Substituent Effects in Acetal Hydrolysis

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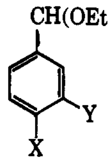
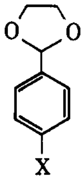
The rates of hydrolysis of a series of substituted benzaldehyde diethyl acetals and the corresponding 2-(substituted phenyl)-1,3-dioxolanes have been measured in 50% dioxane–water (v./v.) at 30°. Both series of compounds hydrolyze by a specific acid A-1 mechanism and give plots of log k_H *vs.* σ with marked curvature for *para*-substituted compounds. By employing *meta*-substituted benzaldehyde diethyl acetals ρ was determined to be -3.35. The diethyl acetals each hydrolyze 30 to 35 times faster than does the corresponding dioxolane derivative. This difference is in each case due to a less favorable entropy of activation for the cyclic compound. Positive values of ΔS^* were found for all the diethyl acetals, but the dioxolanes have ΔS^* values from -6.9 to -9.6 e.u. Enthalpies of activation are nearly constant for corresponding compounds in the two series. Within each series the large rate differences are due to differences in ΔH^*.

The acid-catalyzed hydrolysis of acetals has been found to be a specific acid-catalyzed reaction[1,2] with the accepted mechanism involving a fast pre-equilibrium protonation of the acetal followed by a unimolecular rate-determining decomposition of the protonated intermediate to an alcohol and a resonance-stabilized carbonium ion.[3] This mechanism has been arrived at with the aid of evidence such as the lack of racemization at the alcohol carbon atom,[4] the proportionality between the logarithm of the rate constant and the Hammett acidity function, H_0,[5] and the much faster rates of hydrolysis in D_2O than in water ($k_{D_2O}/k_{H_2O} = 2.0$–3.0).[2,6] Thus, with the mechanism quite well established, acetal hydrolysis is an ideal reaction for the study of substituent effects on the rate constants[7] and activation parameters of an acid-catalyzed reaction. The hydrolysis of a series of substituted benzaldehyde diethyl acetals (I–VIII) and a series of the corresponding 2-(substituted phenyl)-1,3-dioxolanes (IX–XIII) was therefore studied so that the Hammett $\sigma\rho$ treatment[8] could be applied to substituent effects and a comparison could be made of activation parameters for hydrolysis of analogous cyclic and acyclic compounds.



I, Y = H; X = OCH_3
II, Y = H; X = CH_3
III, Y = H; X = H
IV, Y = H; X = Cl
V, Y = H; X = NO_2
VI, Y = OCH_3; X = H
VII, Y = CH_3; X = H
VIII, Y = NO_2; X = H



IX, X = OCH_3
X, X = CH_3
XI, X = H
XII, X = Cl
XIII, X = NO_2

Experimental

Materials.—Diethyl acetals of substituted benzaldehydes (compounds I–VIII) were synthesized by treating the commercially obtained aldehydes with a mixture of equimolar quantities of triethyl orthoformate and absolute ethanol. A drop of ethanolic HCl was added as a catalyst. After allowing the mixture to stand 24 hr. at room temperature, anhydrous potassium carbonate was added to neutralize the excess acid. The excess ethanol was removed by flash evaporation and the residual liquid was distilled. The properties of the products are given in Table I.

TABLE I

PROPERTIES OF SUBSTITUTED BENZALDEHYDE DIETHYL ACETALS

Compd.	Substituent	B.p., °C. (mm.)	$n^{25}D$	Ref.
I	*p*-OCH_3	103–104 (3.5)	1.4899	*a*
II	*p*-CH_3	68–69 (2)	1.4785	*b*
III	H	89 (7)	1.4771	*c*
IV	*p*-Cl	92–93 (2)	1.4922	*d*
V	*p*-NO_2	135.5 (3.5)	1.5082	*e*
VI[f]	*m*-OCH_3	90 (1.8)	1.4896	
VII	*m*-CH_3	75 (3)	1.4838	*b*
VIII	*m*-NO_2	114–115 (2)	1.5053	*a*

