Summary

1. The synthesis of hydroxy-ethyl vinyl ether is described.

2. It is shown that this vinyl derivative in contact with a trace of concentrated acid undergoes instantaneous rearrangement into ethylidene glycol.

3. The latter change is offered as strong support for a mechanism proposed for the acetal reaction postulating a "vinyl" derivative as an intermediate product.

4. This mechanism is elaborated so as to include similar reactions such as those occurring in glucoside and polysaccharide formation.

MONTREAL, CANADA

VINYL DERIVATIVES: THEIR RELATIONSHIP TO SUGARS AND POLYSACCHARIDES[1]

BY HAROLD S. HILL[2]

In a preceding[3] paper dealing with the mechanism of acetal formations, the synthesis of hydroxy-ethyl vinyl ether and its rearrangement into ethylidene glycol are described. The extreme ease and the instantaneous character of the latter change led to the suggestion that unsaturated derivatives of the vinyl type may be the intermediates through which many other reactions of hydroxy compounds take place. From the application of this idea to the transformation of the sugars and polysaccharides, it was concluded that an unsaturated sugar[4] such as (IV) which may be considered as a vinyl derivative occupies a position of importance in a logical scheme picturing the mechanism of such reactions as occur in glucoside and polysaccharide formation.

The present paper describes the synthesis of additional vinyl derivatives, their transformations, and shows that the relationship indicated above is in fact a close one.
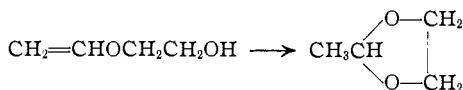
It seemed desirable first of all to show that the rearrangement of hydroxy-ethyl vinyl ether into ethylidene glycol

$$CH_2=CHOCH_2CH_2OH \longrightarrow CH_3CH \begin{matrix} O-CH_2 \\ | \\ O-CH_2 \end{matrix}$$

represents a general tendency toward cyclization in derivatives of this type. For this purpose the synthesis of hydroxypropyl vinyl ether (I) was undertaken, since this compound on rearrangement should give as readily the six membered cyclic acetal (II)

$$CH_2=CHOCH_2CH_2CH_2OH \longrightarrow CH_3CH \begin{matrix} O-CH_2 \\ | \\ CH_2 \\ | \\ O-CH_2 \end{matrix}$$

I   II
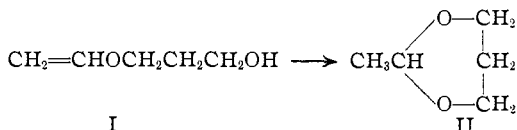
Hydroxypropyl vinyl ether (I) was synthesized, starting with paracetaldehyde. This was brominated at a low temperature and the product condensed *in situ* with trimethylene glycol, giving in good yield bromoethylidene trimethylene glycol. The action of sodium on this halogen acetal gave (I) in 85% yield through its sodium salt, the changes being represented as follows

$$(CH_3CHO)_3 + 2Br_2 \longrightarrow [(CH_2BrCHO)_2CH_3CHO] + 2HBr$$

$$CH_2BrCHO + HOCH_2CH_2CH_2OH \longrightarrow CH_2BrCH \begin{matrix} O-CH_2 \\ | \\ CH_2 \\ | \\ O-CH_2 \end{matrix}$$

$$CH_2BrCH \begin{matrix} O-CH_2 \\ | \\ CH_2 \\ | \\ O-CH_2 \end{matrix} + 2Na \longrightarrow CH_2=CHOCH_2CH_2CH_2ONa$$

$$CH_2=CHOCH_2CH_2CH_2ONa + H_2O \longrightarrow CH_2=CHOCH_2CH_2CH_2OH + NaOH$$
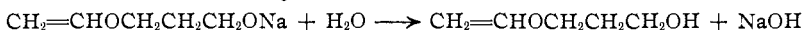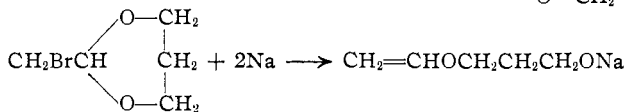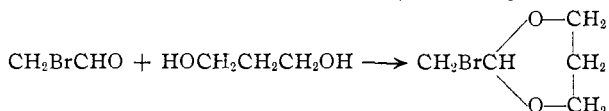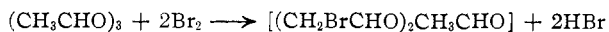
Hydroxypropyl vinyl ether resembles closely its lower homolog previously described.[3] It undergoes the same violent, quantitative rearrangement into (II) when brought into contact with a trace of 50% sulfuric acid or dry hydrogen chloride.

