Catalyzed by *Pseudomonas* sp. K-10 (Table III). To a 0.01 M solution of the (±)-methyl sulfinylalkanoate in hexane was added 1-butanol (10.0 equiv) and 1.0 mass equiv of *Pseudomonas* sp. K10. The resulting suspension was stirred at 45 °C for the time indicated. The reaction was then filtered through celite to remove the enzyme (washing with Et_2O). Removal of the volatiles and separation of the crude mixture by flash chromatography gave the pure optically active methyl and *n*-butyl sulfinylalkanoates.

(*S*)-(−)-*n*-Butyl [(4-chlorophenyl)sulfinyl]acetate: using 0.116 g (0.500 mmol) of (±)-**2**. The resulting suspension was stirred at 45 °C for 27 h. After flash chromatography (30% EtOAc in hexane), 0.059 g (50%) of (*R*)-(+)-**2** was obtained as colorless crystals: 79% ee. Also obtained was 0.057 g (42%) of (*S*)-(−)-*n*-butyl [(4-chlorophenyl)sulfinyl]acetate as colorless crystals: R_f 0.7 (50% EtOAc in hexane); $[\alpha]^{25}_D$ −49° (*c* 0.20, EtOH); >95% ee; ^{1}H NMR δ 7.63 (d, *J* = 8.52 Hz, 2 H), 7.51 (d, *J* = 8.52 Hz, 2 H), 4.09 (t, *J* = 6.6 Hz, 2 H), 3.85 (d, *J* = 13.64 Hz, 1 H), 3.65 (d, *J* = 13.64 Hz, 1 H), 1.33 (m, 2 H), 0.90 (t, *J* = 7.27 Hz, 3 H); ^{13}C NMR δ 175.8 (C), 164.5 (C), 141.7 (C), 129.7 (CH/CH_3), 125.7 (CH/CH_3), 66.0 (CH_2), 61.7 (CH_2), 30.4 (CH_2), 19.0 (CH_2), 13.6 (CH/CH_3); IR ($CHBr_3$) 3020 (st), 1730 (st), 1570 (wk), 1470 (md), 1290 (md), 1150 (st), 1050 (md), 1070 (md) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 207 (15), 81 (43), 28 (100); HRMS calcd for $C_{12}H_{15}O_3ClS$ 274.0430, found 274.0431. **(*S*)-(−)-*n*-Butyl (2-naphthylsulfinyl)acetate**: using 0.124 g (0.500 mmol) of (±)-**5**. The resulting suspension was stirred at 45 °C for 28 h. After flash chromatography (25% acetone in hexane), 0.030 g (24%) of (*R*)-(+)-**5** was obtained as colorless crystals: 85% ee. Also obtained was 0.044 g (30%) of (*S*)-(−)-*n*-butyl (2-naphthylsulfinyl)aceate as colorless crystals: R_f 0.5 (25% acetone in hexane); $[\alpha]^{25}_D$ −68° (*c* 0.60, EtOH); 91% ee; ^{1}H NMR δ 8.23 (s, 1 H), 7.93 (m, 3 H), 7.62 (m, 3 H), 4.09 (t, *J* = 6.6 Hz, 2 H), 3.92 (d, *J* = 13.58 Hz, 1 H), 3.75 (d, *J* = 13.58 Hz, 1 H), 1.48 (m, 2 H), 1.24 (m, 2 H), 0.90 (t, *J* = 7.27 Hz, 3 H). **(*S*)-(−)-*n*-Butyl 3-[(4-chlorophenyl)sulfinyl]propanoate**: using 0.123 g (0.500 mmol) of (±)-**8**. The resulting suspension was stirred at 45 °C for 55 h. After flash chromatography (25% EtOAc in hexane), 0.031 g (25%) of (*R*)-(+)-**8** was obtained as colorless crystals: >95% ee. Also obtained was 0.047 g (33%) of (*S*)-(−)-*n*-butyl 3-[(4-chlorophenyl)sulfinyl]propanoate as colorless crystals (recrystallized from acetone/hexane): R_f 0.6 (50% EtOAc in hexane); mp 60–61 °C; $[\alpha]^{25}_D$ −62° (*c* 0.40, EtOH); 90% ee; ^{1}H NMR δ 7.53 (m, 4 H), 4.05 (t, *J* = 6.5 Hz, 2 H), 3.19 (m, 1 H), 2.89 (m, 2 H), 