[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY, UNIVERSITY OF WISCONSIN]

Structure of Reactants and the Extent of Acetal Formation

BY NELS MINNÉ AND HOMER ADKINS

A study of the relationship between the concentration at equilibrium in the acetal reaction and the structure of the alcohol and aldehyde has been continued, particularly with reference to the effect of the structure of the alcohol upon the extent of its reaction with tetrahydrofurfural.[1,2] The object of the experimentation was to measure the effect of various typical structures upon carbon to oxygen linkages.

Tables I and II contain a summary of all the reliable data, obtained in this Laboratory during the past ten years, upon the effect of the structure of the alcohol and aldehyde upon the conversion at equilibrium in the acetal

TABLE I

REACTION OF ACETALDEHYDE AND TETRAHYDROFURFURAL WITH VARIOUS ALCOHOLS

			Acetaldehyde			Tetrahydrofurfural		
Alcohol	B. p., °C.	Mm.	Moles alc. per mole of ald.	% Conv.	K_e	Moles alc. per mole of ald.	% Conv.	K_e
Phenylpropyl	127–130	17	11	99 M	13.30	5	95 M	9.48
n-Octyl	189–190	740	..	...	...	5	95 M	9.48
n-Hexyl	154–157	738	..	...	...	5	95 M	9.48
n-Lauryl	M. p. 24		..	...	...	5	90 M	4.03
Isoamyl	43–44	11	11	99 M	13.30	.	...	...
β-Aminoethyl			..	.. S	6.85	.	...	...
n-Amyl	134–135	740	11	98 M	6.48	5	89 M	3.55
β-Phenylethyl	120–121	27–30	11	98 M	6.48	5	89 M	3.55

---

[1] Adkins and Wade Adams, THIS JOURNAL, **47**, 1368 (1925); Hartung and Adkins, *ibid.*, **49**, 2517 (1927); Street and Adkins, *ibid.*, **50**, 162 (1928); Adkins and Broderick, *ibid.*, **50**, 178 (1928); Adkins, Semb and Bolander, *ibid.*, **53**, 1853 (1931).

[2] There has apparently been little done outside of this Laboratory upon the effect of the structure of the reactants upon the concentration at equilibrium in the acetal reaction. Attention should, however, be called to the very extensive studies of Skrabal and co-workers upon the rate of hydrolysis of acetals in rather dilute water solutions [*Z. Electrochem.*, **33**, 322 (1928), and *Z. physik. Chem.*, **122**, 357 (1926)]. The work of Herold and Wolf [*ibid.*, **B5**, 124 (1929), **B12**, 165 (1931)] upon the extent of hemiacetal formation as measured by absorption in the ultraviolet is also of interest. Their observations upon the effect of structure upon the extent of the hemiacetal reaction are, for the fifteen cases which they studied, in general agreement with the observations made in this Laboratory upon the extent of the acetal reaction with the same pairs of reactants. However, their prediction that the alcohols of higher molecular weight would show a decreasing affinity for acetal formation is not borne out by observations herewith reported. Further, their view that the efficacy of calcium chloride as a catalyst for the acetal reaction is due to its removing water from the sphere of reaction is not in accord with the results previously reported [Adams and Adkins, THIS JOURNAL, **47**, 1358 (1925)] upon experiments intended to test out that hypothesis. They have apparently overlooked this paper as well as another upon hemiacetal formation [Adkins and Broderick, *ibid.*, **50**, 499 (1928)].

TABLE I (*Concluded*)