It is probable, therefore, that such instantaneous cyclizations represent a general type reaction and may be looked for in all hydroxy-alkyl vinyl ethers where the hydroxyl group is in the β- or γ-position.[5]

The next step was to show that a vinyl derivative will undergo reactions analogous to that of glucoside formation. For this purpose it was necessary to block off the free hydroxyl group of (I) by methylation, giving the methyl ether (III), the latter being conveniently prepared in good yield

[5] This is presumably an example of the still more general tendency toward cyclization exhibited by many classes of compounds having a hydroxyl in the 3- or 4-position to an unsaturated group, as evidenced by the formation of lactones, cyclic acid anhydration, oxidic forms of sugars and cyclic oxides. The first three involve the addition of a hydroxyl to a C=O, while in the last it is to a C=C group formed by an initial dehydration.

by the action of sodium on bromo-ethylidene trimethylene glycol, as indicated above, and the subsequent *in situ* reaction of the sodium salt of (I) with methyl iodide.

Comparison of this new ether with the postulated anhydro glucose (IV) shows the following relationships
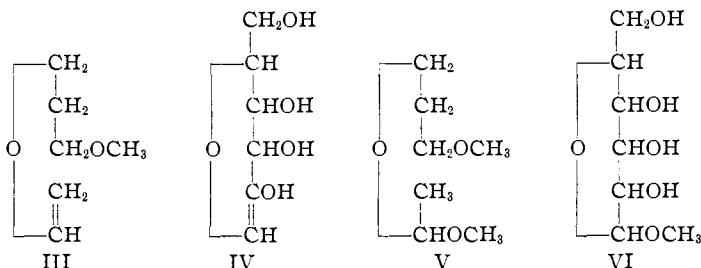

If (IV) is the intermediate in the formation of α-methyl glucoside (VI), then (III) under the same conditions should give the corresponding mixed acetal or "vinylide" (V).
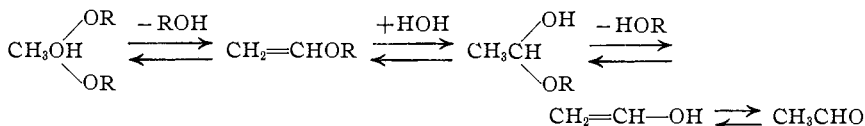
It was found that (III) on being mixed with an equimolecular amount of methyl alcohol and brought in contact with a trace of dry hydrogen chloride, undergoes an instantaneous reaction, the saturation in the molecule disappearing completely. Examination of the products disclosed that an interesting secondary reaction had taken place, for not only was the "vinylide" (V) found, but also a considerable amount of dimethyl acetal, $CH_3CH(OCH_3)_2$. Using an excess of methyl alcohol in the experiment, the latter acetal was formed almost exclusively.

It is considered that these results strongly support the general theory of vinyl derivatives as intermediates, for they indicate the labile character of the alcohol residue in acetals and point toward the existence of an equilibrium, however slight, between the saturated acetal on the one hand and a vinyl derivative on the other.

If other alcohols are present, there may be secondary additions to the vinyl derivative and the equilibrium is continually displaced until the most stable system is attained. It appears that, in general, the lower alcohols tend to displace those higher in a series. This phenomenon is similar to that of *alcoholysis* and the analogous well-known displacements in the acetal series. Presumably the mechanism is in all cases the same, passing as indicated through the intermediate vinyl stage.
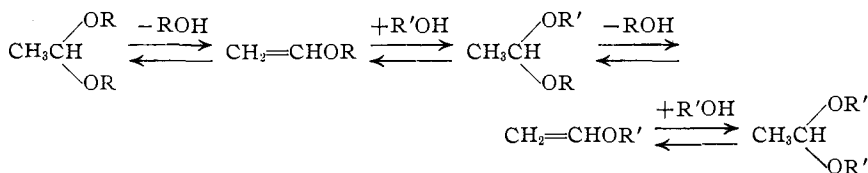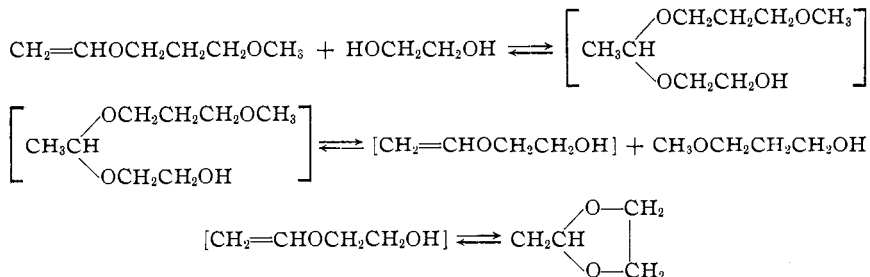
Hydrolysis, then, may be an identical reaction. Water instead of a lower alcohol adds onto the intermediate vinyl ether, shifting the equilibrium continually to the right. Analogous secondary equilibria are then established between the half acetal thus formed and vinyl alcohol and acetaldehyde.