[a] L. Claisen, *Ber.*, **31,** 1010 (1898); J. Klein and E. D. Bergman, *J. Am. Chem. Soc.*, **79,** 3452 (1957). [b] H. W. Post, *J. Org. Chem.*, **5,** 244 (1940). [c] E. Fischer and G. Giebe, *Ber.*, **30,** 3053 (1897). [d] J. Klein and A. Y. Meyer, *J. Org. Chem.*, **29,** 1035 (1964). [e] J. N. Zaganiaris, *Ber.*, **71B,** 2002 (1938); M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79,** 4016 (1957). [f] *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.68; H, 8.54.

The 2-(substituted phenyl)-1,3-dioxolanes (compounds IX–XIII) were prepared by reacting the appropriate aldehyde with ethylene glycol in refluxing benzene. A trace of *p*-toluenesulfonic acid was added as a catalyst. Water was continuously removed from the reaction by azeotropic distillation with the benzene. At the conclusion of the reaction the mixture was washed with 1 *M* sodium hydroxide solution. The benzene extract was dried over anhydrous sodium sulfate. The benzene

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(1) J. N. Brønsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

(2) M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **77,** 3146 (1955).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 334.

(4) H. K. Garner and H. J. Lucas, *J. Am. Chem. Soc.*, **72,** 5497 (1950); J. M. O'Gorman and H. J. Lucas, *ibid.*, **72,** 5489 (1950).

(5) D. McIntyre and F. A. Long, *ibid.*, **76,** 3240 (1954); C. A. Bunton, T. A. Lewis, D. R. Llewellyn, and C. A. Vernon, *J. Chem. Soc.*, 4419 (1955).

(6) W. J. C. Orr and J. A. V. Butler, *ibid.*, 330 (1937); M. Kilpatrick, *J. Am. Chem. Soc.*, **85,** 1036 (1963).

(7) M. M. Kreevoy and R. W. Taft, Jr., [*ibid.*, **77,** 5590 (1955)] found that electron withdrawal hindered the reaction. The value of ρ^* was -3.60 for substitution at the α-carbon.

(8) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

TABLE II

PROPERTIES OF 2-(SUBSTITUTED PHENYL)-1,3-DIOXOLANES

Compd.	Substituent	B.p., °C. (mm.)	M.p., °C.	n_D^{25}	Ref.
IX	p-OCH$_3$	97–98 (1.5)		1.5341	*a*
X	p-CH$_3$	88 (2.4)		1.5213	*b*
XI	H	61–62 (1)		1.5258	*c*
XII	p-Cl	123.5 (11.5)		1.5381	*c*
XIII	p-NO$_2$		90		*b*

[a] M. Sulzbacher, E. Bergmann, and E. R. Pariser, *J. Am. Chem. Soc.*, **70**, 2827 (1948). [b] E. J. Salmi and K. Kyrki, *Suomen Kemistilehti*, **19B**, 97 (1946). [c] A. Rieche, E. Schmitz, and E. Beyer, *Ber.*, **91**, 1935 (1958).

was removed by flash evaporation and the residual liquid was purified by distillation through a Nester–Faust spinning-band column. The properties of the products are given in Table II.