			Acetaldehyde			Tetrahydrofurfural		
Alcohol	B. p., °C.	Min.	Moles alc. per mole of ald.	% Conv.	K_e	Moles alc. per mole of ald.	% Conv.	K_e
β-Phenylethyl			5	92 M	5.38	.	...	...
n-Heptyl	80–82	16–17	5	92 M	5.38	5	95 M	9.48
n-Heptyl			..	...	...	3	87 M	11.40
n-Butyl	114–115	740	11	96 B	3.08	5	80 M	1.44
n-Butyl			11	96 M	3.08	.	...	...
Tetrahydrofurfuryl	85–86.5	28	..	...	...	5	80 M	1.44
Isobutyl	106	738	11	96 M	3.08	5	78 M	1.22
Isobutyl			11	(93 A)	...	.	...	...
Methyl	63.5–64	739	11	95 B	2.41	5	86 M	2.34
Methyl			11	94 A	1.95	.	...	...
Ethyl	77–77.5	738	11	92 H	1.40	5	79 M	1.26
Ethyl			11	91 B	1.21	.	...	...
Ethyl			11	91 A	1.21	.	...	...
Ethyl			11	91 M	1.21	.	...	...
β-Iodoethyl			11	91 S	1.21	.	...	...
n-Propyl	95–96	740	11	90 A	1.06	5	80 M	1.44
n-Propyl			11	90 S	1.06	.	...	...
β-Chloroethyl	128	740	11	90 M	1.06	5	76 M	1.04
β-Chloroethyl			5	76 M	1.04	.	...	...
β-Chloroethyl			3	62 M	1.10	.	...	...
β-Ethoxyethyl			11	89 S	0.94	5	79 M	1.26
β-Methoxyethyl	121–122	740	11	89 S	.94	5	72 M	0.77
Benzyl	199–200	734	11	89 M	.94	5	79 M	1.26
Allyl	94–95.5	738	11	88 S	.84	5	72 M	0.77
β-Bromoethyl			11	87 S	.76	.	...	...
β-Nitroethyl			11	83 S	.52	.	...	...
Cyclohexylcarbinol	84	13	5	56 M	.26	.	...	...
Cyclohexanol	157–158	740	5	56 M	.26	5	88 M	3.15
Pentanol-2	116–117.5	738	11	72 M	.23	.	...	...
β-Carbethoxyethyl			11	66 S	.155	.	...	...
Butanol-2	98–99	738	11	64 H	.136	5	65 M	0.47
Butanol-2			11	63 M	.128	.	...	...
Octanol-2	78	12	5	46 M	.130	5	90 M	4.03
Octanol-2			..	...	...	3	86 M	4.30
Propanol-2	80–80.5		11	59 H	.101	5	49 M	0.166
Propanol-2			11	60 B	.107	.	...	...
Tert.-butyl	81.5	738	5	23 M	.019	5	38 M	0.073
Tert.-butyl			11	31 A	.015	.	...	...
Tert.-amyl	100	738	11	21 A	.006	.	...	...
Tert.-amyl			11	21 M	.006	.	...	...
β-Cyanoethyl	129–131	33	..	...	...	5	32 M	0.045

reaction. The data for the eighty-five acetals have been arranged in two tables, the first containing the data for the acetals of acetaldehyde and tetrahydrofurfural and the second for a miscellaneous group of acetals. The acetals are arranged in Table I in the order of decreasing value of K_e for acetals of acetaldehyde, and in Table II simply in order of decreasing

TABLE II

EXTENT OF REACTION OF VARIOUS ALCOHOLS AND ALDEHYDES

Alcohol	Aldehyde	Moles alc./Moles ald.	% Conv.	K_e
Isobutyl	*n*-Butyr-	11	(96 A)	
Isobutyl	*n*-Butyr-	11	98 M	6.48
Methyl	*n*-Butyr-	11	(96 A)	
Methyl	*n*-Butyr-	11	97 M	4.22
n-Propyl	*n*-Butyr-	11	94 A	1.95
Ethyl	Aminoacet-	11	93 H	1.63
Ethyl	Hept-	10	92 H	1.37
Ethyl	Cyanacet-	13	93 H	1.30
Ethyl	Bromoacet-	11	91 H	1.21
n-Butyl	*n*-Butyr-	11	91 M	1.21
Ethyl	*n*-Butyr-	11	(92 A)	
Ethyl	*n*-Butyr-	11	91 H	1.21
Ethyl	*n*-Butyr-	11	91 M	1.21
Ethyl	Propion-	11	(89 A)	
Ethyl	Propion-	11	91 H	1.21
Ethyl	Isobutyr-	11	(84 A)	
Ethyl	Isobutyr-	11	86 M	0.68
Heptyl	Furfur-	5	68 M	.58
Ethyl	β-Chloroprop-	11	84 H	.56
Ethyl	Glycolic	11	75 H	.28
Butanol-2	*n*-Butyr-	11	74 M	.26
Octanol-2	*n*-Butyr-	5	53 M	.20
Ethyl	Acrylic	11	68 H	.176
Octanol-2	Benz-	5	49 M	.160
Methyl	Furfur-	11	61 A	.114
Methyl	Furfur-	5	42 Bl	.100
Cyclohexylcarbinol	Isobutyr-	5	42 M	.100
n-Butyl	Benz-	11	56 Sb	.083
Ethyl	Benz-	11	56 Sb	.083
Propanol-2	*n*-Butyr-	11	(59 A)	
Propanol-2	*n*-Butyr-	11	53 M	.069
Propanol-2	Propion-	11	50 A	.057
Ethyl	Furfur-	11	44 Bl	.039
Ethyl	Furfur-	11	45 M	.041
Ethyl	*m*-Nitrobenz-	11	42 A	.034
Tert.-butyl	*n*-Butyr-	11	38 M	.026
Propanol-2	Isobutyr-	11	(37 A)	
Propanol-2	Isobutyr-	11	33 M	.018
Ethyl	Cinnam-	11	(36 A)	
Ethyl	Cinnam-	11	29 H	.013
Ethyl	Croton-	11	27 H	.011
Propanol-2	Furfur-	11	25 A	.009
Propanol-2	Benz-	11	19 Sb	.005
Propanol-2	Cinnam-	11	19 A	.005
Tert.-butyl	Isobutyr-	11	18 M	.004
Octanol-2	Furfural	5	11 M	.003
Tert.-butyl	Furfural	6	0 M	.000

