1332 (SO_2), 1170 (SO_2), 1094 cm^{-1} (C–O); ^1H NMR δ 3.18 (s, MeO), 4.51 (d, J = 4.1 Hz, CHOR), 4.55 (dd, J_{HCCH} = 4.1 Hz, J_{HCNH} = 8.5 Hz, CHN), 5.77 (d, J = 8.5 Hz, NH), 6.70–6.75 (m, 2 ortho H of Ph), 6.77–6.84 (m, 2 ortho H of Ph), 6.89–7.08 (m, 3 aromatic H, 7.09–7.29 (m, 5 aromatic H), 7.31–7.41 (m, 1 aromatic H), 7.54–7.62 (m 2 ortho H of $PhSO_2$). Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.76; N, 3.81. Found: C, 68.53; H, 5.84; N, 4.08.

***threo*-N-(2-Ethoxy-1,2-diphenylethyl)benzenesulfonamide (*threo*-4b)**: mp 93–95 °C; IR 3300 (NH), 1329 (SO_2), 1166 (SO_2), 1093 (C–O), 1076 cm^{-1} (C–O); ^1H NMR: δ NMR: δ 1.13 (t, J = 7.0 Hz, OCMe), 3.23 (m_c, 1 H of OCH_2), 3.36 (m_c, 1 H of OCH_2), 4.27 (d, J = 6.6 Hz, C*H*OR), 4.35 (dd, J_{HCCH} = 6.6 Hz, J_{HCNH} = 3.8 Hz, CHN), 5.74 (d, J = 3.7 Hz, NH), 6.93–7.27 (m, 12 aromatic H), 7.34–7.44 (m, 1 aromatic H), 7.45–7.51 (m, 2 ortho H of $PhSO_2$). Anal. Calcd for $C_{22}H_{23}NO_3S$: C, 69.26; H, 6.08; H, 3.67. Found: C, 69.02; H, 6.26; N, 3.23.

***erythro*-N-(2-Ethoxy-1,2-diphenylethyl)benzenesulfonamide (*erythro*-4b)**: mp 113–115 °C; IR 3290 (NH), 1327 (SO_2), 1168 (SO_2), 1092 (C–O), 1077 cm^{-1} (C–O); ^1H NMR δ 1.14 (t, J = 7.0 Hz, OCMe), 3.23 (m_c, 1 H of OCH_2), 3.39 (m_c, 1 H of OCH_2), 4.53 (dd, J_{HCCH} = 4.0 Hz, J_{HCNH} = 8.7 Hz, CHN), 4.62 (d, J = 4.0 Hz, CHOR), 5.63 (d, J = 8.8 Hz, NH), 6.72–6.79 (m, 2 ortho H of Ph), 6.79–6.86 (m, 2 ortho H of Ph), 6.90–7.31 (m, 8 aromatic H), 7.32–7.42 (m, 1 aromatic H), 7.56–7.63 (m, 2 ortho H of $PhSO_2$). Anal. Calcd for $C_{22}H_{23}NO_3S$: C, 69.26; H, 6.08; N, 3.67. Found: C, 69.24; H, 6.14; N, 3.63.

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Registry No. *cis*-1, 1689-71-0; *trans*-1, 1439-07-2; *cis*-2, 110143-77-6; *trans*-2, 110143-78-7; *threo*-3a, 42746-79-2; *erythro*-3a, 6941-71-5; *threo*-4a, 110143-79-8; *erythro*-4a, 110143-80-1; *threo*-4b, 110143-81-2; *erythro*-4b, 110143-82-3.

Micellar Catalysis of Organic Reactions. 20.† Kinetic Studies of the Hydrolysis of Aspirin Derivatives in Micelles

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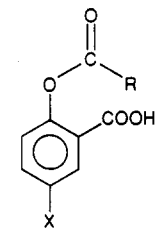
Introduction

The hydrolysis of 2-(acetyloxy)benzoic acid (aspirin) (1) has been studied extensively because of its pharmaceutical importance and also because of its chemical interest.[1] The pH–rate profile[2] shows a plateau between pH 5 and 9, and above pH 9 the rate increases as the pH is increased. In the plateau region, it has been concluded that the mechanism of reaction involves intramolecular general base catalysis by the ionized carboxy group.[1] At higher pH (>9), hydrolysis by the normal $B_{AC}2$ mechanism (hydroxide attack at the carbonyl carbon of the ester) is observed.

