Solvent-Induced Change in the Rate-Limiting Step of Acylal Hydrolysis

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Benzaldehyde methyl hemiacetal is an intermediate in the acid-catalyzed hydrolysis of α-methoxybenzyl esters (acylals, eq 1) and also in that of benzaldehyde dimethyl

$$\underset{\text{OCOR}}{\text{PhCH(α)OCH}_3} + H_2O \xrightarrow[-\text{RCOOH}]{\text{HA}} \underset{\text{OH}}{\text{PhCH(α)OCH}_3} \xrightarrow{\text{HA}} \text{PhCHO} + CH_3OH \quad (1)$$

acetal. It is generally believed that formation of the hemiacetal in these reactions is rate-determining and that its subsequent decomposition is fast.[1,2] There are, however, known examples of acylal and acetal hydrolysis in which decomposition of the hemiacetal intermediate is either slower than its formation[3-5] or where the steps occur at comparable rates.[6-8]

In order to learn more about the relative velocities and the effect of solvent on the two steps of the reaction in eq 1, the rates of hydrolysis of α-methoxybenzyl formate, acetate, and propionate in succinic acid buffer solutions were measured in H_2O and H_2O–DMSO mixtures. In these hydrolytic reactions all substrates form the same hemiacetal intermediate.

Experimental Section

Materials. Benzaldehyde dimethyl acetal was synthesized conventionally from the purified reagents.[9] α-Chlorobenzyl methyl ether was prepared by treating benzaldehyde dimethyl acetal with freshly distilled acetyl chloride and thionyl chloride under nitrogen.[10,11] The extent of conversion of the acetal into chloride was checked by ^1H NMR spectroscopy; the signal of the α-proton of the acetal was at δ 5.33 and that of the chloride at δ 6.33. α-Methoxybenzyl esters were prepared as 1-alkoxyalkyl esters previously[12] from the α-chloro ether and sodium salts of the appropriate carboxylic acids. The products were identified by ^1H and ^{13}C NMR spectroscopy. The boiling points and ^1H and ^{13}C NMR chemical shift data are shown in Table I.

Succinic acid buffer solutions, 0.01 mol dm^{-3} of NaHSuc and Na_2Suc, were prepared from succinic acid (Merck, p.a.) and sodium hydroxide (Merck, p.a.).

Dimethyl sulfoxide (Baker, p.a.) for the solvent mixtures was distilled from calcium hydride at reduced pressure, bp 66 °C/10 mmHg.

Deuterium oxide (Merck, 99.75%) and dimethyl sulfoxide-d_6 (Aldrich, 99.9 atom %) were used as received.

Kinetics. Rate measurements were made spectroscopically with Cary 17D UV and JEOL 400-MHz NMR spectrometers at 15 °C. UV spectroscopy was used to monitor the appearance of benzaldehyde absorbance at 248 nm. ^1H NMR spectroscopy was used to measure the hemiacetal concentration and the rate of decomposition of the starting material as well. The substrate concentration was ca. 1–2% in the NMR method but, because of the strong benzaldehyde absorption, only 0.01–0.02% in the UV measurements.

First-order rate constants were determined from the semilogarithmic plots of $(A_\infty - A_t)$ against time.