value of K_e. The observer of each reaction mixture has been indicated by a letter placed after the percentage conversion for the acetal (A for Adams B for Broderick, Bl for Bolander, H for Hartung, M for Minné, S for Street and Sb for Semb).[3]

One of the primary objects of this investigation was to ascertain whether, if an alcohol, for example, gave the same percentage conversion at equilibrium with two aldehydes, a second alcohol would give the same conversion with one aldehyde as with the other. In seeking an answer to this question nineteen alcohols have been tested with acetaldehyde and tetrahydrofurfural. Among these there is fair agreement in fifteen cases between the values of K_e for the reaction of the alcohol with the two aldehydes. With eight of these fifteen alcohols there is almost perfect agreement, that is to say, the percentage conversion at a given ratio of reactants is not more than 1% different for one aldehyde than for the other. However, the four secondary and tertiary alcohols listed below show a very different conversion with acetaldehyde as compared with tetrahydrofurfural: cyclohexanol, 56 and 88%; butanol-2, 46 and 65%; octanol-2, 46 and 90%; *tert.*-butyl, 23 and 38%. These results indicate very definitely that the relative affinity manifested by two compounds for the formation of a given type of linkage is not independent of the second component of the reaction.

The effect of lengthening the chain of the alcohol is not so clear in the case of the data for acetaldehyde as it is for tetrahydrofurfural, since most of the determinations for the former aldehyde were made for such a high ratio of alcohol to aldehyde that the conversions for this type of alcohol are so high that small differences between alcohols are not apparent. The values of K_e for tetrahydrofurfural and the primary alcohols with normal chains and the carbon content indicated in parentheses are: (1) 2.34, (2) 1.26, (3) 1.44, (4) 1.44, (5) 3.55, (7) 9.48, (8) 9.48, (12) 4.03. The values for the same aldehyde with three secondary alcohols are propanol-2, 0.166; butanol-2, 0.47; and octanol-2, 4.03. Somewhat similar values hold for the reaction of four secondary alcohols with acetaldehyde. These values

---

[3] All of the values for K_e reported by Adams, Broderick, Hartung and Street have been recalculated and a majority of them have been checked by experiment if two observers had not previously done so. The values of K_e were recalculated upon the basis of concentrations expressed in mole fractions. The values of K_e reported in the earlier papers were calculated upon concentrations of moles per liter and comparisons between aldehydes made upon the calculated values of the decrease in free energy. These original calculations were ill advised for two reasons. First, compounds which show the same percentage conversion but have a different molecular volume will have therefore different values of K_e, and so appear to have different affinity values when as a matter of fact they are identical in their chemical behavior in the acetal reaction. Second, the use of values for the decrease of free energy so calculated adds nothing significant to the comparison of aldehydes and alcohols in the acetal reaction and is open to misinterpretation.

indicate that affinity in acetal formation first decreases slightly with increase in length of the carbon chain and then materially increases.

