The Hydration and Polymerisation of Succinaldehyde, Glutaraldehyde, and Adipaldehyde

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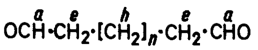
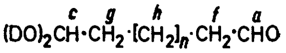
The ^{1}H n.m.r. spectra of solutions of succinaldehyde, glutaraldehyde, and adipaldehyde in deuterium oxide have been studied. At room temperature, the major component of solutions of succinaldehyde and glutaraldehyde is a cyclic monohydrate which is accompanied by the free aldehyde $OCH\cdot CH_2\cdot[CH_2]_n\cdot CH_2\cdot CHO$, the acyclic monohydrate $(DO)_2CH\cdot CH_2\cdot[CH_2]_n\cdot CH_2\cdot CHO$, and the dihydrate $(DO)_2CH\cdot CH_2\cdot[CH_2]_n\cdot CH_2\cdot CH(OD)_2$; at higher temperatures the free aldehyde content increases, mainly at the expense of the cyclic monohydrate. Adipaldehyde, by contrast, forms only the acyclic dihydrate. Although the undiluted aldehydes polymerise readily, their neutral aqueous solutions are stable for long periods; acidification induces rapid polymerisation. A common mechanism is suggested for hydration and polymerisation.

AQUEOUS solutions of aliphatic dialdehydes, especially glutaraldehyde, are widely used as cross-linking reagents for proteins, both technologically in the tanning of leather,[1] and scientifically in the preparation of protein crystals and proteinaceous tissues for *X*-ray crystallography, electron microscopy, and other studies.[2] As a preliminary to an investigation of the chemical nature of the cross-linking reaction, it seemed desirable to elucidate the nature of the reagent and the present paper deals with the nature of aqueous solutions of three aliphatic dialdehydes, *viz.*, succinaldehyde, glutaraldehyde, and adipaldehyde; a preliminary account of the work on glutaraldehyde has been published.[3] Other workers have shown that aqueous solutions of glyoxal contain both open-chain and cyclic (dimeric) hydrates,[4] whereas malonaldehyde is not detectably hydrated in aqueous solution, in which it exists mainly as the mono-enol.[5]

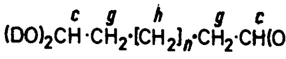
^{1}H N.m.r. spectroscopy has been found [6] to be a powerful tool for studying the hydration of aliphatic monoaldehydes and we accordingly have studied the n.m.r. spectra of succinaldehyde (I; $n = 0$), glutaraldehyde (I; $n = 1$), and adipaldehyde (I; $n = 2$) in deuterium oxide solution over a range of concentration and, in the first two cases, temperature. Our results are interpreted in terms of an equilibrium between the anhydrous aldehyde (I), the open-chain monohydrate (II) and dihydrate (III), and the cyclic monohydrate (IV); in view of the opinions of Korn *et al.*[7] we have also considered the possible presence of the cyclic dimeric hemihydrate (V). The equilibria are set up rapidly and no attempt was made to measure the rates of hydration. The spectra were analysed in terms of the eight types of proton (*a*—*h*) indicated in the formulae. Integration of the peaks and application of the appropriate simultaneous equations enabled the proportions of the components (I)—(V) in the solutions to be calculated, although only in the case of succinaldehyde was complete analysis possible without supplementary assumptions.


$\overset{a}{OCH}\cdot\overset{e}{CH_2}\cdot[\overset{h}{CH_2}]_n\cdot\overset{e}{CH_2}\cdot\overset{a}{CHO}$

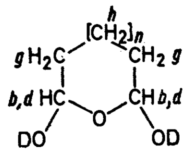
(I)


$(DO)_2\overset{c}{CH}\cdot\overset{g}{CH_2}\cdot[\overset{h}{CH_2}]_n\cdot\overset{f}{CH_2}\cdot\overset{a}{CHO}$

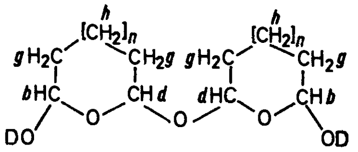
(II)


$(DO)_2\overset{c}{CH}\cdot\overset{g}{CH_2}\cdot[\overset{h}{CH_2}]_n\cdot\overset{g}{CH_2}\cdot\overset{c}{CH}(OD)_2$

(III)



(IV)



(V)