Kinetic Measurements.—The rates of hydrolysis of compounds I–XIII were measured in 50% dioxane–water[9] (v./v.) at a constant ionic strength of 0.1 M made up with KCl. The rates were measured spectrophotometrically with a Zeiss PMQ 11 spectrophotometer by following the increase in optical density due to the aldehyde product. The rates were generally followed to 75% completion. Infinity points were taken at 10 half-lives and again at 20 to 30 half-lives and were stable. The pseudo-first-order constants (k_{obsd}) were obtained from the slopes of plots of log $[(\mathrm{O.D.}_\infty - \mathrm{O.D.}_i)/(\mathrm{O.D.}_\infty - \mathrm{O.D.}_t)]$ *vs.* time. Constant temperature was maintained in the kinetic runs by circulating water at 30 ± 0.1°, from a Haake Model F constant-temperature circulating bath, through a Zeiss constant-temperature cell holder. The apparent pH of each solution was measured on a Model 22 Radiometer pH meter standardized with aqueous buffers. At pH values less than 3.0, pH was held constant by excess HCl. At pH values above 3.0, formate and acetate buffers were employed. Varying the concentration of buffer at constant pH had no effect on rate. The change in rate of hydrolysis produced by varying the substituent group was so large that it was not possible to study all of the compounds at one pH. In order to make a comparison, therefore, a second-order rate constant was calculated for each compound by dividing k_{obsd} by a_H. The glass electrode gives the correct pH reading in concentrated dioxane–water mixtures.[10] If the pH meter reading in this mixed solvent differed from the true pH there would, of course, be an error in the absolute values of the second-order constants, but the relative rates for the compounds studied would be correct. Hydrolysis of acetals in 50% dioxane–water over the pH range studied gives plots of log k_{obsd} *vs.* apparent pH which are straight lines with slope of −1.0.

In work utilizing 99.8% D$_2$O as solvent, the glass electrode correction formula of Fife and Bruice[11] was employed in the determination of a_D.[12]

In the determination of activation energies from slopes of plots of log k_{obsd} *vs.* $1/T$, points were obtained at four temperatures (20, 30, 40, and 50°). The rates were measured in triplicate at each temperature with an average deviation of 2% in the rate constants.

The kinetic results are presented in Tables III–V.

TABLE III

RATES OF HYDROLYSIS OF SUBSTITUTED BENZALDEHYDE DIETHYL ACETALS AND 2-(*para*-SUBSTITUTED PHENYL)-1,3-DIOXOLANES IN 50% DIOXANE–WATER OR 50% DIOXANE–DEUTERIUM OXIDE[a]

Compd.	λ, mμ[b]	pH	k_{obsd}, min.$^{-1}$	k_H, l. mole^{-1} min.$^{-1}$[c]	k_D, l. mole^{-1} min.$^{-1}$[d]
I	283	5.79[e]	0.0473	29,200	
II	258	4.76[f]	0.0685	3,937	
III	280	4.12[f]	0.0549	723.3	
IV	257.5	2.67	0.388	181.3	541.1
V	267	1.30	0.0923	1.84	5.01
VI	254.5	5.00[f]	0.00453	453.1	
VII	252	4.46[f]	0.0406	1,170	
VIII	250	2.36	0.0108	2.48	
IX	283	4.09[f]	0.0670	824.1	
X	258	2.99	0.122	119.2	335.9
XI	280	2.36	0.111	25.4	70.1
XII	257.5	1.72	0.118	6.19	17.8
XIII	267	1.30	0.00271	0.0541	0.177

[a] $T = 30 \pm 0.1°$, $\mu = 0.1\ M$. [b] Wave length at which appearance of product was followed. [c] $k_H = k_{obsd}/a_H$. [d] $k_D = k_{obsd}/a_D$. [e] Acetate buffer. [f] Formate buffer.

TABLE IV

TEMPERATURE DEPENDENCE OF k_{obsd} FOR HYDROLYSIS OF COMPOUNDS I–V AND IX–XIII IN 50% DIOXANE–WATER[a]

		k_{obsd}, min.$^{-1}$			
Compd.	pH	20°	30°	40°	50°
I	5.79[b]	0.0203	0.0473	0.107	0.218
II	4.76[c]	0.0293	0.0685	0.184	0.381
III	4.12[c]	0.0228	0.0549	0.153	0.356
IV	2.67	0.144	0.388	1.063	
V	1.30	0.0287	0.0923	0.219	0.863
IX	4.09[c]	0.0331	0.0670	0.151	0.288
X	2.99	0.0537	0.122	0.312	0.667
XI	2.36	0.0408	0.111	0.265	0.540
XII	1.72	0.0423	0.118	0.279	0.700
XIII	1.30		0.00271	0.00691	0.0213

[a] $\mu = 0.1\ M$. [b] Acetate buffer. [c] Formate buffer.