Simple branching of the chain has relatively little effect upon the extent of the acetal reaction. Isobutyl alcohol with acetaldehyde and *n*-butyraldehyde shows values which are not essentially different from those for butanol-1. Isobutyraldehyde has a lower value than *n*-butyraldehyde but very little lower than propionaldehyde, which has the same length of chain. However, branching of the carbon chain as exemplified in the cyclohexyl group is rather effective in lowering affinity for acetal formation. Five moles of cyclohexylcarbinol reacted with one mole of acetaldehyde to the extent of only 56% while hexylcarbinol, having the same carbon content, reacted to the extent of 92%. A similar negative though less marked effect of the cyclohexyl group was observed in the reaction of cyclohexylcarbinol with isobutyraldehyde. It was surprising that cyclohexylcarbinol reacted to a less extent with acetaldehyde than did phenylcarbinol despite the unsaturation and general negative character of the benzenoid nucleus.

The effect of an alkene linkage in a molecule either of an alcohol or an aldehyde, but especially the latter, was very marked in lowering affinity for the acetal reaction. Tetrahydrofurfural with ethanol had a value of K_e of 1.26, while furfural had less than one-half the percentage conversion with a value for K_e of 0.041. Propionaldehyde and butyraldehyde had 1.21 while the corresponding unsaturated aldehydes had 0.176 (acrolein) and 0.011 (crotonaldehyde). Benzaldehyde was almost identical with acrolein, and cinnamic aldehyde with crotonaldehyde. Unsaturation in the alcohol was apparently much less effective, as allyl alcohol was 0.84 with acetaldehyde, and 0.77 with tetrahydrofurfural, values which are not so much lower than for propanol-1, *i. e.*, 1.06 and 1.44.[4]

The primary alcohols, if there were no complicating substituent, reacted with acetaldehyde to the extent of about 90% at a ratio of one mole of aldehyde to 5 moles of alcohol, while secondary alcohols gave conversions less than one-half as great. Simple *tert.* alcohols reacted with acetaldehyde to about one quarter the extent of the primary alcohols, the value of K_e for *n*-butyl, *sec.*-butyl and *tert.*-butyl being 3.08, 0.136 and 0.019, respectively. However, with alcohols and aldehydes of more complicated structure these relationships are far from being so simple. For example, cyclohexylcarbinol, a primary alcohol, behaved like a *sec.* alcohol in its reaction with acetaldehyde and isobutyraldehyde, having values of K_e of 0.26 and 0.100. Similarly octanol-2 behaved like a simple secondary alcohol with acetaldehyde (K_e 0.130) but with tetrahydrofurfural it had a value of 4.03, which is materially higher than that shown by the simple

---

[4] It must be kept in mind that while unsaturation *decreased* the extent of the acetal reaction it greatly *enhanced* the rate of the reaction. Furfural, for example, reacted several hundred times as rapidly as tetrahydrofurfural under the same conditions but it proceeded less than one-half as far.

primary alcohols. Octanol-2 also gave a higher conversion with benzaldehyde than did any of the primary alcohols. In contrast with the abnormally high value of octanol-2 for benzaldehyde and tetrahydrofurfural was its abnormally low value (0.003) for furfural, with which it reacted to less than half the extent of propanol-2.

The effect of the phenyl group upon the acetal reaction might be ascribed to a combination of unsaturation and branching of the carbon chain but it seems simpler to regard it as a substituent. If the phenyl group in benzyl alcohol is regarded as substituted in methanol, then it had a small influence in decreasing the reaction with acetaldehyde or tetrahydrofurfural to the extent of about 7%. However, when substituted in ethyl or propyl alcohol the phenyl group increased the extent of the acetal reaction just as did the corresponding large alkyl groups. When directly attached to the aldehyde group as in benzaldehyde, the affinity of the aldehyde for acetal formation was low, being only 56% with 11 moles of ethanol to 1 mole of benzaldehyde, and not much greater than that given by furfural. When the phenyl group was further from the aldehyde group, as in cinnamic aldehyde, it was almost without effect since crotonic and cinnamic aldehydes gave approximately the same conversions with ethanol.

Certain substituents in ethanol show the following values of K_e in the reaction with acetaldehyde: iodo the same as the unsubstituted ethanol, 1.21, chloro 1.06, methoxy and ethoxy 0.94, bromo 0.76, nitro 0.52, and carbethoxy 0.155. When some of these groups were substituted in acetaldehyde they showed the following values for K_e in the reaction with ethanol: amino 1.63, cyano 1.30, bromo 1.21 and chloromethyl 0.56. The most striking effect was the negativity of the cyano group in β-cyanoethyl alcohol (ethylene cyanohydrin), which reacted with tetrahydrofurfural to the extent of only 32% (K_e = 0.045).