Most of the previous studies of aspirin hydrolysis have been carried out in aqueous solution, although this is possibly not the most appropriate medium from which to draw conclusions regarding the stability of aspirin in biological systems. Studies in the presence of biological membranes would be of considerably more relevance. Micelles have long been recognized to be simplistic models of biological membranes.[3,4] Thus, it follows that a study of the hydrolysis in the presence of micelles may be a better model than studies in water from which to draw conclusions concerning the stability of aspirin in biological systems.

Previous work[5] on the hydrolysis of aspirin has shown that in the presence of micelles of cetyltrimethylammonium bromide (CTAB), intramolecular general base catalysis at pH 6–8 is less efficient than in water, whereas the normal $B_{AC}2$ hydrolysis (at pH >9) is slightly catalyzed. Computer simulation[6] of the variation of the observed rate of reaction (k_ψ) with surfactant concentration at pH 12, however, has shown that for the best fit the second-order rate constant in the micellar pseudophase (k_2^m) is approximately 100 times smaller than that for reaction in water. The slight observed catalysis is due to concentration of the substrate within the micellar pseudophase for which the binding constant, K_s, is 190–340 M^{-1}, depending on the hydroxide concentration. It was also found that the second-ordder rate constant (k_2^m) calculated from computer simulation varied with hydroxide concentration (k_2^m) = 0.09 – 0.147 M^{-1} m^{-1}). Constant values of K_s and k_2^m, independent of hydroxide concentration, were obtained by a more recent iterative calcualtion method[7] in which the value of β, the fraction of micellar head groups neutralized, was allowed to vary with the hydroxide and surfactant concentrations.

One of the important factors for reactions in micelles is the orientation of the substrate molecule in the micellar pseudophase and the resultant location of the reaction center. For this reason, we chose to study the hydrolysis of some derivatives (2, 3) of aspirin (1) containing hydrophobic chains.



1, X = H; R = CH_3
2, X = H; R = C_7H_{15}
3, X = C_8H_{17}; R = CH_3

It was hoped that the orientation of the substrate in the micelle would vary as the site of the hydrophobic chain was varied and the effect of this on the kinetics of hydrolysis has been studied. Some support for the conclusions based on the kinetic results has been obtained from NMR studies[8] and the observation of viscoelasticity in some systems.[9]

Results and Discussion

Reaction in Basic Solution (pH 12.0). Weak catalysis was observed for all compounds ranging from 2.2 (compound 2) to 6.3 (compound 3). In all cases, the rate–[CTAB] profile exhibited a maximum corresponding to complete solubilization of the substrate in the micellar

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Table I. Estimated Micellar Parameters[a] for the Basic Hydrolysis (pH 12.00) of Compounds 1-3 at 56.4 °C

substr	cat.[b]	K_s, M^{-1}	k_2^w, M^{-1} s^{-1}	k_2^m, M^{-1} s^{-1}
1	3.3	360	0.809	0.0127 (64)[c]
2	2.2	1715	0.297	0.0020 (149)[c]
3	6.3	2085	0.578	0.0115 (50)[c]

[a] Using $K_{Br}^{OH} = 2$; $\beta = 0.8$; cmc 3×10^{-4} M. [b] Ratio of optimum rate in presence of CTAB to rate in water. [c] Value in parentheses is the ratio of the rate in water to the calculated rate within the micellar pseudophase (k_2^w/k_2^m).

pseudophase. The concentration of CTAB required to achieve maximum rate varied between 1 and 4 mM, depending on the hydrophobicity of the substrates. The kinetic data for these reactions were subjected to a computer simulation using the method of Rodenas and Vera[10] to determine the best values of K_s, k_{Br}^{OH}, and k_2^m. These results are in Table I.