2.55 (m, 1 H), 1.58 (m, 2 H), 1.52 (m, 2 H), 0.91 (t, *J* = 7.3 Hz, 3 Hz, 3 H); ^{13}C NMR δ 172.0 (C), 156.0 (C), 142.0 (C), 129.6 (CH/CH_3), 125.5 (CH/CH_3), 65.1 (CH_2), 51.3 (CH_2), 30.5 (CH_2), 26.1 (CH_2), 19.1 (CH_2), 13.7 (CH/CH_3); IR ($CHBr_3$) 3020 (st), 1730 (st), 1600 (md), 1470 (md), 1150 (st), 1050 (md), 1020 (md) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 288 (1, M^+), 28 (100); HRMS calcd for $C_{13}H_{17}O_3ClS$ 288.0587, found 288.0587. **(*S*)-(−)-10-Undecen-1-yl [(4-Chlorophenyl)sulfinyl]acetate.** The transesterification procedure described above was used with 2.00 g (8.60 mmol, 1.00 equiv) (±)-**2**, 4.31 mL (21.5 mmol, 2.50 equiv) of 10-undecen-1-ol in place of the *n*-BuOH and only 2.0 mass equiv of *Pseudomonas* sp. K10. The resulting suspension was stirred at 45 °C for 35 h. After flash chromatography (20% EtOAc in hexane) 1.1 g (55%) of (*R*)-(+)-**2** was obtained as colorless crystals: 59% ee. The (*S*)-(−)-10-undecenyl [(4-chlorophenyl)sulfinyl]acetate and the excess 10-undecen-1-ol were not separated by the flash chromatography. Thus the 10-undecen-1-ol was transformed into its tetrahydropyranyl derivative to facilitate its removal. To a solution of the mixture in CH_2Cl_2 (50 mL) were added 3.92 mL (43.0 mmol, 5.00 equiv) of 3,4-dihydro-2*H*-pyran and a catalytic amount of *p*-toluenesulfonic acid monohydrate. The reaction was stirred at 25 °C for 5 h. Removal of the volatiles in vacuo and purification by flash chromatography (10% acetone in hexane) gave 0.42 g (13%) of (*S*)-(−)-10-undecenyl [(4-chlorophenyl)sulfinyl]acetate as an oil: R_f 0.14 (10% acetone in hexane); $[\alpha]^{25}_D$ −58° (*c* 0.45, EtOH); >95% ee; ^{1}H NMR δ 7.64 (d, *J* = 8.5 Hz, 2 H), 7.51 (d, *J* = 8.5 Hz, 2 H), 5.80 (m, 1 H), 4.94 (m, 2 H), 4.07 (t, *J* = 6.8 Hz, 2 H), 3.85 (d, *J* = 13.6 Hz, 1 H), 3.66 (d, *J* = 13.6 Hz, 1 H), 2.03 (m, 2 H), 1.57 (m, 2 H), 1.10–1.40 (m, 12 H); ^{13}C NMR δ 177.0 (C), 164.5 (C), 141.6 (C), 139.1 (CH/CH_3), 129.7 (CH/CH_3), 125.7 (CH/CH_3), 114.1 (CH_2), 66.3 (CH_2), 61.6 (CH_2), 33.8 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 25.7 (CH_2); IR (neat) 3500 (md), 1732 (st), 1650 (md), 1276 (md), 1090 (md), 1055 (md), 1011 (md) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 370 (0.4, M^+), 159 (100); HRMS calcd for $C_{19}H_{27}O_3ClS$ 370.1369, found 370.1369.

Acknowledgment. Financial support for this work was obtained from the donors of the Petrolium Research Fund, administered by the American Chemical Society. NMR studies were performed using instrumentation purchased, in part, with funds from the the National Science Foundation. We also thank Ms. Petra Jensen for some preliminary data related to these experiments.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for selected compounds (20 pages). Ordering information is given on any current masthead page.