TABLE V

ACTIVATION PARAMETERS FOR SUBSTITUTED BENZALDEHYDE DIETHYL ACETALS AND 2-(SUBSTITUTED PHENYL)-1,3-DIOXOLANES IN 50% DIOXANE–WATER

Compd.	ΔH^*, kcal./mole	ΔS^*, e.u.[a]
I	14.2	+0.7
II	15.8	+2.0
III	16.5	+1.0
IV	17.3	+1.0
V	20.2	+1.3
IX	13.2	−9.6
X	15.2	−6.9
XI	15.5	−8.9
XII	16.9	−7.1
XIII	19.7	−7.3

[a] Calculated at 30°. The rate constants have the units l. mole^{-1} sec.$^{-1}$.

Results and Discussion

It has been observed that a straight-line relationship is obtained when the logarithms of the rate constants for the acid-catalyzed hydrolysis of substituted phenyl-β-D-glucopyranosides[13,14] are plotted *vs.* σ, the Hammett substituent constant. Electron withdrawal in the phenoxy portion of the molecule should decrease the equilibrium concentration of protonated intermediate but at the same time should increase its ease of heterolysis. Thus, these two effects tend to cancel, giving rise to a ρ value of small magnitude (−0.66 and −0.48).[13,14] The negative values would indicate that ease of protonation is the more important of the two effects.

Varying a substituent in the aldehyde portion of the molecule, as in substituted benzaldehyde diethyl acetals, will also influence the rate of hydrolysis by

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[9] Dioxane was purified according to the procedure of L. F. Fieser ["Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., p. 284].

[10] H. P. Marshall and E. Grunwald, *J. Chem. Phys.*, **21**, 2143 (1953).

[11] T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

[12] The relationship, pD = pH meter reading + 0.40, has been found in D$_2$O at 25°; P. K. Glasoe and F. A. Long, *ibid.*, **64**, 188 (1960). That the same relationship holds in 50% dioxane–D$_2$O is an assumption.

[13] R. L. Nath and H. N. Rydon, *Biochem. J.*, **57**, 1 (1954).

[14] L. K. Semke, N. S. Thompson, and D. G. Williams, *J. Org. Chem.*, **29**, 1041 (1964).

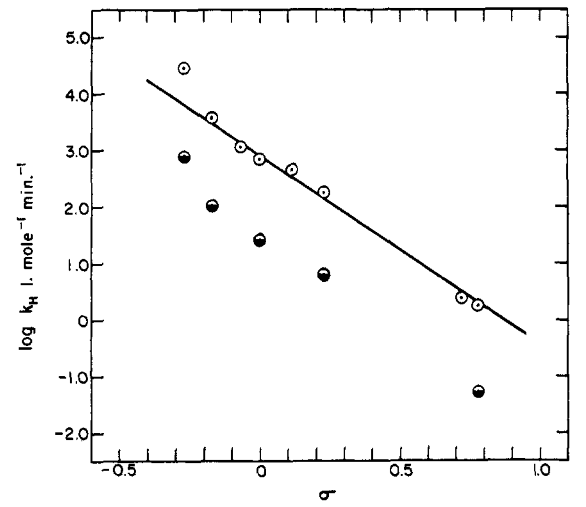

Figure 1.—Plots of log k_H *vs.* σ, the Hammett substituent constant, for diethyl acetals of substituted benzaldehydes, ⊙, and 2-(substituted phenyl)-1,3-dioxolanes, ●; $T = 30°$.