$[X]_w$ and $[X]_m$ refer to the concentrations of the ion X^- in the aqueous phase and in the micellar pseudophase, respectively, relative to the total volume of solution, so that

$$[X] = [X]_m + [X]_w$$

m_x is the fraction of X^- counterions relative to the total number of micellar CTA^+ ions. Since, if the surfactant concentration is sufficient for micelles to form, $[CTA]_w$ = cmc,

$$[CTA]_m = [CTA] - \text{cmc}$$

$$\text{and } [X]_m = m_X[CTA]_m$$

In the CTAB systems

$$k_2 = \frac{k_w + (k_m K_s - k_w) m_{OH}[CTA]_m/[OH]}{1 + K_s[CTA]_m} \quad (1)$$

where m_{OH} can be obtained from

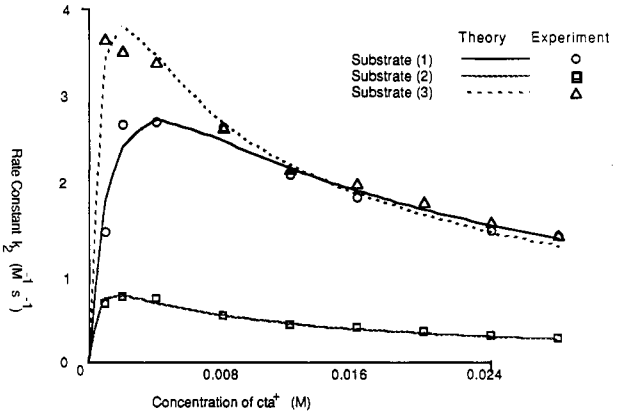
$$m_{OH}^2(K_{Br}^{OH} - 1)[CTA]_m + m_{OH}[[OH] + K_{Br}^{OH}[Br] - \beta(K_{Br}^{OH} - 1)[CTA]_m] - \beta[OH] = 0 \quad (2)$$

$K_{Br}^{OH} = ([Br]_w[OH]_m)/([OH]_w[Br]_m)$ is the phase distribution equilibrium constant, $K_s = [S]_m/([S]_w[CTA]_m)$ is the substrate–micelle binding constant, k_w is the second-order rate constant for the reaction in the aqueous phase, and k_m is the rate constant for the reaction in the micellar phase, given by

$$\text{rate} = k_m \frac{[S]_m[OH]_m}{[CTA]_m}$$

The variation of observed rate with detergent concentration for compounds 1–3 is shown in Figure 1. The solid lines represent calculated values of k_2 using the parameters listed in Table I and eq 1 and 2. In line with previous reported results,[11] a unique set of parameters was not achieved, since the values of K_{Br}^{OH} and k_2^m are compensatory and a good fit could be obtained with a number of combinations of these parameters. Rodenas and Vera[6] have previously studied the basic hydrolysis of compound 1 and they used $K_{Br}^{OH} = 2$. Although we have worked at a higer temperature than Rodenas and Vera, we too used $K_{Br}^{OH} = 2$ for all compounds and observed a better fit for this value of the exchange constant than with the more normal value of 20.

In our calculations we have used 3×10^{-4} M for the cmc (critical micelle concentration) of CTAB. Bunton has reported[12] that the cmc of CTAB is reduced in the presence of NaOH. A much better fit of experimental data to the calculated data was obtained by using this value for the cmc rather than 9×10^{-4} M as is commonly assumed.[7,10]



Basic hydrolysis of aspirin derivatives in CTAB solutions.

Figure 1. Variation of the second-order rate constants, k_2, with CTA concentration for substrates 1–3. The curves are predicted from the parameters in Table I and eq 1 and 2.