Acylal Hydrolysis. The pH-Independent Breakdown of 7-Oxo-6,8-dioxabicyclo[3.2.1]octane

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The hydrolysis of the bicyclic acylal 7-oxo-6,8-dioxabicyclo[3.2.1]octane in water is rapid and pH independent from pH 1–12 (k_0 = 6.0 × 10^{-3} s^{-1} at 20 °C). This reaction proceeds at nearly the same rate in D_2O as in H_2O (k_{H_2O}/k_{D_2O} = 1.1) and is uncatalyzed by buffer. Therefore, the reaction is a unimolecular breakdown to a resonance-stabilized oxocarbonium ion; i.e., the acylal is hydrolyzing like an acetal with a good leaving group and not like an ester. The ^{1}H and ^{13}C NMR spectra indicate a diaxial conformation for the substituents at C-1 and C-5 with moderate distortion of the tetrahydropyran ring. There is a large upfield shift for carbon at C-3 as compared with the corresponding carbon (C-4) of tetrahydropyran (8.8 ppm) or 2-ethoxytetrahydropyran (3.8 ppm). The rapid pH-independent unimolecular breakdown reaction is due to a relatively favorable ΔS* (−2.6 eu) and the lack of effective reversibility of that reaction.

The hydrolysis of both cyclic and acyclic acylals has been extensively studied.[1-5] These compounds combine the structural features of both acetals and esters and can therefore hydrolyze by mechanisms typical of either type

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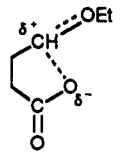
Table I. Carbon-13 NMR Spectra of Tetrahydropyran Derivatives[a]

	V		tetrahydropyran[b]	2-carbomethoxytetrahydropyran[b]	2-ethoxytetrahydropyran
C-5	103.8	(C-2)	68.7	76.3	97.7
C-4	26.8	(C-3)	26.9	28.9	30.1
C-3	15.0	(C-4)	23.8	22.9	18.8
C-2	23.8	(C-5)	26.9	25.4	24.9
C-1	72.0	(C-6)	68.7	68.1	61.2
C=O	172.8			171.9	
OCH_2					61.9
OCH_3				51.9	
CH_3					14.4

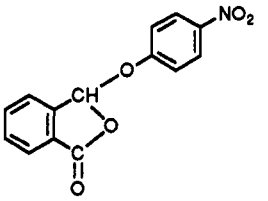
[a] Carbon numbers without parentheses refer to the corresponding carbons of V employing the bicyclic numbering of structure V. The numbers in parentheses refer to the carbons of the tetrahydropyran ring system. [b] Reference 21.

of compound. The plots of log k_{obsd} vs pH have an ascending arm at high pH with a slope of +1.0, which undoubtedly reflects attack of hydroxide ion at the carbonyl group. However, at pH values near neutrality there is a large pH-independent region in the profiles.[3,5] In the hydrolysis of γ-ethoxy-γ-butyrolactone[3] this pH-independent reaction is very likely a unimolecular breakdown to a resonance-stabilized oxocarbonium ion (I). This



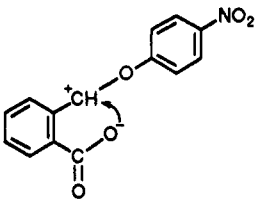
I

mechanism occurs because the leaving group is of low basicity and also to take advantage of the great stabilization provided to the developing oxocarbonium ion by the adjoining ethoxy group. Brown and Bruice[5] found that 1-β-D-glucopyranosyl benzoate and analogous O-methylated derivatives also hydrolyze in a pH-independent reaction at pH > 3 probably via unimolecular breakdown to an oxocarbonium ion and benzoate ion. Similar pH-independent unimolecular reactions are found in the hydrolysis of acetals and acetal analogues having very good leaving groups.[6-12] On the other hand, the acylal 3-(*p*-nitrophenoxy)phthalide (II) hydrolyzes with attack of water and amine bases at the carbonyl group,[4] i.e., like an ester. In that case an intermediate oxocarbonium ion would be very unstable. The carboxylate anion that would be formed in a unimolecular reaction would also be sterically held adjacent to the oxocarbonium ion so that a



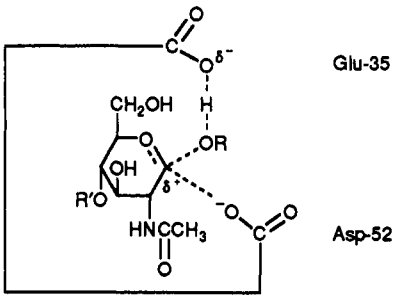
II

unimolecular reaction would be markedly reversible (III). These factors then contribute to the observed bimolecular ester-like reaction.



