Isotope Exchange Studies with Diethyl Acetals in Ethanol and Their Mechanistic Implications to Protolytic Reactions of Acetals and Vinyl Ethers

A. Kankaanperä, P. Salomaa,* P. Juhala, R. Aaltonen, and M. Mattsén

Contribution from the Department of Chemistry, University of Turku, Turku, Finland. *Received May 19, 1972*

Abstract: Rates of transacetalization of diethyl acetals in ethanol and those of formation of vinyl ethers from acetals have been measured using carbon-14 and tritium labeling. Combining the results with those obtained for the ethanolysis of vinyl ethers, complete free energy profiles could be depicted for the formation of vinyl ethers from acetals. These indicated that the relative free energy levels of the consecutive transition states depend greatly on the polarity of the aldehyde component. Mechanistic implications to the hydrolytic cleavage of acetals and vinyl ethers have been discussed.

As a result of a considerable body of kinetic studies, the main features of the hydrolyses of acetals and vinyl ethers are now well understood.[1-5] Both reactions proceed through similar oxo carbenium ions. Until quite recently, the formation of these ions from acetals was assumed to involve invariably a fast preequilibrium protonation, followed by rate-determining heterolysis of the protonated substrate. However, a number of cases are now known in which the proton transfer becomes the rate-determining stage.[5-15] Irrespective of the relative barrier heights of the protonation and heterolysis steps, the oxo carbenium ion is always produced at a rate which is the same as the overall rate of hydrolysis. In the hydrolysis of vinyl ethers, a similar oxo carbenium ion is also formed; proton transfer to the β position of the carbon–carbon double bond is the rate-determining stage. The simplified schemes for the above reactions are thus the following.

$$\mathrm{RCH_2CH(OR')_2} \xrightarrow{\mathrm{H^+}} \mathrm{RCH_2CH(OR')(\overset{+}{O}HR')} \xrightarrow{-\mathrm{R'OH}}$$

$$\mathrm{RCH_2CH{=}\overset{+}{O}R'} \xleftarrow{\mathrm{H^+}} \mathrm{RCH{=}CHOR'}$$

$$\Big\downarrow \mathrm{H_2O}$$

$$\mathrm{RCHO + R'OH + H^+}$$

In water solution, the oxo carbenium ion is rapidly decomposed to give an aldehyde and alcohol as the ultimate products. Thus the mutual interconversion of a vinyl ether and acetal through their common intermediate cannot be studied, and no detailed conclusions can be drawn about the effects of similar structural alterations on the solvolytic behavior of the two classes of compounds. In alcohol solution, however, this interconversion can be readily investigated by means of isotope labeling.

The primary aim of the present work was to elucidate the energetics of the overall reactions from acetals to vinyl ethers, and *vice versa*. Although some information on the relative barrier heights of acetal and vinyl ether hydrolysis was available from earlier studies,[16] more detailed kinetic data were required before any generalizations could be made. The experimental methods were the following. First, the relative basicities of the acetals were estimated by the ir-band shift method. Second, the transacetalization rates of diethyl acetals labeled with carbon-14 at the ethoxyl group were measured in ethanol. Third, detritiations of acetals labeled in the aldehyde methyl group (or substituted methyl group) were studied in the same solvent. Fourth, the rates of ethanolysis of the corresponding vinyl ethers were determined. Fifth, the equilibria between acetals and vinyl ethers were studied in dilute solutions in ethanol. Sixth, the rate of dedeuteration was measured for one of the acetals, in order to elucidate the influence of isotopic substitution. All the abovementioned experiments were extended over a wide range of temperatures.

Experimental Section

Vinyl Ethers. Ethyl vinyl ether (Fluka AG) was purified by distillation.

1-Chloro-2-ethoxyethene was prepared from 1-chloro-2,2-diethoxyethane (Schuchardt). At elevated temperatures and under acidic conditions this acetal decomposes to vinyl ether and alcohol. The acetal was added dropwise to tetraline containing dissolved *p*-toluenesulfonic acid as the catalyst. The reaction mixture was kept at 200°. The 1-chloro-2-ethoxyethene and ethanol formed were much more volatile than the acetal and could be easily removed by distillation. The distillate was collected into quinoline to prevent the reverse reaction, the back-formation of the acetal. The ethanol was then extracted from the distillate into water, and the residue was fractionated. The fraction boiling from 110 to 135° was collected for further purifications. As shown by its nmr spectrum, this fraction was a mixture of the cis and trans isomers of the vinyl ether. The pure isomers were isolated using a Perkin-Elmer F 21 preparative gas chromatograph. The purities of the isomers were controlled both by gas chromatography and nmr spectroscopy. The nmr spectra were recorded with a Perkin-Elmer

---

[1] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, pp 447–448.

[2] E. H. Cordes, *Progr. Phys. Chem.*, 4, 1 (1967).

[3] P. Salomaa, A. Kankaanperä, and M. Lajunen, *Acta Chem. Scand.*, 20, 1790 (1966).

[4] A. J. Kresge and Y. Chiang, *J. Chem. Soc. B*, 53, 58 (1967).

[5] T. H. Fife, *Accounts Chem. Res.*, 5, 264 (1972).

[6] T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, 90, 4081 (1968).

[7] A. Kankaanperä and M. Lahti, *Acta Chem. Scand.*, 23, 2465 (1969).

[8] E. Anderson and B. Capon, *Chem. Commun.*, 390 (1969).

[9] A. Kankaanperä and M. Lahti, *Acta Chem. Scand.*, 23, 3266 (1969).