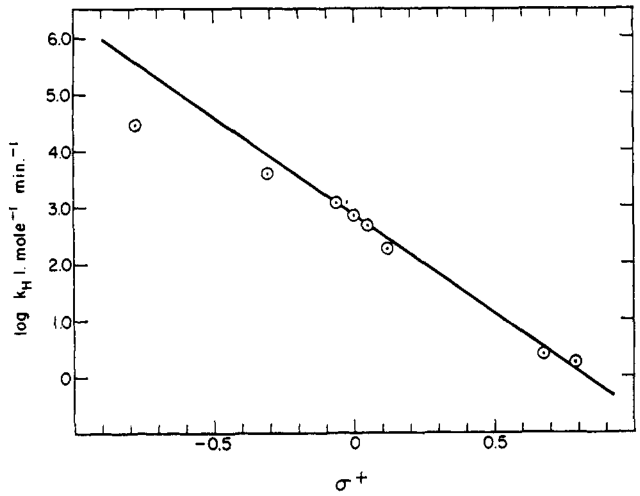

Figure 2.—Plot of log k_H *vs.* σ^+ for diethyl acetals of substituted benzaldehydes; $T = 30°$.

altering the equilibrium concentration of the protonated intermediate and its ease of heterolysis but, in addition, the ability of the substituent to stabilize the incipient carbonium ion will be quite important. Electron withdrawal should hinder protonation, make departure of the leaving group more difficult, and destabilize the carbonium ion intermediate; therefore, a large negative ρ would be expected. If the substituents can interact with the carbonium ion through a resonance effect, a curved plot of log k_H *vs.* σ should be obtained. It can be seen in Figure 1 that with acetals of substituted benzaldehydes the deviation from linearity is great, the point for the *p*-methoxy-substituted compound lying well above the line obtained for *meta* substituents. Employing the *meta*-substituted compounds ρ was found to be −3.35. It might be expected that if the transition state had a great deal of carbonium-ion character a better correlation would be obtained with σ^+ constants[15] than with the σ constants, but this is not the case. The point for anisaldehyde diethyl acetal falls far below the best line in a plot of log k_H *vs.* σ^+ (Figure 2). Thus, the σ^+ constants are overcompensating for interaction of the substituent with the carbonium ion. This may be the result of resonance interaction with the carbonium ion by the adjoining ethoxy group or it might indicate that the transition state resembles a protonated acetal much more closely than it does a carbonium ion. Kreevoy[16] has previously suggested, from application of the Hammond principle, that the transition state for hydrolysis of acetals of conjugated aldehydes should be much more like the protonated starting state than that for acetals of unconjugated aldehydes.

In cases of known A-1 reactions, where the protonated intermediate is breaking down through a unimolecular rate-determining decomposition, positive entropies of activation have been observed in numerous instances[17] in contrast to the large negative entropies of activation found normally for A-2 reactions involving attack by solvent on the protonated intermediate.[18] Examples are now known of acid-catalyzed hydrolysis reactions of cyclic compounds which give some evidence pointing to an A-1 mechanism but which also have ΔS^* values that are small negative numbers. Thus, small negative ΔS^* values were found for epoxide hydrolysis[17,19] and for hydrolysis of γ-ethoxy-γ-butyrolactone.[20] Also, the acid-catalyzed hydrolysis reactions of a series of cyclic 1,3-dioxolone derivatives have recently been reported to have ΔS^* values ranging from −4.0 to −8.7 e.u.,[21] while the hydrolysis of acyclic mixed acetal–acylals, such as methoxymethyl acetate and ethoxymethyl acetate, is characterized by positive ΔS^* values.[22]