Owing to the symmetry of the molecule, the 60 MHz ^{1}H n.m.r. spectrum of succinaldehyde (I; $n = 0$) in deuteriochloroform is very simple, consisting of two sharp singlets, at τ 0·19 and 7·22, with areas in the ratio 1 : 2, arising from the aldehyde (*a*) and methylene (*e*) protons respectively. The spectra of solutions in deuterium oxide are much more complex (Figure 1); for analysis the spectra were divided into five bands assigned to the various types of proton as shown in Table 1. Band *A* is made up of a singlet and a triplet with a very small coupling constant, due to the *a* protons in (I; $n = 0$) and

TABLE 1

Band	*A*	*B*	*C*	*D*	*E*
Chemical shift/τ	0·20	4·2—4·55	4·86	7·09	7·2—8·5
Protons	*a*	*b* + *d*	*c*	*e*	*f* + *g*

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[1] L. Seligsberger and C. Sadlier, *J. Amer. Leather Chemists' Assoc.*, 1957, **52**, 2; M. L. Fein and E. M. Filachione, *ibid.*, p. 17; M. L. Fein, E. W. Harris, J. Naghski, and E. M. Filachione, *ibid.*, 1959, **54**, 488; E. M. Filachione, M. L. Fein, E. W. Harris, F. P. Luvisi, A. H. Korn, W. Windus, and J. Naghski, *ibid.*, p. 668, C. W. Cater, *J. Soc. Leather Trades Chemists*, 1963, **47**, 259; 1965, **49**, 455; J. H. Bowes and C. W. Cater, *J. Appl. Chem.*, 1964, **14**, 296; *Biochim. Biophys. Acta*, 1968, **168**, 341.

[2] D. S. Sabatini, K. Bensch, and R. J. Barnett, *J. Cell Biol.*, 1963, **17**, 19; F. A. Quiocho and F. M. Richards, *Proc. Nat. Acad. Sci. U.S.A.*, 1964, **52**, 833; F. A. Quiocho, W. H. Bishop, and F. M. Richards, *ibid.*, 1967, **57**, 525; G. N. Reeke, J. A. Hartsuck, M. L. Ludwig, F. A. Quiocho, T. A. Steitz, and W. N. Lipscomb, *ibid.*, 1967, **58**, 2220; D. Hopwood, *Histochemie*, 1969, **17**, 151.

[3] P. M. Hardy, A. C. Nicholls, and H. N. Rydon, *Chem. Comm.*, 1969, 565.

[4] E. B. Whipple, *J. Amer. Chem. Soc.*, 1970, **92**, 7183.

[5] A. A. Bothner-By and R. K. Harris, *J. Org. Chem.*, 1965, **30**, 254; W. O. George and V. G. Mansell, *J. Chem. Soc.* (*B*), 1968, 132.

[6] P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, 1967, **89**, 749 and references cited.

[7] A. H. Korn, S. H. Feairheller, and E. M. Filachione, *J. Mol. Biol.*, 1972, **65**, 525.

(II; $n = 0$), respectively. Band B is a complex multiplet made up of the X components of two ABX systems; it is ascribed to the b and d protons of the *cis*- and *trans*-isomers of the cyclic monohydrate (IV; $n = 0$) coupled to the g protons. The downfield component (τ *ca.* 4·3) is much larger than the upfield (τ *ca.* 4·4) and by analogy with glutaraldehyde is ascribed to the *trans*-isomer; although the overlap is too great for the proportions of the isomers to be determined precisely, there is *ca.* 75% of the *trans*-isomer in the mixture in 6—37% solutions. Band C is a superposition of two nearly identical triplets (J 5 Hz); these are ascribed to the c protons of the acyclic monohydrate (II; $n = 0$) and dihydrate (III; $n = 0$) and the presence of two triplets in this band is good evidence for the presence of the two acyclic hydrates in the mixture. Band D is a sharp singlet and arises from the e protons of the unhydrated dialdehyde. Band E is very complex and contains contributions from the f and g protons of all the species present in the solution. At the downfield end of band E a triplet (τ 7·21; J 7 Hz) is clearly distinguishable; this is due to the f protons of the acyclic monohydrate and, although accurate integration is not possible, its area relative to that of band D is about what would be expected on the basis of the proportion of (I) to (II) calculated from the areas of the other bands (Table 2).