[10] A. Kankaanperä, *Suom. Kemistilehti B*, 42, 460 (1969).

[11] E. Anderson and B. Capon, *J. Chem. Soc. B*, 1033 (1969).

[12] E. Anderson and T. H. Fife, *J. Amer. Chem. Soc.*, **91**, 7163 (1969).

[13] T. H. Fife and L. H. Brod, *ibid.*, **92**, 1681 (1970).

[14] E. Anderson and T. H. Fife, *ibid.*, **93**, 1701 (1971).

[15] M. Lahti and A. Kankaanperä, unpublished results for the hydrolysis of a number of unsymmetrical acetals.

[16] P. Salomaa and A. Kankaanperä, *Acta Chem. Scand.*, **20**, 1802 (1966).

R 10 spectrometer, in solutions in carbon tetrachloride with tetramethylsilane as the internal standard. Nmr spectra: the more volatile isomer, δ 1.26 (3 H, CH_3), 3.67 (2 H, CH_2), 5.31 (1 H, CH), and 6.50 ppm (1 H, CH); the less volatile isomer, δ 1.30 (3 H, CH_3), 3.85 (2 H, CH_2), 4.94 (1 H, CH), and 6.17 ppm (1 H, CH). The coupling constants for the hydrogens attached to the carbon–carbon double bond were 11.8 and 4.2 cps for the more and less volatile isomers, respectively. It has been shown previously that the more volatile isomer is the trans form, and the less volatile isomer the cis form.[17,18] The chemical shifts and the coupling constants for the hydrogen atoms attached to the carbon–carbon double bond are in agreement with the previous assignments.

1,1-Dichloro-2-ethoxyethene was prepared from the diethyl acetal of dichloroacetaldehyde (The British Drug Houses, Ltd.) through its acid-catalyzed decomposition. *p*-Toluenesulfonic acid was used as the catalyst, and the ethanol and 1,1-dichloro-2-ethoxyethene formed were distilled off through a Vigreux column. The fraction boiling between 78 and 145° was collected. After the alcohol had been extracted from the distillate into water, the residue was dried over anhydrous calcium chloride and purified by fractional distillation: bp 144.3–144.5° (760 Torr); nmr spectrum δ 1.30 (3 H, CH_3), 3.86 (2 H, CH_2), and 6.37 ppm (1 H, CH).

Labeling of Acetals with Carbon-14. Two alternative methods were applied. In both these methods labeled ethanol was used, and in both cases its activity could be transferred almost quantitatively to the acetal. In the first method, the acid-catalyzed transacetalization reaction was utilized. The second method was based on the alcoholysis of vinyl ethers in equivalent amounts of anhydrous ethanol in which some radioactive ethanol, labeled at the methylene carbon, had been added.

The labeling of the diethyl acetal of acetaldehyde was performed by the second method. Ethyl vinyl ether (21.6 g) was dropped into anhydrous ethanol (13.8 g) which contained 25 μCi of ethanol-^{14}C (The Radiochemical Centre, Amersham, England). A small quantity of *p*-toluenesulfonic acid was present as the catalyst. After the highly exothermic reaction, the mixture was neutralized with sodium ethoxide and purified by fractional distillation: bp 102–103°; nmr spectrum δ 1.20 (6 H, CH_3), 1.32 (3 H, CH_3), 3.3–3.9 (4 H, CH_2), and 4.72 ppm (1 H, CH). Other signals could not be detected. A 1-μl sample had an activity of about 10^3 counts/min.

1-Chloro-2,2-diethoxyethane was labeled using the first method, by transacetalizing 10 g of the commercial acetal (Schuchardt) with 20 μCi of the labeled ethanol. The catalyst was *p*-toluenesulfonic acid as above. A small quantity of hydroquinone was added to the mixture to prevent polymerization. The reactants were sealed into a glass vial and immersed for 20 hr in an oil bath at 120°. After neutralization with sodium ethoxide, the acetal was purified by fractional distillation: bp 71–72° (30 Torr); nmr spectrum δ 1.22 (6 H, CH_3), 3.3–3.8 (6 H, CH_2), and 4.66 ppm (1 H, CH). Other signals were not observed. The measured activity of a 1-μl sample was about 500 counts/min.

1,1-Dichloro-2,2-diethoxyethane was labeled by the same method as the corresponding monochloro derivative. As the alcoholysis of the dichloro derivative was slower, a longer reaction time was required (4 days). The methods of purification and analysis were those above. Nmr spectrum: δ 1.25 (6 H, CH_3), 3.68 (4 H, CH_2), 4.52 (1 H, CH), and 5.48 ppm (1 H, CH). A 1-μl sample gave 500 counts/min.

Labeling of Acetals with Tritium. Acetals which were tritium labeled at the aldehyde methyl (or chloro-substituted methyl) group could be readily prepared by alcoholyzing the corresponding vinyl ethers in ethanol which contained hydroxylic tritons. On the basis of the well-established mechanism of the hydrolysis of vinyl ethers,[3,4] which must be also applicable to the similar alcoholysis reaction, it could be concluded that the triton would be transferred from the solvent to the β position of the carbon–carbon double bond

$$\mathrm{CH_2{=}CHOEt + T^+ \longrightarrow CH_2TCH{=}\overset{+}{O}Et \xrightarrow{EtOH} CH_2TCH(OEt)_2}$$

Another method was also used. As discussed above, the acid-catalyzed decomposition of acetals yields the corresponding vinyl ethers, but if the reaction products are not isolated, the reverse formation of acetals takes place, the equilibrium favoring acetals under ordinary conditions. Thus, if a small amount of tritiated water is added to an acetal, protium–tritium exchange occurs at the carbon atom in question leading to the desired labeling. When this method was used, relatively high temperatures were required to complete the reaction.