The extents of the reactions of the three methylcyclohexanols with tetrahydrofurfural were also determined. Samples of the three structural isomers (each a mixture of geometrical isomers) were obtained from the Eastman Kodak Company and upon fractionation showed the following boiling points: 2-methylcyclohexanol 162–163.5°, 3-methylcyclohexanol 168.5–170°, 4-methylcyclohexanol 169.5–171.5°. These compounds just after distillation gave the following conversions to acetal when allowed to react (5 moles) with tetrahydrofurfural (1 mole): 2-methylcyclohexanol 85%, 3-methylcyclohexanol 50% and 4-methylcyclohexanol 60%. Samples of the 2-methyl and the 4-methyl compound prepared in this Laboratory by hydrogenation of the corresponding phenols over nickel at 175°, 120–200 atmospheres, and having the same boiling points as the Eastman products, gave conversions in the acetal reaction of 87 and 82%, respectively. The first of these values is in good agreement with that obtained with the Eastman product while the value for the 4-methyl compound is

22% higher than previously observed. Moreover, the sample of the 3-methyl compound gave, when allowed to stand for several months after distillation and before use, a conversion of 68%, or 18% higher than when freshly distilled. All of these variations are understandable since it is well known that different methods of hydrogenation produce different proportions of isomers, and that one geometrical isomer is labile, so that changes in their proportion may occur on standing. The conclusion seems inescapable that different geometrical isomers show different affinity values for acetal formation although this must be confirmed by ascertaining the affinity for acetal formation of the pure *cis* and *trans* isomers of the three structurally different methylcyclohexanols.[5]

Experimental Part

Tetrahydrofurfural has apparently not hitherto been prepared in any considerable quantities. Scheibler, Sotscheck and Friese[6] prepared as much as 6 g. of "crude product" in a single experiment and unreported amounts of a relatively pure compound. The quantities needed for the investigation described herewith were relatively large so that it was necessary to make a thorough study of its preparation. Bolander[1] worked out the first step, *i. e.*, the preparation of furfural acetal. The procedure for the hydrogenation of furfural acetal in good yield to tetrahydrofurfural acetal over a nickel catalyst was developed by Covert and Connor.[7] The third step in the preparation of the desired aldehyde, that is, the hydrolysis of tetrahydrofurfural acetal, proved to be a difficult one because of the readiness with which the aldehyde is resinified and also because of the difficulty of separating it from the alcohol and water in the mixture after hydrolysis. It appears unnecessary to give a detailed account of the various modifications of the procedure which were made in developing a satisfactory process, so it must suffice to describe briefly the preferred procedures.

One mole (174 g.) of diethyl tetrahydrofurfural acetal with 15 moles of water (270 g.) and 0.015 g. of hydrogen chloride were placed in a 2-liter 3-necked flask provided with a reflux condenser, a mechanical stirrer with a mercury seal, and a thermometer. The reaction mixture was heated on a steam-bath at 80° with stirring for five to ten hours, the mixture being homogeneous after about one hour. When hydrolysis was complete, as determined by a titration of an aliquot by the sodium sulfite method, the hot solution was left just acid to litmus by almost neutralizing with solid sodium carbonate (about 0.5 g.). It was found advisable to calculate the amount of sodium carbonate necessary by titrating an aliquot with 0.02 N sodium carbonate solution using methyl orange as an indicator. The reaction mixture was then rapidly cooled and 150 g. of anhydrous sodium sulfate added. After several hours the liquid was filtered off the sodium sulfate and another portion of the drying agent added. The process was repeated until 500 g. of sodium sulfate had been used, the drying process requiring twenty-four hours. The dried product was then fractionated at 6–10 mm. from a 250-ml. flask through a Widmer column having a spiral 24 cm. in length. The fraction 25–35° was about 60% aldehyde, while that from 35–45° was fairly pure. The lower fraction was dried with sodium sulfate together with the aldehyde (5–10 g.) extracted with ether from the 500 g. of sodium sulfate used earlier in the process. All the aldehyde was then carefully refrac-

---

[5] The separation of the isomers has just been reported. Skita and Faust, *Ber.*, **64B**, 2878 (1931); Hückel and Hagenguth, *ibid.*, 2892.

[6] Scheibler, Sotscheck and Friese, *ibid.*, **57**, 1443 (1924); *ibid.*, **58**, 1961 (1925).