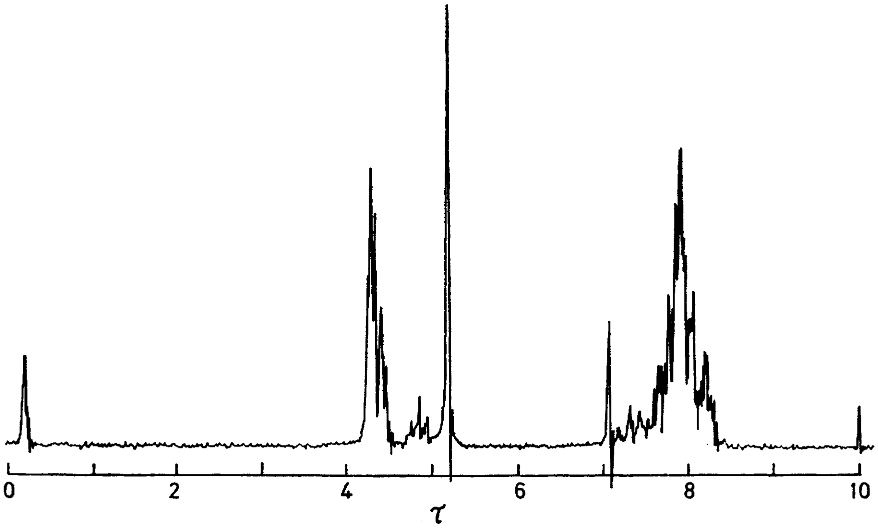


FIGURE 1 60 MHz ^{1}H n.m.r. spectrum of succinaldehyde in D_2O (10·5%; 33·5 °C). The singlet at τ 5·17 is due to DOH

TABLE 2

Composition of solutions of succinaldehyde (I; $n = 0$) in deuterium oxide

	Initial aldehyde concn.		Composition of solute (mol %)				Equilibrium constant K_x			
t/°C	(%)	$(x_I)_0$ *	(I)	(II)	(III)	(IV)	$(I) \rightleftharpoons (II)$	$(I) \rightleftharpoons (III)$	$(I) \rightleftharpoons (IV)$	$(I)(\rightleftharpoons V)$ †
33·5	5·92	0·0144	4·6	8·4	7·9	79·1	1·85	1·78	17·5	13,007
33·5	10·52	0·0266	4·5	7·7	9·5	78·3	1·78	2·25	18·1	7394
33·5	19·50	0·0545	4·5	9·9	7·7	77·8	2·32	1·91	18·2	3421
33·5	37·11	0·1207	5·2	8·0	9·1	77·7	1·79	2·36	17·4	1142
33·5	54·69	0·2192	5·1	10·2	5·6	79·1	2·80	2·14	21·6	655
		Mean ‡	4·7	8·5	8·6	78·2	1·94	2·08	17·8	
65	10·52	0·0266	21·3	9·3	9·3	60·1	0·447	0·459	2·90	
75	10·52	0·0266	24·2	11·0	11·0	53·8	0·465	0·482	2·28	
85	10·52	0·0266	35·5	13·4	8·9	42·2	0·387	0·264	1·22	

* x = Mol fraction. † Alternative to (IV), see text. ‡ Excluding 54·69% solution.

The compositions of the solute in solutions of succinaldehyde in deuterium oxide, calculated from the areas of bands A—E, over a range of concentrations (5·9—54·7%) at 33·5 °C and in 10·5% solution at three higher temperatures are given in Table 2; three equilibrium constants by which the system can be described are also given in the Table. The equilibrium constant $K_{I \rightleftharpoons V}$ ($= x_V/x_I^2 . x_{D_2O}$) (x = mole fraction) for the equilibrium between the free aldehyde (I) and the cyclic hemihydrate (V), it being assumed that 2 moles of this replace one of (IV), is also given for the experiments at 33·5 °C. It will be seen that whereas $K_{I \rightleftharpoons IV}$ is satisfactorily constant for the four more dilute solutions, $K_{I \rightleftharpoons V}$ is not; for this reason we conclude that there is little, if any, cyclic hemihydrate in these solutions. The high value for $K_{I \rightleftharpoons IV}$ in the most concentrated solution and the apparent lower proportion (65%) of the *trans*-isomer of (IV) may, however, be due to the presence of some cyclic hemihydrate in concentrated solutions. At 33·5 °C the cyclic monohydrate (IV) is the main organic component of the system, there being very little free aldehyde present; as the temperature is raised the amount of free aldehyde increases greatly, mainly at the expense of the cyclic monohydrate.

The 60 MHz ^{1}H n.m.r. spectrum of glutaraldehyde (I; $n = 1$) in deuteriochloroform shows the expected three peaks, *viz.*, a triplet (τ 0·26; J 1·5 Hz) for the CHO protons, a triplet (τ 7·45; J 6·5 Hz) with some second-order splitting for the *e* methylene protons, and a complex multiplet centred at τ 8·08 for the *h* methylene protons, with relative areas 1 : 2 : 1. The spectra of solutions in deuterium oxide are much more complex and the region between τ 4·6 and 5·3 is only fully resolved at 100 MHz (Figure 2); the spectrum can be divided for analysis into six bands which are assigned to the various types of proton as in Table 3.