The tritium labeled diethyl acetal of acetaldehyde was prepared by alcoholyzing ethyl vinyl ether in an acid solution in which a small quantity of tritiated water (The Radiochemical Centre, Amersham, England) had been added. Ethyl vinyl ether (21.6 g) was added dropwise to anhydrous ethanol (13.8 g) containing 1 μl of tritiated water (5.0 mCi) and a small amount of *p*-toluenesulfonic acid. After reaction the mixture was neutralized with sodium ethoxide and fractionated, bp 102–103° (760 Torr). Nmr signals other than those of the corresponding unlabeled acetal could not be observed. The activity of the product was *ca.* 180,000 counts $\mathrm{min}^{-1}/1\ \mu l$.

When labeling 1-chloro-2,2-diethoxyethane with tritium, the acetal (10 ml) was sealed into a vial together with 1 μl of the tritiated water and a small amount of *p*-toluenesulfonic acid. The reaction mixture was kept at 120° for 3 days. The product was neutralized with sodium ethoxide and purified by distillation, bp 71–72° (31 Torr). The nmr spectrum was free from signals other than those measured for the nontritiated acetal. The activity of the preparate was of the same magnitude as that of the tritiated diethyl acetal of acetaldehyde.

The tritium labeling of 1,1-dichloro-2,2-diethoxyethane took place in a similar way, bp 82–84° (18 Torr). The nmr spectrum indicated no traces of impurities.

Deuteration of Acetal. The derivative deuterated at the aldehydic β carbon was prepared for 1,1-dichloro-2,2-diethoxyethane only. The method was similar to that used for the tritiation of this acetal. The acetal (5 g) and ethanol-d_1[19] (5 g) were sealed into a vial together with a small quantity of deuteriosulfuric acid. After keeping the mixture for 1 week at 110°, the nmr analysis indicated that the degree of deuteration at the carbon in question was *ca.* 65%. The excess alcohol was removed by distillation. The same procedure was then repeated using 5 g of fresh ethanol-d_1. After this treatment, the degree of deuteration had been increased up to *ca.* 80%. Further deuteration was not considered economical for the kinetic measurements, in which the primary concern was to determine the rate of the change in the degree of deuteration. The reaction mixture was neutralized with sodium ethoxide, ethanol was distilled off, and the crude product was fractionated under reduced pressure. The fraction boiling at 52–53° (3–4 Torr) was collected. Nmr spectrum: δ 1.25 (CH_3), 3.68 (CH_2), and 4.52 ppm (CH). A signal at δ 5.48 ppm, which was that of the nondeuterated form, was also recorded. Its peak area, when compared with that of the protons at 4.52 ppm, indicated that the preparate contained 18.5% of the protioacetal.

Kinetics of Detritiation and Carbon-14 Exchange Reactions. The kinetics of detritiation and carbon-14 exchange reactions of acetals were studied in dilute solutions of perchloric acid in ethanol. The acetal present in a sample taken from the reaction mixture was distributed between the sample solution and a suitable solvent in which only an insignificant amount of the ethanol was extracted. The most satisfactory results were obtained by the following procedure. A 5-ml sample of the acetal–ethanol solution was pipetted into 20 ml of aqueous sodium carbonate solution (135 g/l.). The best extracting solvent found was a mixture of anisole and cyclohexane in a volume ratio of 1:3. This solvent (10-ml portions) was used for each extraction. By this method more than 95% of the acetal present in the original solution was extracted into the organic phase. The ethanol content of the anisole–cyclohexane phase was negligible. Although the extraction of the acetal was not quite quantitative, it was of no significance from the point of kinetic measurements. If the same procedure was always carefully followed when analyzing samples taken from the reaction mixtures, the same proportion of the acetal present was always distributed to the anisole–cyclohexane layer and, consequently, the change in activity was proportional to the progress of reaction.

---

(17) J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 74, 271 (1955).

(18) P. Laszlo and P. v. R. Schleyer, *Bull. Soc. Chim. Fr.*, 87 (1964).

(19) Ethanol-d_1 was prepared by hydrolyzing ethyl orthoformate with D_2O in the presence of some deuteriosulfuric acid

$$\mathrm{HC(OEt)_3 + D_2O \xrightarrow{D^+} 2EtOD + HCOOEt}$$

The very volatile product, ethyl formate, could be easily distilled off, and the remaining ethanol-d_1 then purified by fractional distillation. This simple and economical method has not been described earlier. When ethyl orthoformate is used in a small excess, the yield of deuterioethanol is almost quantitative.

The solvent in the kinetic experiments was anhydrous ethanol, purified by standard methods.[20] Perchloric acid was used as the catalyst. Its concentration varied between 0.0008 and 0.2 M, depending on the rate of the reaction followed. In cases in which concentrations less than 0.005 M had to be used, the actual H^+ concentration was determined kinetically, by measuring the rate of transacetalization of diethyl acetal. As the rate of this reaction was also determined at higher acid concentrations, the relatively low hydronium ion concentrations of the solutions in question could be calculated from the observed first-order rate coefficients.