[7] Covert, Connor and Adkins, THIS JOURNAL, **54**, 1655 (1932).

tionated, from 35 to 50 g. being obtained, b. p. 35–37° (8 mm.). The excess water may also be largely removed by fractionation at 25–32° (13–15 mm.) through a Widmer column having a spiral 35 cm. in length and the residue dried as described above. About 15–20% of the aldehyde was lost in the water distillate but the yield of aldehyde obtained was about the same as by the less tedious process described above.

The yield of diethyl furfural acetal from furfural was from 15 to 20%, the yield of the tetrahydrofurfural acetal was 75 to 80%, while the conversion of the latter to tetrahydrofurfural in eight preparations was 35 to 50%. This is an over-all yield of 4 to 8% of tetrahydrofurfural based upon the furfural.

Tetrahydrofurfural is a colorless, somewhat viscous liquid of acrid though not sharp odor. It has the following constants: b. p 144–145° corr. (740 mm.); d_4^{25} 1.10947; n_D 1.4700 to 1.4708; M_D 24.54, calcd., 24.72. Samples of the aldehyde during the course of several weeks became yellow, solid particles appeared and formic acid was apparently produced. The aldehyde showed no signs of change at 20–25° in a desiccator during the course of a week. Scheibler, Sotscheck and Friese in their first publication on tetrahydrofurfural gave the following constants: b. p. 45–47° (29 mm.), b. p. 142–143° (779 mm.). d_4^{20} 1.0501, n_D 1.47036, M_D 26.60. In their second paper they report d_4^{20} 1.0727, n_D 1.43658, M_D 24.43. The writers found that products of n_D 1.4330 to 1.4350 showed a lower tetrahydrofurfural content by titration than did the product n_D 1.4700–1.4708.

Di-(β-Ethoxyethyl) Acetal of Tetrahydrofurfural.—The di-(β-ethoxyethyl) acetal of furfural was prepared from furfural and β-ethoxyethanol (cellosolve) by the method described for the diethyl acetal. Three moles of furfural, 18 moles of cellosolve and 0.0036 g. of hydrogen chloride were allowed to react for four days until the conversion to the acetal was 40% of the theoretical. The water, cellosolve and furfural were then largely removed by distillation up to 76° at 18 mm. through a Widmer column. The residue was then fractionated at 2 to 4 mm. through a heated Widmer column. A yield of 212 g. of acetal (27.4%), b. p. 131–132° (2 mm.), 259° (740 mm.) was obtained.

The acetal (104 g.) was hydrogenated during the course of four hours at 150°, 130–200 atm., over 4 g. of a nickel catalyst of the ammonium carbonate type.[4] The product was fractionated twice through an electrically heated Widmer column. Twenty-eight grams (69%) of di-(β-ethoxy ethyl) acetal of tetrahydrofurfural, b. p. 131–136° (4–5 mm.), was obtained. There was an additional yield of slightly impure material corresponding to 8%. The compound was analyzed not only for carbon and hydrogen (see Table III) but a weighed sample was also subjected to hydrolysis and the tetrahydrofurfural so produced titrated. The amount of aldehyde formed was 98.8% of the amount calculated from the weight of acetal taken. Cellosolve (4.5%) (0.044 mole) and the β-ethoxyethyl ether of tetrahydrofurfuryl alcohol (6.7%) (0.040 mole) were also produced during the process of hydrogenating the acetal of furfural. The correspondence in molecular equivalents of cellosolve and ether formed indicates that these two compounds may be considered to be formed as in the hydrogenation and splitting of ethyl furfural acetal.[4]

Determination of the Concentration of Aldehydes.—The sodium sulfite method of titration was used for the determination of all the aldehydes except benzaldehyde, for which the hydrogen peroxide method was used. The acid solution for the sulfite method was not only standardized against the appropriate aldehyde but in the presence of the alcohol which would be in the sample later submitted to analysis. The ratio of alcohol to aldehyde in the sample used for standardization should be the same as that in the sample to be analyzed. The importance of this is evidenced by the following. A solution of sulfuric acid which was 0.202 *N* against sodium carbonate was 0.241 *N* against furfural, 0.2335 *N* against tetrahydrofurfural and 0.222 *N* against acetaldehyde, in the presence of ethanol. However, in the presence of an alcohol (in the ratio of alcohol to aldehyde which existed at equilibrium starting with the reactants in a 5 to 1 ratio) the normality figure for tetrahydrofurfural must be multiplied by 1.008 for cellosolve, 1.22 for heptyl, 1.72 for benzyl, 1.85 for phenylethyl and 3.64 for phenylpropyl alcohol. The factor for furfural in the presence of heptyl alcohol was 1.19 and 1.18 for octanol-2.