Possible explanations for negative ΔS^* values in A-1 reactions of cyclic compounds are high solvation of the conjugate acids or transition states, or restriction of rotation about the breaking bond in the transition state.[17] That one or both of these effects is probably important in the hydrolysis of cyclic acetals can be seen from a consideration of the activation parameters in Table V for the hydrolysis of the series of substituted benzaldehyde diethyl acetals and the corresponding 2-(substituted phenyl)-1,3-dioxolanes. These two series of compounds are, of course, identical except that the acetal is cyclic in the case of the dioxolane derivatives. The diethyl acetals each hydrolyze 30 to 35 times faster than does the corresponding dioxolane and this difference in reactivity is due entirely to a less favorable ΔS^* for the cyclic compound. Activation enthalpies are constant within 1.0 kcal./mole for corresponding compounds in the two series. The diethyl acetals all have positive ΔS^* values, from +0.7 to +2.0 e.u., while the dioxolanes all have negative ΔS^* values ranging from −6.9 to −9.6 e.u. The large rate differences between compounds within a series are due to differences in ΔH^*. There would seem to be no reason to suspect a change

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[15] Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 485 (1957).

[16] M. M. Kreevoy, *Tetrahedron*, **5**, 233 (1959).

[17] F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).

[18] For a recent review, see L. L. Schaleger and F. A. Long, in "Advances in Physical Organic Chemistry," Vol. I, V. Gold, Ed., Academic Press Inc., New York, N. Y., 1963, p. 1.

[19] The D_2O solvent isotope effect is consistent with an A-1 reaction; however, the pressure effect on rate is more consistent with an A-2 mechanism: J. Koskikallio and E. Whalley, *Trans. Faraday Soc.*, **55**, 815 (1959).

[20] T. H. Fife, *J. Am. Chem. Soc.*, **87**, 271 (1965): $k_{D_2O}/k_{H_2O} = 2.37$.

[21] P. Salomaa, *Suomen Kemistilehti*, **B37**, 86 (1964). The D_2O solvent isotope effects were not reported.

[22] P. Salomaa, *Acta. Chem. Scand.*, **11**, 239 (1957).

in mechanism either for corresponding compounds in the two series or for compounds within a series. Thus, in 50% dioxane-D_2O as the solvent, $k_D^{D_2O}/k_H^{H_2O} > 2.7$ for compounds IV, V, and X-XIII. These values are typical of an A-1 mechanism.[23] The constancy of the ΔS^* term for compounds within a series would certainly lend strong support to the idea that the mechanism is the same for all of them.

Both positive and small negative values of ΔS^* have been obtained for acid-catalyzed hydrolyses of methyl-substituted 1,3-dioxolanes.[24] There would appear to be no reason why either type of value should not be possible for an A-1 reaction but the present data show that an A-1 cleavage of a five-membered ring can have a ΔS^* value from 8 to 10 e.u. more negative than for the exactly analogous open-chain compound.

Acknowledgment.—This work was supported by grants from The National Institutes of Health and the American Cancer Society.

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[23] F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

[24] P. Salomaa and A. Kankaanpera, *Acta Chem. Scand.*, **15**, 871 (1961).

Reactions of Alkanesulfonyl Chlorides with Ketene N,N- and O,N-Acetals

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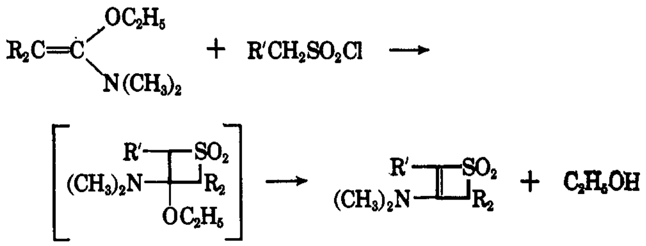
Methanesulfonyl chloride reacts with ketene N,N- and O,N-acetals in the presence of triethylamine in a nonpolar solvent to give 3-(dialkylamino)thiete 1,1-dioxides, but, if polar solvents are used with N,N-acetals, the predominant products are the acyclic sulfonylketene N,N-acetals. Some reactions of the 3-(dialkylamino)-thiete 1,1-dioxides are described.

