB system, J = 9 Hz, 6-H and 7-H), 4.55 (2 H, s, chloromethyl); mass spectrum, m/z 226 (P^+), 191 (P^+ – Cl). Anal. Calcd for $C_9H_7ClN_2O_3 \cdot 0.75H_2O$: C, 45.01; H, 3.56; N, 11.66. Found: C, 44.83; H, 2.82; N, 11.21. The hydrogen percentage obtained experimentally deviates widely from the theoretical value. The ^{1}H NMR and mass spectra indicate that the material is pure and the assigned structure correct, however.

2-(Hydroxymethyl)-5,8-dihydroxyquinazolin-4(3*H*)-one (2c). To a mixture consisting of dimethyl sulfoxide (10 mL) and water (2 mL) was added 33 mg (0.12 mmol) of **2b**. The reaction mixture was degassed at room temperature for 30 min with N_2 and then heated at 55 °C under an N_2 atmosphere for 10 h. The completed reaction was extracted with ethyl acetate to remove **2c**. Evaporation of the extracts to a residue in vacuo was followed by addition of 1 mL of ethanol. Crystallization of **2c** occurred upon addition of 5 mL of water: 16 mg (64%) yield; TLC (butanol, acetic acid, water [5:2:3]) Rf = 0.64; ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 12.35 (1 H, br s, 5-OH), 10.98 (1 H, br s, 8-OH), 8.96 (1 H, br s, N(3)-H), 7.13 and 6.69 (2 H, AB system, J = 9 Hz, aromatic), 5.42 (1 H, br s, OH of 2-hydroxymethyl), 4.42 (2 H, s, methylene of 2-hydroxymethyl); mass spectrum (EI), m/z 208 (P^+).

2-(Bromomethyl)quinazoline-4,5,8(3*H*)-trione (1a). To an ice bath chilled mixture of 50 mg (0.184 mmol) **2a** in 1 mL of dry methanol was added 70 mg (0.308 mmol) of DDQ. The reaction mixture was stirred for 30 min with continued chilling. Crystallized **1a** was filtered off and washed with diethyl ether. Recrystallization of **1a** was carried out by dissolution in hot acetone followed by addition of hexane: 15.8 mg of the hydrate (32%) yield; mp 177–181 °C dec; TLC (chloroform, methanol [9:1]) R_f = 0.09; IR (KBr) 3182, 3156, 3070, 1722, 1701, 1677, 1569, 1546, 1465, 1104 cm^{-1}; ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 7.00 and 6.87 (2 H, AB system, J = 10.4 Hz, aromatic), 4.42 (2 H, s, bromomethyl); mass spectrum (EI), m/z 268 (P^+, ^{79}Br) 270 (P^+, ^{81}Br). Anal. Calcd for $C_9H_5BrN_2O_3 \cdot 0.5H_2O$: C, 39.16; H, 1.46; N, 10.16. Found: C, 40.34; H, 1.89; N, 9.92.

2-Methyl-5,8-dimethoxyquinazolin-4(3*H*)-one (7). A solution of 325 mg (1.65 mmol) of **5**[28] in 15 mL of acetic anhydride was stirred at room temperature for 3 h. Acetylated **5** formed as a white precipitate, which was filtered and dried under vacuum: 310 mg (79%) yield; mp 195–196 °C. Anal. Calcd for $C_{11}H_{14}N_2O_4 \cdot 0.25H_2O$: C, 54.42; H, 6.64; N, 11.53. Found: C, 54.30; H, 6.11; N, 11.59.

The acetylated derivative (90 mg, 0.378 mmol) was combined with 20% aqueous NaOH (20 mL) and refluxed for 4 h. The reaction mixture was then diluted with 50 mL of water and adjusted to pH 6 with acetic acid. The cyclized product **7** crystallized from solution upon chilling: 70 mg (84%) yield; mp 264–265 °C; TLC (chloroform, methanol [9:1]) R_f = 0.26; IR (KBr) 3317, 2990, 2903, 1689, 1635, 1581, 1489, 1329, 1268, 1178, 1094, 815 cm^{-1}; ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 7.23 and 6.85 (2 H, AB system, J = 9 Hz, aromatic), 3.80 and 3.77 (6 H, 2 s, 5,8-dimethoxy) 2.29 (3 H, s, 2-methyl). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.92; H, 5.62; N, 12.53. Found: C, 60.01; H, 5.42; N, 12.72.