The performance of the kinetic runs took place as follows. About 100 ml of the acidified ethanol solution was thermostated to the desired temperature, the bath temperature being controlled within ±0.02°. After *ca.* 1 hr, the acetal (0.1–1% by volume) was injected with simultaneous, vigorous shaking. The samples were withdrawn with a 5-ml semiautomatic pipet,[21] and run immediately to the sodium carbonate solution. About 15 samples were taken at intervals. The final samples were taken after *ca.* 10 half-lifes. At temperatures higher than 55° another procedure was followed. The reaction components were mixed at room temperature, and 5-ml samples were sealed into separate glass ampoules, which were simultaneously brought to the thermostat. In this method, the reactions were stopped by immersing the ampoules in an ice–water bath. For the analyses, the contents of the ampoules were carefully rinsed to the sodium carbonate solution. The acetal was then extracted with the anisole–cyclohexane mixture as above.

For the liquid scintillation counting analyses, 5-ml samples were pipetted from the anisole–cyclohexane layer and brought to the vials of a Wallac Decem-NTL^{314} scintillation counter. In each sample the volume of the scintillation liquid (4 g of diphenyloxazole and 100 mg of *p*-bis(*o*-methylstyryl)benzene in 1 l. of toluene) was 10 ml. The counting times varied from 30 sec to 0.5 hr, depending on the activity of the sample. The counting time was chosen in such a way that the overall change in the count rate during the reaction was at least 200,000 counts.

In some control experiments the aqueous phase was also studied. Because the reaction product, the radioactive ethanol, went to this phase, increasing activities were recorded during the progress of the reactions. A water soluble scintillation liquid was used for these experiments. The rate coefficients derived in this way differed by less than 4% from those obtained by analysis of the anisole–cyclohexane extracts. However, the standard errors for each run were smaller for the organic phase analyses (*ca.* ±0.3% as compared with ±1.0% for analyses of the water phase). Therefore the analysis of the anisole–cyclohexane phases was preferred.

Dedeuteration Rates. The dedeuteration of 1-deuterio-1,1-dichloro-2,2-diethoxyethane was studied in dilute perchloric acid (0.2 M) in ethanol. The concentration of the acetal was *ca.* 0.3 M. Samples of the reaction mixture (2 ml) were sealed into glass ampoules and immersed simultaneously in a thermostated oil bath at 121.5°. The ampoules were then removed from the bath at suitable intervals, and the reaction was brought to a stop in an ice-water mixture as above. The progress of the reaction was followed with a Perkin-Elmer R 10 nmr spectrometer. Before analysis, the acetal was first extracted into carbon tetrachloride, as the peaks of the solvent ethanol overlapped with those of the methine protons. The following procedure was applied. The reaction mixture was poured into 1 ml of 1 M sodium carbonate solution in water, and the acetal was extracted from this mixture into 0.9 ml of carbon tetrachloride. To remove the small amount of ethanol which had been also extracted, the carbon tetrachloride solution was shaken with a 1-ml portion of water. After this operation, the characteristic peaks of the acetal only could be found in the spectrum. At least ten integrals were run for each sample, and their average value was then used for the calculation of the rate coefficients. In addition to the intensity of the 1 H (5.48 ppm), which increased during the reaction, the intensity of 2 H (4.52 ppm) of 1,1-dichloro-2,2-diethoxyethane was followed, as it provided an excellent internal standard for measuring the degree of deuteration at the 1 position.

Alcoholysis (Acetalization) of Vinyl Ethers. The kinetic measurements were conducted in dilute perchloric acid solutions in ethanol. The progress of alcoholysis was followed by uv spectrophotometry from the rate of decrease of the carbon–carbon double bond absorption at 235 nm. After the reaction solution had been thermostated in the cell housing to the desired temperature, the vinyl ether was injected. The initial concentration of the substrate was about 0.05 M. After vigorous shaking, the cell compartment was closed and the absorbances were recorded at intervals. A Perkin-Elmer 46 BCD spectrophotometer equipped with a constant-temperature cell compartment was used.

The spectrophotometric method could not be applied to the alcoholysis of 1,1-dichloro-2-ethoxyethene. The slowness of this reaction of ordinary temperatures necessitated the use of temperatures higher than the normal boiling point of the solvent. The reactions were hence conducted in sealed ampoules, and their progress was followed by gas chromatography, both from the disappearance of the peak of the vinyl ether and from the appearance of the acetal peak. The concentration of the catalyst perchloric acid was about 0.2 M, and that of the vinyl ether of similar magnitude. Some anisole (*ca.* 0.03 M) was present in the reaction mixture as the internal standard for the analyses. The technical performance of the reactions in sealed ampoules was that used in the dedeuteration studies (see above).

Basicities of Acetals. The ir-band shift method described previously[22] was used. The solutions contained *ca.* 0.5 mol/l. of methanol-d_1 dissolved in the acetal under study. The basicities of the acetals were estimated from the measured band shifts utilizing the linear correlation between the O–D band shifts and the pK_a values of the conjugate acids. At least ten parallel experiments were made in each case. The standards were based on aliphatic and aromatic ethers.[22]

Equilibrium between Acetal and Vinyl Ether in Ethanol. In the case of the dichloro derivatives only, the standard free energy difference between the acetal and vinyl ether was small enough to be directly measured. In the other cases studied, the equilibrium constants were derived indirectly from the results of kinetic measurements. With the dichloro derivatives, both the acetal and vinyl ether were used as the initial reactants. The equilibrations were performed in dilute perchloric acid in ethanol (0.2 M). The initial concentration of acetal or vinyl ether varied from 0.06 to 0.3 M. The reaction mixtures were kept thermostated at 70° for 1 month. The compositions of the equilibrium mixtures were analyzed with a Perkin-Elmer F 11 gas chromatograph. To calculate the molar concentrations of the components at equilibrium, standard solutions containing weighed amounts of the acetal and vinyl ether in known volumes of ethanol were analyzed simultaneously.