The reactions of alkanesulfonyl chlorides with compounds containing electron-rich double bonds, such as enamines,[2,3] ketene acetals,[4] ketene O,N-acetals, and ketene N,N-acetals,[5] have been reported recently. This paper is a more detailed account of our earlier work with ketene O,N- and N,N-acetals.

The historical concepts and backgrounds for the production of sulfenes by the action of tertiary amines on alkanesulfonyl chlorides have been thoroughly reviewed by Truce and Norell.[4] The presence of sulfene intermediates in the cycloadditions described in the articles cited previously has been given consideration, but only recently have sulfenes been proved to be intermediates in reactions involving alkanesulfonyl chlorides.[6,7]

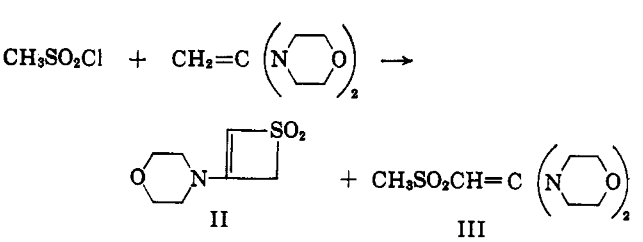
Ketene O,N-acetals, when treated with alkanesulfonyl chlorides in the presence of triethylamine (TEA), yield 3-(dialkylamino)thiete 1,1-dioxides (I). This cycloaddition is similar to the reaction of sulfenes with enamines and ketene acetals because the products are four-membered rings (thietanes) that are formed by 1,2-cycloaddition of a sulfene with a compound containing an electron-rich double bond. The products I, however, are thietes which may have arisen from β-elimination of an alcohol from the intermediate thietane structure.

Ketene N,N-acetals react with alkanesulfonyl chlorides in the presence of triethylamine to give 3-(dialkylamino)thiete 1,1-dioxides and 2-alkylsulfonyl-1,1-bis(dialkylamino)ethylenes. In most cases both types of products are formed, but in widely varying amounts depending upon the polarity of the solvent used and the nature of the alkane group of the sulfonyl chloride.



Ia, $R = H$; $R' = H$
b, $R = CH_3$; $R' = H$
c, $R = CH_3$; $R' = C_3H_7$

Highly polar solvents and higher alkane groups on the sulfonyl chlorides favor the formation of acyclic products, while the use of methanesulfonyl chloride and lower polarity solvents favors cyclic product formation. 4,4'-Vinylidenedimorpholine, methanesulfonyl chloride, and triethylamine in tetrahydrofuran (THF) gave the thiete dioxide II in 79% crude yield. Its infrared spectrum[8] showed that a small amount of the acyclic derivative III was present. II was purified by recrystallization from benzene. Using the same reactants in benzene, II was obtained in 69% crude yield. The use of highly polar solvents favored formation of the acyclic derivative III. When treated in acetonitrile, methanesulfonyl chloride, 4,4'-vinylidenedimorpholine, and triethylamine gave III in 48% yield after purification and in N,N-dimethylformamide gave III in 58% yield after purification. The infrared spectra of the crude reaction mixtures obtained when using highly polar solvents showed the products to be pri-



II III

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[1] To whom all inquiries should be sent.

[2] G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **84**, 313 (1962).

[3] G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962).

[4] W. E. Truce and J. R. Norell, *J. Am. Chem. Soc.*, **85**, 3231 (1963).

[5] R. H. Hasek, P. G. Gott, R. H. Meen, and J. C. Martin, *J. Org. Chem.*, **28**, 2496 (1963).

[6] J. F. King and T. Durst, *J. Am. Chem. Soc.*, **86**, 287 (1964).

[7] W. E. Truce, R. W. Campbell, and J. R. Norell, *ibid.*, **86**, 288 (1964).

[8] Infrared spectra were determined on a Baird AB-2 instrument.