Table II. Derived Kinetic Data (at 0 and 2 mM CTAB) for the Intramolecular General Base Catalyzed Hydrolysis of Compounds 1-3 at pH 7.25 in the Presence of CTAB and in Water

	E_a, kJ mol^{-1}		ΔS^*, J mol^{-1} K^{-1}		SIE[a]	
compd	0	2	0	2	0	2
1[b]	71 ± 2.6	77.8 ± 2.3	−118 ± 7	−103 ± 7	2.4	2.4
2	73.2 ± 2	78.8 ± 2.1	−115 ± 6	−104 ± 6.5	1.9	2.6
3	72.6 ± 1.7	95.1 ± 1.7	−113 ± 5	−52 ± 5	3.1	2.1

[a] Solvent isotope effect, i.e., k_{H_2O}/k_{D_2O}. [b] Results for compound 1 from ref 5, 4 mM CTAB, pH 6.

The rate constant for reaction within the micelle, k_2^m, was insensitive to the value of the cmc, but the binding constant, K_s, was greatly affected. Unreasonably high values of K_s (6000 and 18 500) were obtained for the hydrophobic substrates 2 and 3 by using cmc = 9×10^{-4} M, whereas the values obtained using cmc = 3×10^{-4} M were more reasonable (Table I).

In all cases, the rate constant for reaction within the micellar pseudophase is considerably smaller than that for reaction in water. The observed catlysis is due mainly to concentration of the substrate within the micellar pseudophase as shown by the magnitude of the binding constant (K_s). The reaction of compound 2 is noteworthy because at 0.01 M NaOH at high CTAB concentrations (>24 mM) and at 0.05 M NaOH at 2 mM CTAB, the observed rate is actually slower than that for the reaction in water at the same hydroxide concentration. This presumably is a manifestation of the larger k_2^w/k_2^m rate ratio for this compound.

For the other compounds, catalysis is observed for all hydroxide and CTAB concentrations studied.

Reaction at pH 6–8. For both compounds, the plateau region of the pH–rate profile has been reached in phosphate buffered solution between pH 6–8 and the reaction at this point is slower in the presence of CTAB than in water. Above pH 9, the rate of reaction increased due to the incursion of the B_{AC}^2 mechanism.

Derived kinetic data (solvent isotope effects and activation parameters) for the hydrolysis of compounds 1–3 are in Table II. It can be seen that the slower hydrolysis of compounds 1–3 at pH 6–8 in the presence of CTAB is due to an increase in the energy of activation which outweighs a favorable change in the entropy of activation.

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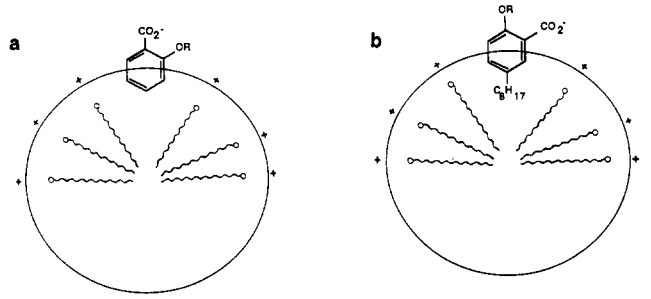

Figure 2. Schematic representation of the orientation of (a) substrates 1 (R = $COCH_3$) and 2 (R = COC_7H_{15}) and (b) substrate 3 (R = $COCH_3$) solubilized by a CTAB micelle.

As for aspirin itself, the mechanism occurring in the plateau region of the pH–rate profiles for compounds 2 and 3 is most likely to be intramolecular general base catalysis by the ionized carboxylate group. This is indicated by the solvent isotope effects (Table II) (k_{H_2O}/k_{D_2O} = 1.9 to 3.1), which confirm the involvement of a water molecule in the rate-determining transition state. Reaction involving intramolecular nucleophilic catalysis would require a solvent isotope effect of unity.[1] These results do not exclude the possibility of concurrent reactions by intramolecular general base catalysis and intramolecular nucleophilic catalysis.[13] However, the substantial negative values of the entropy of activation (Table II) is further evidence of intramolecular general base catalysis which is a bimolecular process. Intramolecular nucleophilic catalysis is a unimolecular process which would be characterized by a much more favorable entropy of activation.[14]