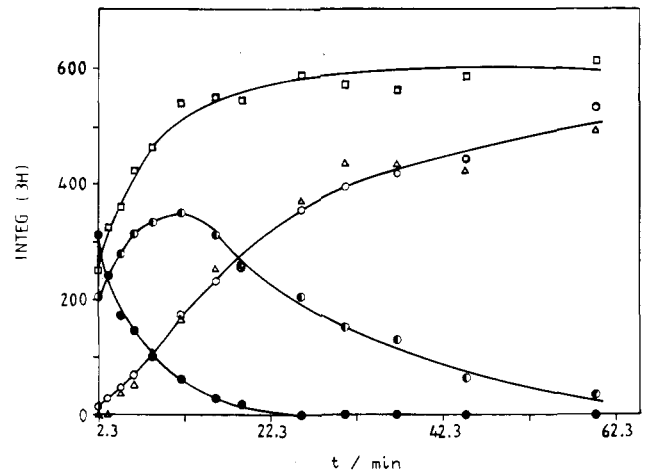

Figure 1. Progress of the decomposition of α-methoxybenzyl propionate in succinate buffer solution (X(DMSO) = 0.2, 15 °C) as described by the proton integrals (3 H or 3 × 1 H) of the reaction species as a function of time: (A) $PhCH(OCH_3)OCOC_2H_5$ (●); (B) $PhCH(OCH_3)OH$ (◐); (C) CH_3OH (○), PhCHO (△), C_2H_5COOH (□).

Results and Discussion

α-Methoxybenzyl formate, acetate, and propionate decompose in the acid-catalyzed hydrolysis through a common hemiacetal intermediate. The rates of formation of the product (Table II) obeyed first-order kinetics and were identical for all the studied acylals at low content of DMSO. This indicates rate-limiting decomposition of the benzaldehyde methyl hemiacetal. When the mole fraction of DMSO was increased to 0.2 for acetate and propionate and 0.3 for formate derivative, first-order kinetics was no longer obeyed. Further increases of DMSO made the reactions of the acetate and propionate derivatives follow again first-order kinetics, the rates differing now from each other.

For more insight into the decomposition of these acylals, the reactions were followed in the succinic acid buffer solution, where X(DMSO) was 0.2, also by ^1H NMR spectroscopy. The chemical shifts of the α-protons of the starting materials were δ 6.60–6.70 downfield from the internal tetramethylsilane, TMS (Table I). Approximately 2 min after the dissolution, a signal corresponding to the α-proton of the hemiacetal was seen at 5.54 ppm. The above shift values are in a good agreement with those reported by Capon[3] (δ 6.48 and 5.44 ppm, respectively) for α-methoxybenzyl acetate and its hemiacetal in acetic acid buffer solution. The progress of the hydrolytic decomposition of α-methoxybenzyl propionate in a succinate buffer solution against time is shown in Figure 1.

The integrals of the proton signals can be considered as equivalent to the concentrations of the reaction species. The concentration of the starting material (A) decreases exponentially and the concentration of the hemiacetal (B) reaches a maximum and then decreases. The concentrations of the products (C), methanol and benzaldehyde, increase slowly at first but that of propionic acid rises rapidly and approaches its maximum, i.e., its final concentration, at the same time as the concentration of the hemiacetal. Toward the end of the reaction all product concentrations approach to the initial concentration of the starting material. This is a typical example of the two-step

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Table I. Boiling Points and ^1H and ^{13}C NMR Chemical Shift Data of the Prepared Acylals, $PhCH(OCH_3)OCOR$

		^1H NMR chemical shifts (δ/ppm) in DMSO					
R	bp/°C (p/mmHg)	OCOR	Ph	CH	OMe	OCOMe	$OCOCH_2CH_3$
H	108–110 (15)	8.46	7.40	6.71	3.47		
Me	93–94 (5)		7.40	6.61	3.46	2.12	
Et	127–128 (17)		7.40	6.62	3.45		2.44, 1.07

	^{13}C NMR chemical shifts (δ/ppm) in $CDCl_3$					
R	OCOR	Ph	CH	OMe	OCOMe	$OCOCH_2CH_3$
H	160.6	136.7, 129.5 128.6, 126.4	98.6	56.7		
Me	170.7	137.3, 129.2 128.5, 126.3	98.5	56.45	21.2	
Et	174.1	137.5, 129.1 128.5, 126.3	98.3	56.4		27.8, 9.0

Table II. Rate Constants for the Formation of Benzaldehyde in the Hydrolytic Decomposition of Acylals, $PhCH(OCH_3)OCOR$, in Succinic Acid Buffer Solution at 15 °C. UV Spectroscopic Method

	k(obs)/10^{-3} s^{-1} at X(DMSO) =			
R	0	0.1	0.2	0.3
H	11.06	5.77	3.75	[a]
	10.43	5.74	3.56	
Me	11.41	5.81	[a]	0.342
	10.86	5.69		0.333
Et	10.32	5.59	[a]	0.153
	10.49	5.42		0.157

[a] ln ($A_\infty - A_t$) vs t curved.