Results and Discussion

Oxygen Protonation of Acetals. The basicities of the acetals studied, evaluated by the O–D band shift method,[22] are collected in Table I. Although the ir band shift method is, of course, but an approximate one, it is believed to give fairly good estimates for the relative basicities of structurally similar compounds like those here. It can be seen from the table that the basicities of the studied compounds are not grossly different. This is not surprising, for the acetals differ only in their substituents at a site that is remote from the basic oxygen atom.

Table I. O–D Band Frequencies of Methanol-d_1 in Acetals $RCH(OEt)_2$ and the pK_a Values Derived for the Conjugate Acids at 25°

R	O–D band position,[b] cm^{-1}	pK_a Measured	pK_a Symmetry-corrected	$\Delta G°$,[a] kcal
CH_3	2602.5 ± 0.4	−4.0	−4.3	+5.9
$ClCH_2$	2607.7 ± 0.9	−4.4	−4.7	+6.4
Cl_2CH	2622.0 ± 0.6	−5.6	−5.9	+8.0

[a] $\Delta G°$ is the calculated standard free energy of protonation. [b] Frequency of the O–D band in carbon tetrachloride was 2689.9 ± 0.5 cm^{-1}.

---

[20] A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, London, 1967, p 167.

[21] This pipet was originally designed by M. H. Palomaa a half century ago. Its features have been described by R. Leimu, *et al.*, *Suom. Kemistilehti B*, **19**, 1 (1946), and it enables moderately fast and very accurate sampling.

[22] A. Kankaanperä, *Acta Chem. Scand.*, **23**, 1723 (1969).

Table II. Rate Coefficients for the Acid-Catalyzed Transacetalization of Diethyl Acetals $R_1R_2CHCH(OEt^*)_2$[a] in Ethanol and Derived Kinetic Quantities

R_1	R_2	Temp, °C	k, M^{-1} sec^{-1}	E, kcal/mol	$\Delta S^{\ddagger}_{70}$, eu	$\Delta G^{\ddagger}_{70}$, kcal/mol	k_{70}, M^{-1} sec^{-1}
H	H	15	0.1559				
		25	0.528				
		35	1.556	20.2 ± 0.2	+6 ± 1	17.6 ± 0.1	45 ± 6
		45	4.34				
H	Cl	65	0.522×10^{-2}				
		80	2.49×10^{-2}				
		95	9.00×10^{-2}	21.5 ± 0.7	−7 ± 2	23.4 ± 0.1	$(9.3 \pm 0.9) \times 10^{-3}$
		108.5	21.0×10^{-2}				
		121.4	54.6×10^{-2}				
Cl	Cl	80	1.385×10^{-5}				
		95	4.56×10^{-5}	24.5 ± 2.8	−14 ± 7	28.6 ± 0.3	$(4.3 \pm 1.9) \times 10^{-6}$
		108.5	11.9×10^{-5}				

[a] The asterisk denotes carbon-14 labeling.

The upper limit for the rate coefficient of the reverse deprotonation of the conjugate acid of acetal is about 10^{10} sec^{-1}, which is the rate of a diffusion-controlled proton transfer from a strong acid to water.[23] Supporting experimental evidence is furnished by some recent kinetic and equilibrium data for the hydrolysis of structurally different acetals displaying mechanistic changes from protonation preequilibrium mechanism (A-1) to rate-determining proton transfer (A-SE2).[7,9,10,15] In cases in which the rate of the further decomposition of the protonated substrate to hydrolysis products is higher than about 10^9 sec^{-1}, it has been found that proton transfer from the catalyst acid to the substrate becomes rate determining. Consequently, the rate of proton transfer from the protonated substrate to water must be somewhat lower than 10^9 sec^{-1}. The above value has been tentatively used here as the best estimate when calculating the free energy of activation of this deprotonation process (*cf.* Figure 1 and the discussions below), although its uncertainty does not affect any of the conclusions drawn.

Rates of Oxo Carbenium Ion Formation from Diethyl Acetals in Ethanol. In the transacetalization of acetals, the oxo carbenium ion is formed at the same rate as the final product, irrespective of the particular mechanism, A-1 or A-SE2.[1,2,5–15] Of course, no "transacetalization" of diethyl acetals in ethanol can be ordinarily detected, as the oxo carbenium ion leads back to the initial reactant. However, with acetals labeled in the ethoxyl group with carbon-14, the rate of this transacetalization is accessible to experimental study. The isotope effect of carbon-14 must be negligible here. That is because even the primary carbon isotope effects are relatively small,[24] but, more important, because in the present case the labeling is at a site that is very remote from the reaction center.

$$RCH(OEt)_2 + H^+ \longrightarrow RCH{=}\overset{+}{O}Et + EtOH \longrightarrow RCH(OEt)_2 + H^+$$

The kinetic values for the transacetalization are collected in Table II. Owing to the great variation of the rates with structure, a very wide range of temperatures (15–120°) had to be used when following the reactions. This also enabled an extra- or interpolation of the rate coefficients to a same, single temperature, so that their direct comparison was possible. The observed rate coefficients were subjected to a least-squares analysis, by plotting the values of log k against reciprocal temperatures. The computer program was designed to give the single-temperature rate coefficients with their standard errors, along with the values of the Arrhenius parameters. The calculations also indicated that the linear regression formula was satisfactory enough, for the experimental accuracy did not justify the use of an additional "heat capacity term."