Activation Parameters at pH 7.25. Activation parameters for the hydrolyses of compounds 1–3 in water are identical within experimental error (Table II). In micelles of CTAB, the activation parameters for the hydrolyses of 1 and 2 are identical and similar to those for reaction in water. However, for the hydrolysis of 3 a large change in both the activation energy (ΔE_a = 22 kJ mol^{-1}) and in the entropy of activation ($\Delta\Delta S^{\ddagger}$ = 61 J mol^{-1} deg^{-1}) was observed in the presence of CTAB.

This suggests the possibility of a different alignment in micelles of CTAB for compound 3 than for either of compounds 1 or 2.

NMR studies of sodium salicylate in water and in micelles of CTAB[8] have indicated that the 3-, 4-, and 5-H aromatic resonances shift to lower δ values in the presence of CTAB, while that of the 6-H is much less shifted. This indicates that the 3-, 4-, and 5-H aromatic protons are in a more nonpolar environment in the presence of CTAB than in water, while the 6-H is not affected. Thus, the CO_2^- group projects radially outward from the micelle water interface (Figure 2a, R = H). Similar studies[8] for *m*-hydroxybenzoate ions indicate that the CO_2^- group is tilted toward the micellar surface in which it is embedded. We have carried out a similar study for the aspirin anion and the shifts of the 3-, 4-, and 5-H aromatic resonances to lower δ values and the 6-H aromatic resonance to a slightly higher δ value (Figure S1) in micelles of CTAB indicate a similar alignment to that for salicylate ion. Thus, we suggest that the CO_2^- group of aspirin is radially aligned away from the micellar surface (Figure 2a, R = $COCH_3$). The observation of viscoelasticity for solutions of salicylate ions in micelles of CTAB has been interpreted as being due to the formation of micellar chains. The formation of micellar chains linked through carboxylate ions is most reasonable if the CO_2^- groups are radially aligned away from the micellar surface. If the CO_2^- is tilted toward the micelle surface, it seems that the formation of micelle chains is less likely.[8,9] Viscoelasticity is not observed for solutions of *m*-hydroxybenzoate ions in CTAB. We have observed viscoelasticity for solutions of salicylate ions in CTAB but not for either aspirin or 5-octylsalicylate ions in CTAB. In the case of aspirin, this result can be explained by steric hindrance by the acetyloxy group restricting the formation of micelle chains, although the CO_2^- group is aligned in the required way according to NMR studies. In the case of 5-octylsalicylate, no steric hindrance is present (Figure 2b, R = H), and we thus conclude that the absence of micellar chains and hence viscoelasticity is because the CO_2^- group is tilted toward the micelle surface as for *m*-hydroxybenzoate (Figure 2b, R = $COCH_3$). The anchoring effect of the 5-*n*-octyl chain is presumably sufficient to align the hydroxy group radially away from the micelle surface and to tilt the CO_2^- group toward the micelle surface. Because of the similar kinetic results obtained for compounds 1 and 2, we propose that the CO_2^- groups of these compounds are aligned similarly. Since the CO_2^- group of 1 is aligned radially away from the micelle surface (NMR evidence), we conclude that the alignment of the CO_2^- group of 2 is similar (Figure 2a, R = COC_7H_{15}).

Since NMR studies indicate similar alignment of the CO_2^- groups of aspirin (1) and salicylate, we conclude that the alignment of the CO_2^- groups of 5-octylsalicylate and compound 3 are similar. Furthermore, since viscoelasticity is not observed for solutions of 5-octlsalicylate or compound 3 in CTAB, we conclude that the CO_2^- group of this compound and hence of 3 are tilted toward the micelle surface (Figure 2b).