III

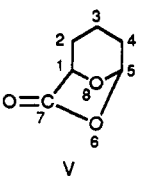
The proposed mechanism for the glycosidase enzyme lysozyme that has received the most attention is that shown in IV in which the carboxylate anion of Asp-52



IV

electrostatically stabilizes the developing oxocarbonium ion.[13,14] If a full covalent bond were formed, then the resulting acylal would necessarily have to react like an acetal via the microscopic reverse pathway; alcohol nucleophiles react to give glycosides rather than esters of Asp-52.[15] Thus, understanding the reactivity of acylals is necessary for a realistic assessment of the proposed mechanisms for the enzymatic reaction.

The oxocarbonium ion produced from a strained cyclic acylal would not be highly susceptible to the reverse ring closure because that would necessitate the reintroduction of strain. However, strained or sterically restricted acylals have not been previously investigated. We have, therefore, in the present work investigated the hydrolysis reactions of the bicyclic acylal 7-oxo-6,8-dioxabicyclo[3.2.1]octane (V).



V

Experimental Section

Materials. 7-Oxo-6,8-dioxabicyclo[3.2.1]octane was prepared from 3,4-dihydro-2*H*-pyrancarboxylic acid, sodium salt by the method of Brezinski et al.[16] The liquid product was distilled,

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Table II. Rate Constants (k_{obsd}, s^{-1}) for Hydrolysis of 7-Oxo-6,8-dioxabicyclo[3.2.1]octane (V) at 20 °C in H_2O (μ = 0.5 M with KCl)

buffer[a]	pH	$10^3 k_{obsd}$ (s^{-1})
HCl	1.1	6.47
chloroacetate	2.6	6.33
formate	3.2	5.70
acetate	4.1	6.25
acetate	4.85	5.34
acetate	5.3	5.39
cacodylate	6.2	4.85
imidazole	7.35	5.97
Tris	7.65	6.21
Tris	8.2	6.62
carbonate	9.15	6.92
carbonate	10.45	6.51
KOH	11.95	7.70

[a] The buffer concentration was 0.02 M.

bp 65 °C (3 mm), n^{20}_D 1.4588 (lit.[16] bp 65 °C (3 mm), n^{20}_D 1.4582): ^{1}H NMR δ 5.70 (1 H, narrow) and 4.13 (1 H, narrow); ^{13}C NMR (Table I). 2-Ethoxytetrahydropyran was prepared by the procedure of Woods and Kramer:[17] bp 58–60 °C (36 mm); n^{23}_D 1.4220 (lit.[17] bp 146 °C, n_D 1.4248); ^{1}H NMR δ 4.60 (1 H, narrow); ^{13}C NMR (Table I).

All buffer components were reagent grade. Amine buffer components were either recrystallized or distilled prior to use. Proton NMR spectra were obtained in $CDCl_3$. All chemical shifts are reported in reference to TMS.

Kinetic Measurements. The rates of hydrolysis of V were measured with a recording spectrophotometer. To initiate the reaction one drop of V was added directly by means of a calibrated dropping pipette to 3 mL of the reaction solution maintained at the desired temperature. The hydrolysis reaction was monitored by following the decrease in absorbance at 237 nm. The reactions were pseudo-first-order for at least 4 half-lives. The values of k_{obsd} and subsequent kinetic parameters were calculated with an IBM-370 computer. Appearance of the aldehyde addition compound with 0.01 M semicarbazide at pH > 3.4 was also followed at 225 nm. In these reactions 15–30 μL of a 10^{-2} M solution of V in acetonitrile was injected into 3 mL of the reaction solution. This method has been described previously[18,19] and its accuracy verified.[20] Rate constants determined by this method and by direct spectrophotometric measurement were identical. Reaction-mixture pH values were measured at the temperature of the kinetic determinations.