2-Methyl-5,8-dihydroxyquinazolin-4(3*H*)-one ($4H_2$). A solution of **7** (13 mg, 0.059 mmol) in 1 mL of 48% HBr was heated at 150 °C for 3 h. The reaction mixture was then cooled to room temperature, resulting in crystallization of $4H_2$ as the hydrobromide salt: 9.5 mg (86%) yield; mp 277–280 °C dec; TLC (chloroform, methanol [9:1]) R_f = 0.45; IR (KBr) 3360, 3025, 1661, 1500, 1362, 1204 cm^{-1}; ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 10.89 (1 H, br s, amide proton), 7.32 and 6.87 (2 H, AB system, J = 8.8 Hz, aromatic), 2.58 (3 H, s, 2-methyl); mass spectrum (EI), m/z 192 (P^+). Anal. Calcd for $C_9H_8N_2O_3 \cdot HBr$: C, 39.58; H, 3.32; N, 10.26. Found: C, 39.36; H, 3.30; N, 10.13.

2-Methylquinazoline-4,5,8(3*H*)-trione (4). To an ice bath chilled mixture of $4H_2 \cdot HBr$ (70 mg, 0.256 mmol) in 1 mL of methanol was added 88 mg (0.387 mmol) of DDQ. The reaction was stirred at ice-bath temperature for 30 min and then diluted with ~10 mL of ethyl acetate. Crystallized **4** was filtered off and washed with ethyl acetate: 35.8 mg (74%) yield; mp 165–168 °C dec; TLC (chloroform, methanol [9:1]) R_f = 0.19; IR (KBr) 1700, 1683, 1577, 1548, 1481, 1107 cm^{-1}; ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 6.97 and 6.84 (2 H, AB system, J = 10.4 Hz, aromatic), 2.42 (3 H, s, 2-methyl); mass spectrum (EI), m/z 190 (P^+).

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Registry No. **1a**, 117526-26-8; **2a**, 117498-05-2; **2b**, 117498-06-3; **2c**, 117498-07-4; **4**, 117498-11-0; **4H$_2$**, 117498-10-9; **5**, 98991-68-5; **5** (acetyl deriv.), 117498-08-5; **6**, 117498-04-1; **7**, 117498-09-6; 2-(phenoxyacetamido)-3,6-dimethoxybenzamide, 117498-03-0; xanthine oxidase, 9002-17-9.

Notes

Effect of Conjugation on the Rates of the Acid-Catalyzed Hydrolyses of Acetals

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The hydrolyses of acetals and ketals have been extensively investigated.[1] Our recent studies[2] have focused on the effect of acetal structure on the importance of general acid catalysis (*i.e.*, on the relationship between structure and the Brønsted α). For general acid catalysis to be observable for a diethyl acetal/ketal, the structure must be such as to render the acetal/ketal quite reactive. One of the structural features that accomplishes this is conjugation of the reaction center with an aromatic group not containing an electron-withdrawing group. For example, the diethyl acetal of benzaldehyde is 2 orders of magnitude more reactive than the diethyl acetal of acetaldehyde, and general acid catalysis is barely discernable for the former[2a] and has never been observed for the latter.[1]

The question that has generated all this attention is: Does the lack of observing general acid catalysis imply a different mechanism of hydrolysis or does is simply reflect experimental limitations put in place by Brønsted α values approaching unity? The importance of providing a definitive answer to this matter has been diminished by the

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Table I. Second-Order Rate Constants for the Hydrogen Ion Catalyzed Hydrolysis of Selected Acetals[a]

acetal	k_{H^+}, M^{-1} s^{-1}	acetal	k_{H^+}, M^{-1} s^{-1}
PhCH=CHCH(OEt)$_2$	1.3×10^3	PhCH(OEt)$_2$[b]	1.7×10^2
PhC≡CCH(OEt)$_2$	0.13	$CH_3CH_2CH(OEt)_2$[c]	3.0
CH_2=CHCH(OEt)$_2$	56		

[a] 25 °C in aqueous solution, ionic strength <0.1 and not held constant. [b] Reference 2a, ionic strength 0.5 (KCl). [c] Reference 6, ionic strength 0.5 (KCl).

finding that it is the leaving group that plays the more dominant role in producing observable general acid catalysis, and thus it is not at all suprising that the natural substrates of enzymes are hydrolyzed by employing a general acid catalyst, because the leaving group in these cases is comparable in oxxgen basicity to trifluoroethanol. Previous work has shown that even the less reactive acetals containing the trifluoroethoxy group exhibit pronounced general acid catalysis.[2b]

In reviewing structural features that might lead to increased reactivity and hence be suitable candidates for demonstrating the ubiquity of general acid catalysis in the hydrolysis of acetals, we measured the kinetics of hydrolysis of the diethyl acetals of cinnamaldehyde (**1**), phenylpropiolaldehyde (**2**), and acrolein (**3**).