It is interesting to note that the values of activation entropies are greatly dependent on the number of the electronegative chlorine substituents. This can be qualitatively understood in terms of the Hammond principle.[25] If one goes from the acetal of acetaldehyde to those of monochloroacetaldehyde and di-

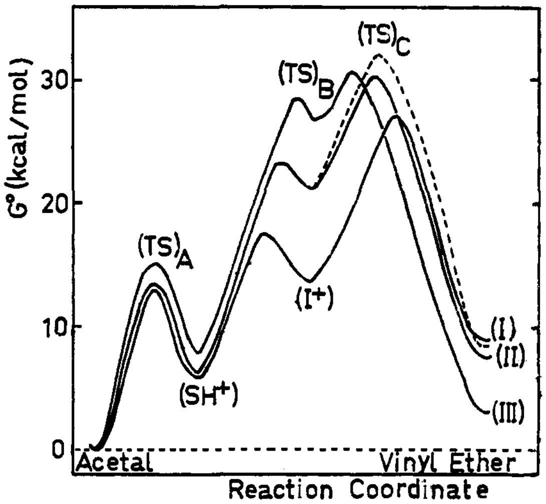


Figure 1. Free energy profiles for the protolytic decomposition of acetals to vinyl ethers in ethanol at 70°: (I) 1,1-diethoxyethane to vinyl ether; (II) 1-chloro-2,2-diethoxyethane to 1-chloro-2-ethoxyethene; (III) 1,1-dichloro-2,2-diethoxyethane to 1,1-dichloro-2-ethoxyethene. The denotations of the transition states are: $(TS)_A$, protonation of the oxygen atom of acetal; $(TS)_B$, formation of the oxo carbenium ion; $(TS)_C$, proton abstraction from the oxo carbenium ion to yield vinyl ether. The intermediates (SH^+) and (I^+) are the protonated acetal and oxo carbenium ion, respectively. In (II), the solid curve refers to the cis vinyl ether and the dashed curve to the trans vinyl ether, respectively. All free energy values have been scaled by assigning zero value for the reactant diethyl acetal in ethanol.

---

(23) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).

(24) A. Fry in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, New York, N. Y., 1970.

(25) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955).

Table III. Rate Coefficients for the Acid-Catalyzed Detritiation of Diethyl Acetals $R_1R_2CH^*CH(OEt)_2$[a] in Ethanol and Derived Kinetic Values

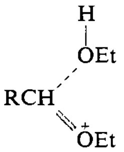
R_1	R_2	Temp, °C	10^5k, M^{-1} sec^{-1}	E, kcal/mol	$\Delta S^{\ddagger}_{70}$, eu	$\Delta G^{\ddagger}_{70}$, kcal/mol	10^5k_{70}, M^{-1} sec^{-1}
H	H	55	0.402				
		70	3.76				
		85	27.2	31.7 ± 0.7	+11 ± 2	27.2 ± 0.0	3.6 ± 0.1
		100	140.1				
H	Cl	80	0.1215				
		95	0.729				
		108.5	1.784	28.2 ± 2.4	−8 ± 6	30.3 ± 0.2	0.038 ± 0.014
		121.5	9.77				
Cl	Cl	95	0.254				
		108.5	0.817	25.8 ± 1.0	−16 ± 3	30.7 ± 0.1	0.019 ± 0.003
		121.5	2.72				

[a] The asterisk denotes tritium labeling.

chloroacetaldehyde, the stability of the intermediary oxo carbenium ion is substantially lowered. Put another way, the free energy level of the ionic intermediate relative to that of the reactant acetal will become much higher. As a consequence, the transition state will resemble more closely the products formed in the rate-determining stage, the oxo carbenium ion and ethanol. An oxo carbenium ion (I) in ethanol represents a very highly ordered state when compared with that of a transition complex (II) in which the alcohol molecule under removal is still more or less tightly bound.

$RCH{=}\overset{+}{O}Et$

I



II

Also, I should be more orderly solvated than II because of its more localized electric field. Both these effects would result in a decrease in entropy when going from II to I.

It is also seen from Table II that the rate coefficients for transacetalization are decreased by as much as seven powers of ten when going from the acetal of acetaldehyde to that of dichloroacetaldehyde. This great structural effect is the result of strong destabilizing effects of the electronegative substituents influencing the formation of the oxo carbenium ion. This observation is in general harmony with the kinetic data for the closely related reaction, the hydrolysis of acetals,[1,2,26] in which electropositive substituents in the aldehyde component strongly accelerate, and electronegative substituents retard the reaction.

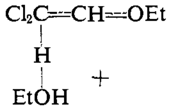
Rates of Formation of Vinyl Ethers from Acetals. The reaction leading from an acetal to vinyl ether may be represented as

$$R_2CHCH(OEt)_2 + H^+ \xrightarrow{(1)} R_2CHCH{=}\overset{+}{O}Et + EtOH \xrightarrow{(2)} R_2C{=}CHOEt + EtOH + H^+$$

In solutions in ethanol, the equilibrium of the overall reaction lies almost quantitatively on the side of the reactant acetal, except at elevated temperatures. Hence, the rate of formation of vinyl ethers cannot be directly measured under the same conditions as that of the first stage, the formation of the oxo carbenium ions (see above). However, the rate of the vinyl ether formation can be evaluated from the rate of detritiation or dedeuteration of the corresponding labeled acetal, like $R_2CTCH(OEt)_2$. Because of hydrogen isotope effects, these measurements do not naturally lead to values which would be strictly applicable to the pure protio system. However, they yield comparable values for the different acetals. Furthermore, as shown below, the effect of the isotopic substitution can be roughly evaluated.