The procedure used in carrying out the studies on concentration at equilibrium was essentially the same as that previously described except in a few particulars. In the case of acetaldehyde a known weight of the aldehyde was sealed up in a glass tube and cooled to 0° before it was introduced into the alcohol. In the case of acetaldehyde, *n*-butyraldehyde and isobutyraldehyde, a titration was made to ascertain the exact concentration of the aldehyde in the alcohol solution before the catalyst was added. The concentration of the catalyst, hydrogen chloride, was 5 milligrams per mole of aldehyde except that in order to secure a sufficiently rapid rate of reaction 100 milligrams of hydrogen chloride per mole of tetrahydrofurfural was used.

Homogeneity of the Reaction Mixtures.—All of the reaction mixtures contained a considerable excess of alcohol over that required for the formation of an acetal. This was in order to prevent the separation of water formed in the reaction. However, the solubility of water in some of the alcohols of higher molecular weight is sufficiently low that it was feared that the high conversions to acetal observed were due in part to the separation of water. However, observations of the reaction mixture under a microscope at a magnification of 350 diameters, even after long standing, failed to show any lack of homogeneity. The solubility of water was found to be greater than 1 ml. in 25 ml. of heptanol-1, or 37.5 ml. of octanol-2. The amount of water formed by the reaction of either of these alcohols with tetrahydrofurfural never exceeded 1 ml. of water in 45 ml. of alcohol, so there seems no reason to doubt that the reaction mixtures were in all cases homogeneous.

Hydrolysis of Acetals.—There has never been any evidence for false equilibria or side reactions under the conditions of these studies. However, the extent of hydrolysis of the diethyl acetals of furfural and of tetrahydrofurfural and of the di-(β-ethoxyethyl) acetal of tetrahydrofurfural was determined. For example, 0.091 mole of diethyl furfural acetal, 0.091 mole of water, 0.27 mole of ethanol and 0.000465 g. of hydrogen chloride were allowed to react at 25°. Thirty-five per cent. of the acetal was hydrolyzed after twenty-five minutes, 55% after fifty minutes and 66% at the end of one and one-half hours; reaction ceased with a total hydrolysis of 67% of the acetal. This value is in excellent agreement with that for synthesis under similar conditions, although less than thirty minutes was required for the completion of synthesis.

Similar experiments were conducted with the acetal of ethanol and of cellosolve with tetrahydrofurfural. The ratio of reactants was 0.01 mole of acetal, 0.03 mole of alcohol, 0.01 of water and 0.001 g. of hydrogen chloride. Hydrolysis had proceeded to equilibrium after about one month. In the case of cellosolve the hydrolysis was 20 to 22%, while for ethanol it was 20 to 21%. These experiments demonstrate again the enormous difference in the rate of reaction of furfural as contrasted with the saturated aldehydes, and also the greater speed of synthesis as compared with hydrolysis.

Isolation of Various Acetals.—Small amounts of a number of acetals of tetrahydrofurfural were isolated, from the reaction mixtures set up for the purpose of determining the extent of the reaction, in essentially the same manner as the ethyl acetal. These products were fractionated as carefully as the small quantity of material involved would permit but in a few cases they were perhaps not entirely free of the alcohol involved. Qualitative tests showed them in every case to be free of tetrahydrofurfural. Their boiling points were in general determined by the capillary tube method described by Kamm[8] except that the determination was made under reduced pressure. The sam-

---

[8] Kamm, "Qualitative Organic Analysis," John Wiley and Sons, Inc., New York, p. 118.

ple was placed in a test-tube 1 cm. in diameter, which was attached to a small reflux condenser the outlet from which led to a vacuum pump. The data on the analysis and certain of the physical constants of these and other compounds not hitherto described are given in Table III.

Time for Attainment of Equilibrium.—The alcohols and aldehydes were allowed to react in a thermostat at 25°. The reaction of furfural and some of the other unsaturated aldehydes was complete after an hour or two, the saturated aldehydes other than tetrahydrofurfural after two days, while the latter required six to eight days. Titrations were usually begun after two days and continued at intervals of two days until variations in analyses were less than 0.5%. In many cases titrations made after several months confirmed the fact that equilibrium was attained in almost all cases after ten days. It was interesting to observe that tetrahydrofurfural, which in the pure state began to deteriorate after a week or so, appeared to remain unchanged for many months in the presence of alcohol.