Table III. Rate Constants for the Hydrolytic Decomposition of Acylals, $PhCH(OCH_3)OCOR$, in Deuteriated Succinic Acid Buffer Solution, X(DMSO) = 0.2, 15 °C. ^1H NMR Method

R	$k_1/10^{-3}$ s^{-1}	$k_2/10^{-3}$ s^{-1}
H		1.04[a]
Me	7.89	1.24
Et	3.07	0.945

[a] Measured by the UV spectroscopic method

reaction A + B → C, where both steps are first order and irreversible.[13] The rate constants k_1 and k_2 can be solved from eq 2 and 3 and are presented in Table III.

$$[B]_t = [A]_0 \frac{k_1}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t}) \quad (2)$$

$$[C]_t = [A]_0 - [A]_t - [B]_t = [A]_0\left[1 - e^{-k_1 t} - \frac{k_1}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t})\right] \quad (3)$$

So, two consecutive reactions, formation of hemiacetal and its decomposition, were found by NMR spectroscopic methods to be operative. The rate constant for the formation of benzaldehyde measured by the UV spectroscopic method is in agreement with the other k_2 values, which are averages of several parallel determinations. The decompositions of α-methoxybenzyl acetate and formate occur faster than that of the propionate because of the better leaving groups since the order of decomposition rates depends on the acidity of the carboxylic acid formed. Two minutes after dissolution no formate and only small acetate signals can be seen in the ^1H NMR spectra while carboxylic acid signals had reached their maxima already.

Therefore, it is understandable, that the formation of benzaldehyde obeys first-order kinetics (Tables II and III) in the hydrolytic decomposition of α-methoxybenzyl formate and that the value of k_1 cannot be solved. In this case the k_2 values are determined from the semilogaritmic plots of ($I_\infty - I_t$) or ($A_\infty - A_t$) against time.

Further increases of DMSO (mole fraction > 0.2) led to the observation of individual first-order kinetics for acetate and propionate derivatives. This indicates that the formation of the common intermediate with rates differing from each other had become the rate-limiting step.

Dimethyl sulfoxide as a solvent has a decisive effect on the relative velocities of the two-step acylal hydrolysis reaction in the succinate buffer conditions. It slows down the specific oxonium ion catalyzed formation more than the general acid catalyzed decomposition of the benzaldehyde methyl hemiacetal as could be expected in light of the effect of DMSO on the buffer equilibria.

A solvent-induced change in the rate-limiting step has also been postulated by Young[14] in the hydrolysis of benzaldehyde dimethyl acetal in pure water and water–dioxane solvent mixtures. It was shown that as the concentration of dioxane is increased, the rate of the acetal hydrolysis decreases faster than that of the hemiacetal hydrolysis, causing the change in the rate-limiting step.

Registry No. α-Methoxybenzyl formate, 119012-14-5; α-methoxybenzyl acetate, 51835-45-1; α-methoxybenzyl propionate, 119012-15-6; benzaldehyde methyl hemiacetal, 55685-73-9.

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Metacyclophanes and Related Compounds. 23. Preparation of Fluorinated [2.2]Metacyclophanes[1]

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Although [2.2]metacyclophanes ([2.2]MCPs) having functional groups such as alkyl,[2] halomethyl,[3] alkoxy,[4] hydroxy,[5] formyl,[6] and fluorine[7] have been reported, there

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