The rate coefficients and derived kinetic values measured for the detritiation reactions are collected in Table III. The values in the table display much smaller variations in the rates of structurally different compounds than those observed for the oxo carbenium ion formation (Table II). It is also seen that, in the case of diethyl acetal of acetaldehyde, the rate of formation of the ionic intermediate is faster than the detritiation rate by six powers of ten. With increasing number of chlorine atoms in the aldehyde component this rate ratio is greatly reduced, being only about 20 for the dichloro compounds. Irrespective of these enormous variations in the relative rates, it is invariably the formation of the vinyl ether that is the slower process. Hence the formation of the oxo carbenium ion is a "fast" preequilibrium process on the route from acetal to vinyl ether.

The moderately small variations with structure of the measured detritiation rates may be thought to be the net result of two opposing factors. As shown above, the free energy level of the oxo carbenium ion is greatly heightened when going from the derivatives of acetaldehyde to those of chloro-substituted acetaldehydes. This factor alone would have a large retarding influence on the rate. However, the subsequent hydrogen ion abstraction from this ionic intermediate, leading to the vinyl ether, will be much more facile for the chloro derivatives. The transition state of this process may be visualized as



An increasing number of chlorine substituents at the β carbon of the aldehyde will enhance the acidity of the proton (or triton) in transit, and thereby greatly lower the free energy level of the transition state. As the

---

(26) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, 77, 5590 (1955).

Table IV. Rate Coefficients for the Acid-Catalyzed Alcoholysis of Vinyl Ethers $R_1R_2C{=}CHOEt$ in Ethanol and Derived Kinetic Data

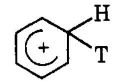
R_1	R_2	Isomer	Temp, °C	k, M^{-1} sec^{-1}	E, kcal/mol	$\Delta S^{\ddagger}_{70}$, eu	$\Delta G^{\ddagger}_{70}$, kcal/mol	k_{70}, M^{-1} sec^{-1}
H	H		15.35	0.1813	17.1 ± 0.9	-5 ± 3	18.1 ± 0.1	21 ± 4
			25.35	0.480				
			35.15	1.420				
			44.05	2.524				
H	Cl	Trans	44.35	4.99×10^{-4}	22.1 ± 1.6	-6 ± 5	23.6 ± 0.1	$(6.7 \pm 0.7) \times 10^{-3}$
		Trans	54.15	12.34×10^{-4}				
		Trans	63.25	43.5×10^{-4}				
		Trans	67.53	49.6×10^{-4}				
		Trans	68.45	54.2×10^{-4}				
H	Cl	Cis	44.35	2.442×10^{-3}	20.6 ± 0.4	-8 ± 1	22.6 ± 0.0	$(2.7 \pm 0.1) \times 10^{-2}$
		Cis	54.15	6.09×10^{-3}				
		Cis	63.25	14.78×10^{-3}				
		Cis	68.45	24.28×10^{-3}				
Cl	Cl		89.52	1.28×10^{-4}	24.9 ± 0.8	-10 ± 2	27.7 ± 0.1	$(1.7 \pm 0.2) \times 10^{-5}$
			99.65	2.94×10^{-4}				
			109.90	8.17×10^{-4}				
			119.90	17.8×10^{-4}				

chlorine substituents are attached to the same carbon atom as the hydrogen under removal, very strong structural effects on the acidities can be readily accounted for.[27]

A comparison of the values of Tables II and III also shows that the changes in the activation entropies follow the same structural pattern; a remarkable decrease in the $\Delta S^{\ddagger}$ values is evident with additional chlorine substituents. As discussed above, this can be explained in terms of more or less oxo carbenium ion-like transition states. It is also interesting to note that the lower detritiation rate with additional chlorine substituents is solely due to the more negative entropies of activation. The energies of activation decrease in the same sequence and have thus an opposing, rate-increasing influence, which is overcompensated by the entropy term.

Dedeuteration of Acetals. To gain an idea about the magnitude of hydrogen isotope effects in the detritiation reactions, the rate of the corresponding dedeuteration reaction was measured in one case, namely in the dedeuteration of the diethyl acetal of dichloroacetaldehyde. The rate coefficient at 121.5°, measured by the nmr techniques, was $(2.55 \pm 0.24) \times 10^{-5}\ M^{-1}$ sec^{-1}. This is seen to be almost identical with the value $(2.65 \pm 0.03) \times 10^{-5}\ M^{-1}$ sec^{-1} measured for the detritiation reaction under the same conditions (Table III).

At first sight the above result seems surprising, as the primary isotope effects of hydrogen are usually very large as, for example, in the case of aromatic hydrogen exchange.[28-34] However, the values of the latter isotope effects refer to cases in which the different isotopes of hydrogen (protons, deuterons, or tritons) are abstracted from the *same* intermediate, *e.g.*, from



Thus the "initial states" of the hydrogen ion abstraction are identical and therefore lead to large differences between the different isotopes. In the present case the situation is different in that the initial state of triton abstraction is the tritiated acetal. Therefore, substantial cancellation of the initial state and transition state isotope effects may occur. If the transition states of proton or triton abstraction are approximated by the respective oxo carbenium ions, the overall isotope effect is equal to the equilibrium constant of the hypothetical reaction (as exemplified by the acetals of acetaldehyde)

$$CH_2TCH(OEt)_2 + CH_3CH{=}\overset{+}{O}Et \rightleftharpoons CH_3CH(OEt)_2 + CH_2TCH{=}\overset{+}{O}Et$$

But isotope effects on equilibria of the above type are usually relatively small,[35] the equilibrium constants differing from unity by a few per cent only. Of course, in the actual transition states, the proton or trition in transit will be more loosely bound than in the reactant acetal. Qualitatively, this would lead to an overall increase in zero-point energy of the above reaction, and to an equilibrium constant smaller than unity. Thus proton abstraction from the protioacetal should be slightly faster than triton abstraction from the corresponding tritioacetal. Unfortunately, the former reaction is not accessible to direct experimental measurement. However, the magnitude of the isotope effects cannot be material enough to alter any of the conclusions drawn below. This is also demonstrated in a later section, in which the equilibrium constant for the acetal–vinyl ether reaction is calculated independently from direct equilibrium measurements, and compared then with the results derived from the detritiation studies.