$$CH_3OH\begin{matrix}/OR\\\\\backslash OR\end{matrix}\underset{}{\overset{-ROH}{\rightleftarrows}}CH_2{=}CHOR\underset{}{\overset{+HOH}{\rightleftarrows}}CH_3CH\begin{matrix}/OH\\\\\backslash OR\end{matrix}\underset{}{\overset{-HOR}{\rightleftarrows}}$$

$$CH_2{=}CH{-}OH\rightleftarrows CH_3CHO$$

Hydrolysis of a glucoside or polysaccharide may proceed along the same lines, namely, through the intermediate unsaturated sugar of the type (IV) which, by adding on water, displaces the partial equilibrium and yields a saturated sugar in its cyclic oxide form. The latter may be considered as a cyclic half acetal. That the reaction rests at this stage and does not proceed far toward the free carbonyl derivative, as in the case with acetals, is due to the general tendency for cyclization to take place in preference to *intermolecular* addition. This is well brought out in the following experiments.
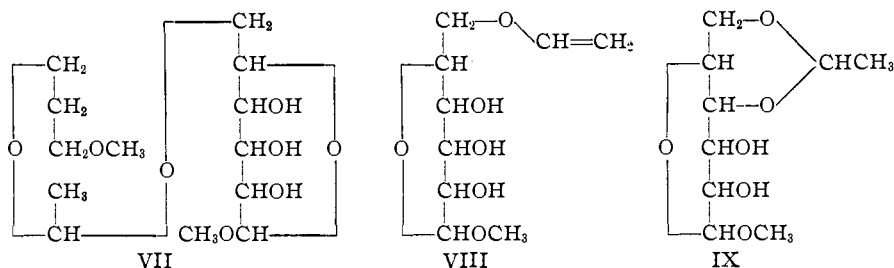
When equimolecular amounts of hydroxypropyl vinyl ether (I) and methyl alcohol are brought in contact with a trace of acid, the main product is ethylidene trimethylene glycol (II) rather than dimethyl acetal or the "vinylide" (V). Here, as in the case of sugars, cyclization is favored.

The reaction of ethylene glycol with methoxypropyl vinyl ether (III) lends further evidence. The products are ethylidene glycol, and monomethyl trimethylene glycol, presumably formed through an intermediate vinyl derivative as follows

$$CH_2{=}CHOCH_2CH_2CH_2OCH_3 + HOCH_2CH_2OH \rightleftarrows \left[CH_3CH\begin{matrix}/OCH_2CH_2CH_2OCH_3\\\\\backslash OCH_2CH_2OH\end{matrix}\right]$$

$$\left[CH_3CH\begin{matrix}/OCH_2CH_2CH_2OCH_3\\\\\backslash OCH_2CH_2OH\end{matrix}\right]\rightleftarrows[CH_2{=}CHOCH_2CH_2OH] + CH_3OCH_2CH_2CH_2OH$$

$$[CH_2{=}CHOCH_2CH_2OH]\rightleftarrows CH_2CH\begin{matrix}/O{-}CH_2\\\\\backslash O{-}CH_2\end{matrix}$$

It may be concluded, therefore, that the resulting cyclic form represents a more stable system than that of the mixed acetal.

Attempts were made to obtain addition reactions between methoxypropyl vinyl ether and α-methyl glucoside, and also glucose, which might be expected to give products related to disaccharides, such as (VII).

$$
\begin{array}{ccc}
\text{VII} & \text{VIII} & \text{IX}
\end{array}
$$

Structure VII:

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        ┌──────CH₃
┌──CH₂   │  CH──────┐
│  CH₂   │  CHOH    │
O  CH₂OCH₃ │ CHOH   O
│  CH₃   O  CHOH    │
│  CH────┘  CHOH    │
└──CH───────CH₃OCH──┘
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Structure VIII:

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        CH₂─O
        │      CH=CH₂
┌──CH   │
│  CHOH
O  CHOH
│  CHOH
└──CHOCH₃
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Structure IX:

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        CH₂─O
        │      CHCH₃
┌──CH   │
│  CH──O
O  CHOH
│  CHOH
└──CHOCH₃
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A great difficulty lay in the mutual insolubility of the vinyl derivative and the sugar. Using α-methyl glucoside, however, a partial reaction took place, the final product being again not the mixed acetal (VII) but rather ethylidene α-methyl glucoside (IX).