The CO_2^- groups of compounds 1 and 2, which are aligned radially away from the micelle–water surface, are in close contact with water on all sides and are thus ideally situated for intramolecular general base catalyzed hydrolysis of the adjacent ester group. For compound 3, the CO_2^- group is tilted toward the micelle surface and is thus not as exposed to water molecules on all sides as that of compounds 1 and 2. Thus, intramolecular general base catalyzed hydrolysis of the adjacent ester group in compound 3 is not as favorable. Furthermore, the closer proximity of the anionic CO_2^- group in compound 3 and the positively charged micellar surface would most likely retard the action of the CO_2^- group as a general base catalyst for electrostatic reasons. Thus, the activation parameters for hydrolysis of compound 3 at pH 7.25 show a larger energy of activation and a less unfavorable entropy of activation than those for either compound 1 or 2.

In basic solution, the site of the reaction center, the carbonyl group of the ester, is of more direct importance than the alignment of the CO_2^- group. For reaction to occur, hydroxide ion must attack the carbonyl group and hence the more buried this group is in to the micelle the slower the reaction. This may explain the larger k_2^w/k_2^m value for compound 2. The CO_2^- group is aligned radially and hence the ester group is tilted toward the micelle surface (Figure 2a). Furthermore, the hydrophobic chain attached to the carbonyl group of 2 may tend to anchor it in the micellar surface to a greater extent than for the other compounds. Thus, attack of hydroxide ion is less favorable, resulting in a larger k_2^w/k_2^m rate ratio.

For compound 1, the less hydrophobic methyl group would not anchor the reaction center as effectively in the micellar surface and for compound 3 the CO_2^- group is

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tilted toward the micelle surface so that the ester group is radially aligned (Figure 2b) and hence more accessible to hydroxide ions.

Experimental Section

Materials. 2-(Octanoyloxy)benzoic acid (**2**), mp 83.5–85 °C (EtOH) (lit.[15] mp 81 °C), was prepared by the acylation of salicylic acid (octanoyl chloride/pyridine in benzene, 2 h at room temperature).

5-1′-Octylsalicylic acid, mp 71–72 °C (lit.[16] mp 72–73 °C), was prepared[16] from methyl salicylate by acylation (octanoyl chloride, $AlCl_3$, CS_2), hydrolysis (OH^-/H_2O), and Clemmensen reduction (ZnHg, HCl). Acetylation (Ac_2O/H^+) gave compound **3**, mp 91–92 °C; found C, 70.0; H, 8.0; $C_{17}H_{24}O_4$ requires C, 69.9; H, 8.2.

2-(Acetyloxy)benzoic acid (**1**) was prepared by the acetylation (Ac_2O/H^+) of salicylic acid.[5] Cetyltrimethylammonium bromide was purified by the method of Mukerjee and Mysels.[17] Distilled water was further purified by using a Millipore system.

Solutions of CTAOH were prepared as described previously.[18]

Kinetic Studies. Stock solutions of substrates (0.01 M in dioxan), CTAB (0.02 M in water), and sodium hydroxide were prepared. Borate buffers (pH 8–10) were prepared from sodium tetraborate solution by the addition of the required amounts of either 0.1 M HCl or 0.1 M NaOH.[19] Phosphate buffers (pH 6–8) were prepared from Analar potassium dihydrogen phosphate by adding the required volume of 0.1 M NaOH.[19] The pH of the solutions was measured at room temperature with a combination electrode and a Radiometer pHM 80 portable pH meter. It has previously been shown[20] that the pH of phosphate buffer varies by less than 0.1 pH unit between 23 and 56 °C. The pH of borate buffer is 0.2 pH unit lower at 56 °C than at 23 °C.

The rate measurements were carried out as described previously,[21] following the absorbance at 297 nm for compound **2** and 303 nm for compound **3**.

NMR spectra of aspirin (8 mM) in D_2O and in the presence of CTAB (10 mM) were determined on a JEOL 200-MHz spectrometer.