Results

The carbon-13 NMR spectral data obtained for 7-oxo-6,8-dioxabicyclo[3.2.1]octane (V) are given in Table I. For comparison purposes, the ^{13}C spectra of tetrahydropyran,[21] 2-carbomethoxytetrahydropyran,[21] and 2-ethoxytetrahydropyran are also given in Table I. Signal assignments were based on the previously assigned spectra for a large series of tetrahydropyran derivatives.[21]

The values of k_{obsd} for hydrolysis of V in water at 20 °C (μ = 0.5 M) to 2-hydroxy-6-carboxytetrahydropyran are pH independent from pH 1 to 12. These rate constants are given in Table II. The average value of k_0 is 6.05 ± 0.50 × 10^{-3} s^{-1}, excluding the k_{obsd} value at pH 11.95. The value of k_{obsd} in D_2O as the solvent at pD = 6.59 is 5.36 × 10^{-3} s^{-1} (k_{H_2O}/k_{D_2O} = 1.1). The rate constants were also measured at 12, 16.5, 23, 32, and 36 °C. The value of ΔH^* is 19.3 kcal/mol, and ΔS^* is −2.6 eu calculated at 25 °C. Buffer catalysis was not observed in these reactions. For example, in imidazole buffer at pH 7.35, k_{obsd} was invariant at buffer concentrations ranging from 0.02 to 0.5 M. Likewise, there was no effect of *N*-ethylmorpholine buffer at pH 7.95 in the same concentration range.

Discussion

Eliel and Giza[22] considered that an equatorial proton at C-2 of a tetrahydropyran derivative would give a sharp peak in the NMR spectrum at 4.53–5.52 ppm, whereas an axial proton will give broadly split peaks at 4.15–4.72 ppm. The narrow peak in the ^{1}H NMR spectrum of V at 5.70 ppm (1 H) is consistent with the presence of an equatorial proton at C-5 (see structure V) and, consequently, an axial substituent group. The peak that can be attributed to the C-1 proton at 4.13 ppm (1 H) is also narrow, as expected for an equatorial proton, but is at higher field than might be anticipated with an equatorial proton in that position.[22]

The ^{13}C NMR spectral data for V in Table I show a large upfield shift at C-3 in comparison with the corresponding carbon (C-4) of tetrahydropyran. This may be due to a diaxial conformation of the –COO– group bridging carbons 1 and 5. A Stuart–Briegleb model shows that if the tetrahydropyran ring has a chair conformation, then the substituents at C-1 and C-5 must be nearly axial. Alkoxy or aryloxy groups at C-2 of tetrahydropyran derivatives prefer the axial position (the anomeric effect).[23] Thus, the ethoxy group of 2-ethoxytetrahydropyran is undoubtedly axial as shown by the ^{1}H NMR spectra. The single sharp peak at 4.6 ppm is in a range expected for an equatorial proton at C-2.[22] The axial –OEt group at C-2 then produces an upfield shift in the ^{13}C chemical shift at C-4. Such γ-diaxial effects give rise to upfield shifts.[24] The upfield shift is intensified with the acylal V at C-3, which is consistent with an axial substituent at C-1 if a chair conformation is assumed for the tetrahydropyran ring. The shifts at C-1 and C-5 are large and downfield as expected with electron-withdrawing substituents at those positions. Carbon-13 NMR spectra of tetrahydropyran derivatives are given in Table I for comparison. There is an indication of a 1,5-diaxial interaction with V in that the chemical shift at C-1 is upfield in comparison with C-2 of 2-carbomethoxytetrahydropyran. However, the shift at C-5 is further downfield than that produced by the ethoxy group of 2-ethoxytetrahydropyran at C-2. There is an upfield shift at C-2 of V in comparison with C-3 of 2-carbomethoxytetrahydropyran and at C-4 in comparison with C-3 of 2-ethoxytetrahydropyran. Therefore, the tetrahydropyran ring of V might be distorted.[24,25] The Stuart–Briegleb model indicates that only moderate distortion is required to close the bridging ring, but that the ensuing bicyclic molecule is then quite inflexible.