As in the preceding scheme, the first stage is logically the formation of (VII), followed by the establishment of an equilibrium with (VIII) and the final rearrangement of this vinyl intermediate into the cyclic acetal (IX). Here also the cylic structure is indicated as being the most stable system.

The extremely rapid and quantitative character of the above reactions (whether they be inter- or intramolecular) of the vinyl derivatives may be taken as evidence that the latter are true intermediates. It also explains their lack of appearance under the conditions occurring in such changes as acetal, glucoside and polysaccharide formation.

Experimental Part

Preparation of Bromo-ethylidene Trimethylene Glycol.—One hundred and thirty-two g. of paracetaldehyde was brominated at $-12°$ as previously described with 320 g. of bromine. After stirring the brominated mixture at $-10°$ for eight hours, 240 g. of trimethylene glycol was slowly added, keeping the temperature below $-10°$. Then the temperature was allowed to rise to $0°$ and the mixture stirred overnight, and later for four hours at $20°$. Extraction with ether was facilitated by the addition of ice water. The ether solution was neutralized with potassium carbonate, washed with 20% sodium hydroxide, water and dried over potassium carbonate. Two fractionations yielded 200 g. (55% reckoned on the bromine used) of bromo-ethylidene trimethylene glycol; b. p. 74–75° (10 mm.).

Preparation of Hydroxy-propyl Vinyl Ether.—Fifty-four g. of bromo-ethylidene trimethylene glycol was dissolved in 150 cc. of absolute ether in a three-necked flask equipped with a reflux condenser and an efficient mechanical stirrer protected from the atmosphere. Fourteen g. of freshly cut sodium was added, cooling the flask enough to keep the reaction from becoming too violent. After stirring overnight, the sludge of accumulated salts was washed with ether through a wire gauze to filter out a small amount of unchanged sodium. Enough water was added to dissolve the salts, the mixture was extracted three times with ether, and the latter solution dried over potassium carbonate. Fractionation yielded 25 g. (85% of the theoretical) of hydroxypropyl vinyl ether; b. p. 64–65° (10 mm.).

Anal. Subs., 0.2003: CO_2, 0.4305; H_2O, 0.1736. Calcd. for $C_5H_{10}O_2$: C, 58.82; H, 9.80. Found: C, 58.61; H, 9.63.

Hydroxypropyl vinyl ether is a colorless oil, strongly unsaturated against bromine in carbon tetrachloride solution, and yielding a monobenzoate with benzoyl chloride in dry pyridine solution. When treated with a few bubbles of dry hydrogen chloride, a violent reaction took place, the unsaturation completely disappearing. Neutralizing with potassium carbonate and distilling gave an almost quantitative yield of ethylidene trimethylene glycol; b. p. 108–110°.

The same transformation catalyzed with 50% sulfuric acid took place with explosive violence.

Reaction of Hydroxypropyl Ether with Methyl Alcohol.—Five and one-tenth g. hydroxypropyl vinyl ether and 1.6 g. of methyl alcohol were treated with a few bubbles of dry hydrogen chloride. After the sharp reaction was over, the products were neutralized with potassium carbonate, filtered and distilled, using a small bead column; 3.5 g. of ethylidene trimethylene glycol was obtained (b. p. 105–110°) as the main product. Using three times the amount of methyl alcohol, the main product was dimethyl acetal (b. p. 63–65°).

Preparation of Methoxypropyl Vinyl Ether.—Ninety g. of bromo-ethylidene trimethylene glycol in 250 cc. of absolute ether was treated with 23 g. of sodium as described above. After stirring overnight, most of the ether was distilled from the reaction flask (care being taken to exclude atmospheric moisture), 80 g. of methyl iodide was added and the mixture refluxed with stirring for sixteen hours. Enough water to dissolve the salts was added cautiously, the mixture extracted twice with ether and the latter solution washed with water and dried over potassium carbonate. Fractionation yielded 40 g. (69%) of methoxypropyl vinyl ether; b. p. 68–78° (152 mm.). Refractionation gave 32 g. of a pure product; b. p. 75–76° (137 mm.).

Anal. Subs., 0.1821: CO_2, 0.4140; H_2O, 0.1687. Calcd. for $C_6H_{12}O_2$: C, 62.07; H, 10.35. Found: C, 62.01; H, 10.28.