PhCH=CHCH(OEt)$_2$ (**1**) PhC≡CCH(OEt)$_2$ (**2**)

CH_2=CHCH(OEt)$_2$ (**3**)

In addition to evaluating the activating effect of conjugation, we were intrigued by the prospect of products or intermediates resulting from "unexpected" reaction at carbons other than at the *pro*-carbonyl. In all cases, however, spectral evidence indicated the presence of the expected aldehyde as the only observable product of hydrolysis. Repetitive scans of the UV spectrum during the course of hydrolysis showed that the entire spectrum changed from that of reactant to that of product in a smooth first-order manner. The rate constants measured were not a function of the wavelength chosen for measurement. Therefore, if attack by water occurs at a carbon other than the *pro*-carbonyl during hydrolysis, it must produce an intermediate that is not observable (either because of a weakly absorbing UV spectrum or because of low concentration) *and* must ultimately lead to the expected aldehyde product. The most likely event is that the intermediate ions **1a** and **2a** simply react like the analogous oxycarbocations, which cannot lose their structural integrity during nucleophilic attack.

PhCH=$\overset{+}{C}$HCHOEt (**1a**) PhC≡$\overset{+}{C}$CHOEt (**2a**)

Thus the reactivities tabulated in Table I simply reflect the energy barrier to formation of the oxycarbocations, as opposed to being complicated by mechanistic differences. It appears that direct conjugation of a double bond with the reaction center increases the rate of hydrolysis by 1 order of magnitude; conjugation of a triple bond decreases the rate of hydrolysis by about 3 orders of magnitude. The deactivating effect of a conjugated triple bond is consistent with results (admittedly somewhat scattered) from solvolysis experiments.[3]

The reactivities contained in Table I suggest that acetals **1** and **3** will show the same sort of marginal general acid catalysis observed in the hydrolysis of benzaldehyde diethyl acetals. Acetal **2** reacts too slowly to allow the suitable experiments to be conducted.

The absence of attack by water at a carbon other than the *pro*-carbonyl carbon simply reflects the directing effect of the aromatic ring conjugated with the multiple bond, i.e., the potential loss of conjugative stabilization requires that the solvent attack the *pro*-carbonyl carbon. This is somewhat unexpected, since the conjugative stabilization can be estimated from heats of hydrogenation data to be about 1-2 kcal/mol for **1** and a negative 1 kcal/mol for **2**.[4] These relatively small energies imply that loss of conjugation of the multiple bond with the aromatic group should not direct the nucleophilic attack as strongly as it apparently does. Perhaps this implies some sort of solvent participation prior to the complete loss of EtOH from the acetal moiety. Such participation is required in order to explain adequately the acid-catalyzed methanolysis/anomerization of glucopyranosides.[5]

Experimental Section

Solutions. Acidic solutions were made with standardized reagent grade hydrochloric acid or reagent grade standard buffers and distilled water. The pH of all solutions was measured experimentally and was consistent with the value calculated from the concentration of the reagents.

Materials. Acetals **2** and **3** were purchased from Aldrich Chemical Co.; acetal **1** was synthesized by using standard procedures.[2a]

Kinetic Method. The general methodology was as reported previously.[2c] Rate constants were measured at two or more wavelengths for each acetal, usually for increasing and decreasing absorbance changes. Absorbance versus time data were recorded with a Beckman Model 25 kinetic system.[2c] Conventional pseudo-first-order rate plot were prepared to calculate k_{obsd} values; k_{H^+} values were obtained from the slope of k_{obsd} versus $[H^+]$ plots (a log-log plot yielded unit slope).

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Synthesis of 2,3-Norbornadienonaphthacene

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Norbornenyl-fused aromatic systems such as compounds **1** and **2** have recently claimed a special interest because of π-facial stereoselectivity.[1] We recently reported an improved synthesis of 2,3-norbornadienoanthracene (**2**)[2] and its application to the synthesis of anthracene annellated norbornenylogues. We now report here the synthesis of the next homologue in this series, the previously un-

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