Acetalization of Vinyl Ethers. Rate coefficients measured for the alcoholysis of vinyl ethers are given in Table IV. A remarkable rate retardation can be noted

---

(27) A. Streitwieser, Jr., and J. H. Hammons, *Progr. Phys. Org. Chem.*, 3, 41 (1965).

(28) V. Gold, R. W. Lambert, and D. P. N. Satchell, *J. Chem. Soc.*, 2461 (1960).

(29) A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, 84, 3975 (1962).

(30) J. Schulze and F. A. Long, *ibid.*, 86, 331 (1964).

(31) B. D. Batts and V. Gold, *J. Chem. Soc.*, 4284 (1964).

(32) L. C. Gruen and F. A. Long, *J. Amer. Chem. Soc.*, 89, 1287 (1967).

(33) J. L. Longridge and F. A. Long, *ibid.*, 89, 1292 (1967).

(34) A. J. Kresge and Y. Chiang, *ibid.*, 89, 4411 (1967).

(35) V. J. Shiner, Jr., in ref 24.

with increasing numbers of chlorine substituents, similar to that found in the transacetalization reactions. It is also interesting to compare the rate coefficients for the cis and trans isomers of the monochloro derivatives. The trans isomer is seen to be more reactive by a factor of about 4. The activation entropies for the alcoholysis reaction are of a magnitude similar to that of the related hydrolysis reaction.[3,4]

Equilibrium between Acetal and Vinyl Ether in Ethanol. These measurements provided some independent support for the free energy differences measured by kinetic methods. Unfortunately, in most cases the equilibria were too far on the side of the reactant acetal, and no accurate values could be derived from direct equilibrium measurements. In the case of the acetal of dichloroacetaldehyde only, the amount of the corresponding vinyl ether present in equilibrium was large enough to be analyzed by gas chromatography. The free energy difference between the final and initial states thus obtained was 3.8 ± 0.2 kcal/mol. In view of possible systematic errors, the above value is in satisfactory agreement with the value 3.05 ± 0.13 kcal/mol calculated from the kinetic data.

Free Energy Profiles for the Overall Reactions. The kinetic and equilibrium results collected in Tables I–IV can be best visualized by the free energy profiles drawn in Figure 1. Profile I shows the different stages leading from the diethyl acetal of acetaldehyde to ethyl vinyl in ethanol. From the measured values it can be calculated that, in dilute solutions in ethanol, the standard free energy difference between the final and initial states is *ca.* 9 kcal/mol. Thus the amount of ethyl vinyl ether present in equilibrium is too small to be detected by direct analysis of the equilibrium mixtures.

In the reactions of the derivatives of monochloroacetaldehyde, the situation is complicated by the presence of two isomeric vinyl ethers. The cis has been found to be the more stable form in the thermodynamic sense; the recent equilibrium data of Okuyama, *et al.*,[36] indicate that the standard free energy difference between the two forms is 0.93 kcal/mol at 70°. However, the thermodynamically more stable cis isomer is alcoholyzed faster than the less stable trans isomer (Table IV). Hence the transition state for the alcoholysis of the trans isomer must be on an energy level that is 1.9 kcal higher than that for the cis isomer. In view of this relatively large free energy difference between the transition states of alcoholysis of the isomeric vinyl ethers, the detritiation (and deprotonation) of the corresponding acetal gives preferentially the cis form. Thus the experimental value of $\Delta G^{\neq}$ for the detritiation must be the height of the energy barrier leading to the cis form. The free energy profiles for the monochloroacetaldehyde derivatives are constructed accordingly in plots II. In this case also, the standard free energy differences between the final and initial states are rather large (7.7–8.6 kcal/mol), and no direct analysis of the equilibrium mixture is possible.

The free energy profile for the derivatives of dichloroacetaldehyde is illustrated in plot III. Two interesting features are evident. First, the transition states of transacetalization and detritiation are on comparable energy levels, in contrast to the great differences seen in the other profiles. Second, the standard free energy difference between the final and initial states is only 3 kcal/mol.

It is thus seen that, with increasing negatively polar character of the aldehyde component, the transition states leading from acetal to the oxo carbenium ion and those leading from this ion to the vinyl ether become gradually closer to each other. With still more electronegative substituents in the aldehyde component than those studied here, one could conceivably raise the energy level of $(TS)_B$ above that of $(TS)_C$. Considering the reverse reaction, the alcoholysis (and related hydrolysis) of vinyl ethers, this would mean a "fast" protonation preequilibrium step prior to further reactions, that is, an "abnormal" mechanism of vinyl ether solvolysis. Experiments designed to find examples of such reactions are underway.

Acknowledgments. Grants for partial support of this research from the Finnish Academy, Division of Sciences, are gratefully acknowledged. We also wish to thank Professor Veikko Nurmikko of the Biochemistry Department, University of Turku, for the use of the liquid scintillation counter of his department.

---

(36) T. Okuyama, T. Fueno, and J. Furukawa, *Tetrahedron*, 25, 5409 (1969).