Purification of Reagents.—The alcohols and aldehydes, other than those that have been described in the preceding paragraphs, were purified as previously described in this series of papers or by standard methods.

Reliability of Data in Tables I and II.—An experienced operator can readily duplicate analyses for aldehyde to within 0.5%, and duplicate his observations on the percentage conversion of an aldehyde to its acetal in different reaction mixtures to within less than 1%. In many cases, as indicated in the tables, different operators have observed percentage conversions which agreed to within less than 1%. However, it seems safer to attach no significance to variations in extents of conversion of less than 3%. The value of K_e changes very rapidly with small changes in the percentage conversion, so that if the latter is very high (93–95%), little significance should be attached to *variations* of K_e. The data on representative acetals presented by Semb and Bolander and in this paper show that the value of K_e is independent of the ratio of reactants and thus is a

TABLE III

ANALYSES AND PHYSICAL CONSTANTS

Compound	B. p., °C.	Mm.	n_D	d_4^{25}	M_D Calcd.	M_D Found	Calcd. % C	Calcd. % H	Found % C	Found % H
Acetals of acetaldehyde										
n-Heptyl($C_{16}H_{34}O_2$)	153	12	1.4288	0.8372	79.12	79.52	74.34	13.27	74.30	13.32
Phenylpropyl($C_{20}H_{26}O_2$)	182–185	2	1.5229	1.0049	90.95	90.64	80.50	8.72	80.32	8.94
Acetal of furfural										
β-Ethoxyethyl($C_{13}H_{22}O_5$)	131–132	2	1.4534	1.0374	67.48	67.27	60.42	8.59	60.03	8.59
Acetals of tetrahydrofurfural										
n-Amyl($C_{15}H_{30}O_3$)	145	9.5					69.70	11.71	69.71	11.67
n-Butyl($C_{13}H_{26}O_3$)	114	9.5					67.76	11.39	67.83	11.45
β-Ethoxyethyl($C_{13}H_{26}O_5$)	135	4	1.4403	1.0095	68.25	68.47	59.58	9.99	59.53	10.06
n-Hexyl($C_{17}H_{34}O_3$)	167–173	15	1.4433				71.26	11.97	71.08	11.95
Phenylethyl($C_{21}H_{26}O_3$)	195–198	3	1.5342				77.25	8.03	77.05	7.90
Phenylpropyl($C_{23}H_{30}O_3$)	226	9.5					77.94	8.54	78.02	8.67
Tetrahydrofurfuryl ($C_{15}H_{26}O_5$)	163	9.5					62.89	9.16	62.13	9.19
Ether										
α-(β-Ethoxy ethyl) Tetrahydrofurfuryl ($C_9H_{18}O_3$)	76	9	1.4360	0.9802	46.47	46.41	62.01	10.42	61.94	10.26

true equilibrium constant. The redetermination and recalculation of results previously reported have led to the elimination as unreliable of the values previously given for isoamyl, β-phenylethyl and benzyl acetals of acetaldehyde, and for the *n*-butyl acetal of butyraldehyde. The percentage conversions reported for the first time in this paper represent on the average six analyses of three different reaction mixtures at equilibrium.

Summary

The extent of reaction of tetrahydrofurfural with a variety of alcohols has been determined and the extent of the reaction of a number of other aldehydes and alcohols has been determined or redetermined and all previous results on the extent of this reaction have been recalculated to a comparable basis. All of these results on the relation of structure to affinity in the acetal reaction have been summarized as briefly as is feasible in Tables I and II and in the ensuing discussion.

The relative reactivity of the secondary and tertiary alcohols with acetaldehyde and tetrahydrofurfural, and the behavior of cyclohexylcarbinol and the three methylcyclohexanols with acetaldehyde all point to an important conclusion, *i. e.*, *the spacial characteristics of a molecule may be an important factor in determining the binding power at a linkage, just as it has long been known that space relationships may modify the rate at which a reaction proceeds. In other words, steric as well as structural factors determine the strength of bonds.*

A process has been developed for preparing tetrahydrofurfural of excellent quality in fair yields. A number of acetals not hitherto described are reported.

MADISON, WISCONSIN

RECEIVED JUNE 30, 1932
PUBLISHED JANUARY 11, 1933