The rate of hydrolysis of V to give 2-hydroxy-6-carboxytetrahydropyran is rapid ($t_{1/2}$ is ~2 min at 20 °C), and k_{obsd} is pH independent over the entire pH range investigated (1–12). This reaction proceeds at nearly the same rate in D_2O as in H_2O, so proton transfer is not occurring in the transition state. The ΔS^* near zero (−2.6 eu) is consistent with a transition state in which water is not significantly restricted.[26] Likewise, there is no cata-

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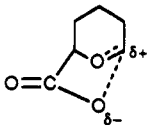
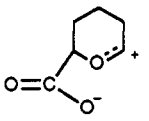
lysis by buffer acids or bases.[27] All of the evidence points to a unimolecular breakdown to an oxocarbonium ion intermediate (VI), which then reacts rapidly with water. The



VI

developing positive and negative charges will be solvated by water, but the extent of solvation will depend on the amount of bond breaking in the transition state. Thus, the acylal is hydrolyzing like an acetal with a good leaving group and not like an ester with nucleophilic attack at the carbonyl group.

The inflexible bicyclic ring system of V should greatly enhance C–O bond breaking. Even though the leaving group does not depart from the molecule, i.e., the carboxylate ion is held near the oxocarbonium ion (VII), there

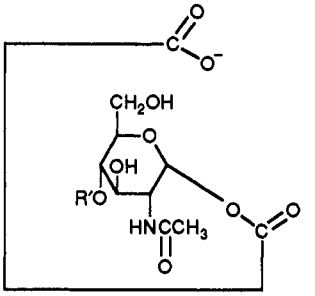


VII

should be no great tendency for the reaction to reverse because that would reintroduce strain and restriction of free rotation. Consequently, the unimolecular reaction is favored over bimolecular attack of water or hydroxide ion (pH < 12) at the carbonyl group.

The hydrolysis reaction is pH independent to nearly pH 12. The first indication of OH^- catalysis appears at pH 11.95. Therefore, an upper limit on a second-order rate constant for hydroxide-ion catalysis is $\sim 0.2\ M^{-1}\ s^{-1}$ at 20 °C. This is considerably less than has been found previously in acylal hydrolysis; γ-ethoxy-γ-butyrolactone has $k_{OH} = 5.0\ M^{-1}\ s^{-1}$ and $k_0 = 3.4 \times 10^{-4}\ s^{-1}$ at 30 °C.[3] Although the unimolecular decomposition reaction of V is facilitated by the bicyclic structure, the hydroxide ion catalyzed reaction is retarded. This is very probably due to a steric effect. Perpendicular attack of OH^- at the carbonyl group would be markedly hindered on one side by the axial hydrogen of C-3. There would also be a steric interaction of a tetrahedral intermediate oxygen with that hydrogen. Likewise, hydronium ion catalyzed hydrolysis is not observed at pH > 1.1, in contrast with other acylals.[3,5]

A possible mechanism of action for the glycosidase enzyme lysozyme involves intracomplex general-acid catalysis by Glu-35 and electrostatic stabilization of the developing oxocarbonium ion by Asp-52 (IV).[13,14] Large electrostatic stabilization effects of that type would require a reasonably close approach of the charges. However, the formation of a full covalent bond between Asp-52 and the reaction center to give an acylal intermediate (VIII) was considered



VIII

unlikely because the distance between C-1 and the oxygen atoms of the Asp-52 carboxyl group, as revealed by X-ray crystallographic analysis at 2-Å resolution,[28] is greater than the covalent bond distance. A conformational change of the enzyme could allow C–O bond formation, but would presumably be energy requiring. Thus, the intermediate VIII would have the characteristics and reactivity of a cyclic acylal and should be strained. The formation of a strained acylal intermediate (VIII) might occur if nucleophilic or electrostatic stabilization of the developing oxocarbonium ion is highly effective in enhancing the glycoside cleavage reaction when the leaving group is poor.[29] The present work shows that indeed such an acylal should break down like an acetal with formation of an oxocarbonium ion.[5]

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(28) Vernon, C. A. *Proc. R. Soc. London, B* **1967**, *167*, 389.

(29) It should be noted, however, that only small rate enhancements due to electrostatic stabilization effects (100–860-fold) have been observed in acetal hydrolysis reactions, even in very favorable cases,[12,30] and the introduction of strain would reduce the stabilization effect greatly.[18]

(30) Cherian, X. M.; Van Arman, S. A.; Czarnik, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 6566.