Viscoelasticity was detected by either swirling the solution and visually observing the recoil of air bubbles trapped in the solution after swirling was stopped[9] or by the absence of a vortex in a rapidly stirred solution. Solutions for these tests were prepared by using equal amounts of CTAOH and substrate (e.g., salicylic acid) to produce a CTA salicylate solution (12 mM).[9]

Solvent Isotope Studies. All the stock solutions (buffers, CTAB) were prepared in D_2O (Australian Atomic Energy Commission) and the substrates were dissolved in dioxane. The reaction mixtures were prepared as for the normal (H_2O) measurements, except that all dilutions were done with D_2O.

Acknowledgment. We gratefully acknowledge the assistance of Aldo Lentini in obtaining the NMR spectra.

Registry No. **1**, 50-78-2; **2**, 70424-62-3; **3**, 95772-48-8; CTAOH, 505-86-2; CTAb, 57-09-0; salicylic acid, 69-72-7; octanoyl chloride, 111-64-8; methyl salicylate, 119-36-8; 5-(1-octyl)salicylic acid, 28488-49-5.

Supplementary Material Available: Observed second-order rate constants for the hydrolysis of compounds **1–3** at pH 12 in water and in the presence of micelles of CTAB (1–28 mM) (Table S1), observed first-order rate constants for the hydrolysis of compounds **2** and **3** in the pH range 6–13 in water and in 2 mM CTAB (Table S2), and ^1H NMR spectra of the aromatic region of substrate **1**: (a) in D_2O; (b) in CTAB (10 mM) (Figure S1) (3 pages). Ordering information is given on any current masthead page.

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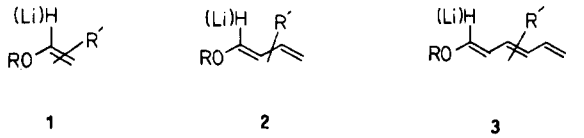
Communications

Stereoselective Synthesis and α-Lithiation of 1-Alkoxy Polyenes

Summary: 4-Alkyl-1,4-dialkoxy-*cis*-2-butenes undergo a regio- and stereoselective base-catalyzed 1,4-elimination to yield all-trans 1-alkoxy dienes and trienes. These dienes and trienes are successfully lithiated α to oxygen when the alkoxy substituent is OCH_2OCH_3 (O-MOM).

Sir: While the α-lithiation of simple enol ethers **1** has enjoyed extensive use in organic synthesis,[1] the corresponding lithiations of dienyl ethers **2** has received less attention[2] and the α-lithiation of trienyl ethers **3** is unknown. In the course of our studies on the directed β-lithiation of certain methoxymethyl (R = CH_2OCH_3 (MOM)) enol ethers,[3] we noted that the MOM group facilitated the α-lithiation of the parent enol ether **1** (R = CH_2OCH_3, R′ = H).[4,5] In an effort to exploit the directing influence of the MOM group, we sought to explore the α-metalation of substituted 1-alkoxy dienes **2** (R = MOM, R′ = alkyl) and alkoxy trienes **3** (R = MOM, R′ = alkyl). In this paper we wish to report the successful deprotonation of these systems, one of which is dependent on the presence of the MOM group, as well as an efficient, ste-



1 **2** **3**

(1) For some recent reviews, see: (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997. (b) Gschwend, H. W.; Rodriquez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(2) (a) Baldwin, J. E.; Hofle, G.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125. (b) Everhardus, R. H.; Grafing, R.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 69. (c) Soderquist, J. A.; Hassner, A. *J. Am. Chem. Soc.* **1980**, *102*, 1577.
(3) (a) McDougal, P. G.; Rico, J. G. *Tetrahedron Lett.* **1984**, *25*, 5977. (b) McDougal, P. G.; Rico, J. G.; Vanderveer, D. G. *J. Org. Chem.* **1986**, *51*, 4492.
(4) Another acetal, the THP group, has been used to direct the α-lithiation of a simple enol ether, see: Hartmann, J.; Stahle, M.; Schlosser, M. *Synthesis* **1974**, 888.
(5) The MOM group has found use in directing the metalations of arenes, see: Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031. It is thought that the additional oxygen of the MOM acetal **1** (R = CH_2OCH_3) aids in the prior complexation of the alkylithium base.

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