Reaction of Methoxypropyl Vinyl Ether with Methyl Alcohol.—Five and five-tenths g. of methoxypropyl vinyl ether was mixed with 1.5 g. of methyl alcohol, cooled and treated with a trace of 40% sulfuric acid. A vigorous reaction took place which was complete in a few seconds. The products were neutralized with potassium carbonate, washed with concd. calcium chloride to remove traces of CH_3OH and $CH_3OCH_2CH_2$, CH_2OH and dried over calcium chloride. Fractionation yielded 1 g. of dimethyl acetal (b. p. 63–65°), 2 g. of intermediate mixture and 3 g. of the mixed acetal $CH_3CH(OCH_3)$-$OCH_2CH_2CH_2OCH_3$ (b. p. 153–155°).

Anal. Subs., 0.2000: CO_2, 0.4142; H_2O, 0.1945. Calcd. for $C_7H_{16}O_3$: C, 56.76; H, 10.81. Found: C, 56.49; H, 10.81.

Reaction of Methoxypropyl Vinyl Ether with Ethylene Glycol. Five and eight-tenths g. of methoxypropyl vinyl ether was mixed with 3.1 g. of ethylene glycol and treated with a few bubbles of dry hydrogen chloride. On shaking a vigorous reaction took place, the unsaturation against bromine in carbon tetrachloride disappearing immediately. The product was neutralized with potassium carbonate and fractionated. The two main products were ethylidene glycol (b. p. 80–83°) and monomethyl trimethylene glycol, b. p. 86–92° (15 mm.). The latter product was further identified by its benzoate prepared in dry pyridine solution.

Anal. (benzoate). Subs., 0.2100: CO_2, 0.5264; H_2O, 0.1269. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 68.40; H, 6.80.

Reaction of Methoxypropyl Vinyl Ether with α-Methyl Glucoside.—Four g. of methoxypropyl vinyl ether was incorporated with 7.5 g. of finely powdered α-methyl glucoside and the mixture treated with a few bubbles of dry hydrogen chloride. Considerable heat was evolved although much of the glucoside did not go into solution.

After allowing to stand for four hours with occasional shaking, the paste was extracted with ether and the latter solution neutralized with solid potassium carbonate, filtered and evaporated in a vacuum. The residue was a small quantity of colorless sirup which crystallized after remaining in a vacuum for several weeks. After crystals were once obtained the sirups were readily crystallized by "seeding." Recrystallization from a mixture of ether and ligroin gave pure ethylidene α-methyl glucose, m. p. 77°.

Summary

1. The synthesis of hydroxypropyl vinyl ether and its methylated derivative is described.

2. The former compound, in contact with a trace of concentrated acid, is shown to rearrange quantitatively into the cyclic acetal, ethylidene trimethylene glycol.

3. Further evidence is brought forward regarding the mechanism of acetal, glucoside and polysaccharide formation, as well as the mechanism of the hydrolysis of this class of compounds.

4. This evidence supports the hypothesis of vinyl derivatives being the intermediates through which transformations of this nature take place.

MONTREAL, CANADA

DIHYDROXY- AND DICHLORO-KETO-HEXAHYDROTRIAZINES

BY JOHN B. EKELEY AND ADRIAN A. O'KELLY

Glyoxal and semicarbazide hydrochloride yield a mono-[1] and a disemi-carbazone.[2] Similarly the aliphatic 1,2-diketones yield disemicarbazones,[3] but not the mono-derivative. Aromatic diketones also yield semicarbazones in alkaline solution,[4] but in acid solution the monosemicarbazones condense to triazine derivatives.[3]

If, on the other hand, semicarbazide hydrochloride and the sodium bisulfite addition products of glyoxal, methyl glyoxal or of aliphatic 1,2-diketones are brought together in molecular proportions in hot water solution, there is a quantitative precipitation of a dihydroxy-keto-hexahydro-α-triazine, the compound being formed by a reaction accompanied by the splitting off of two moles of sodium bisulfite.
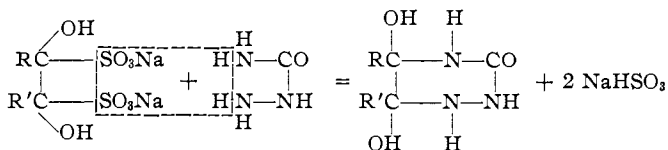
[1] O. Diels, *Ber.*, **35**, 347 (1902).

[2] Harries and Temme, *Ber.*, **40**, 171 (1907).

[3] Posner, *Ber.*, **34**, 3977 (1901).

[4] Thiele and Stange, *Ann.*, **283**, 6, 27 (1894); Biltz and Arnd, *Ber.*, **35**, 346 (1902).