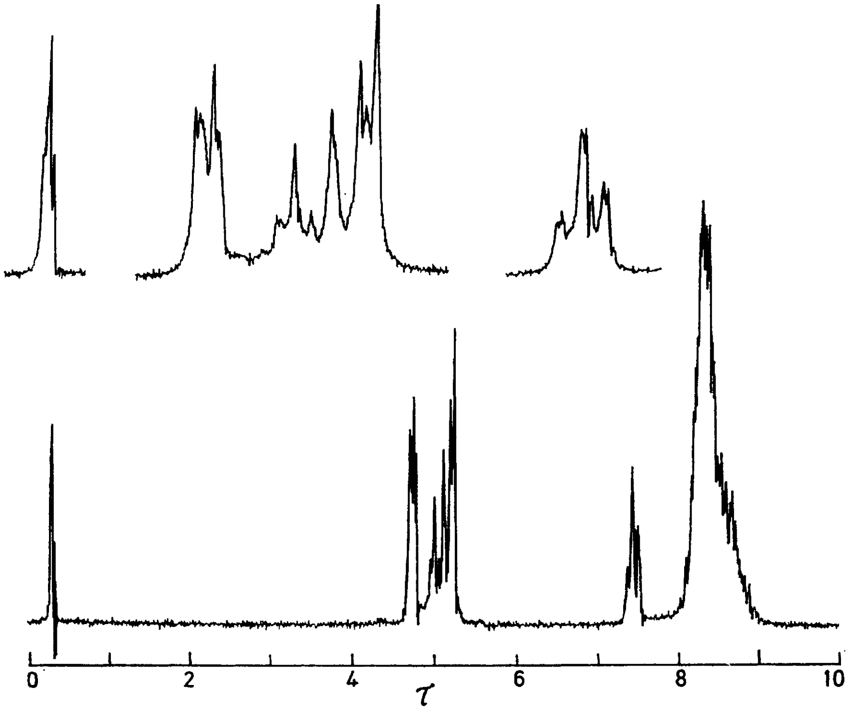
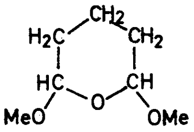


FIGURE 2 100 MHz ^{1}H n.m.r. spectrum of glutaraldehyde in D_2O (17·5%; 30 °C). The singlet at τ 5·22 is due to DOH. The inserts are peaks *A*—*E* expanded 4 times

TABLE 3

Band	*A*	*B*	*C*	*D*	*E*	*F*
Chemical shift/τ	0·27	4·6—4·8	4·98	5·15—5·25	7·38	8·0—9·0
Protons	*a*	*b* + *d*	*c*	*b* + *d*	*e* + *f*	*g* + *h*

The key to the assignment of bands *B*, *C*, and *D* comes from the spectra of the methyl acetals corresponding to (IV; $n = 1$) and (III; $n = 1$). The 100 MHz ^{1}H n.m.r. spectrum of 2,6-dimethoxytetrahydropyran (VI) shows multiplets at τ 5·24 and 5·54, singlets at τ 6·51 and 6·56, and a multiplet at τ 8·35, with relative areas 1·6 : 0·4 : 1·2 : 4·8 : 6·0.



(VI)

$(MeO)_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OMe)_2$

(VII)

The low-field multiplets are the *X* components of two ABX systems and arise from the methine protons coupled to the methylene protons; the two singlets are due to the protons of the methoxy-groups and the upfield multiplet is due to the methylene protons. The identity of the ratios of the areas of the multiplets at τ 5·24 and 5·54 and the singlets at τ 6·56 and 6·51 shows clearly that the two pairs are due to stereoisomerides of (VI); by analogy with *cis*- and *trans*-cyclohexane-1,3-diol[8] we ascribe the downfield multiplet and the upfield singlet to the *trans*-isomer of (VI), which then comprises 80% of the mixture of isomers. The bis(dimethyl acetal) (VII) shows a triplet at τ 5·66 (J 5 Hz) due to the methine protons, a singlet at τ 6·72 due to the methoxy-protons, and a complex multiplet around τ 8·45 due to the methylene protons.

Band *A* in the 100 MHz spectrum of glutaraldehyde in deuterium oxide consists of two superimposed triplets, the larger with τ 0·27, J 1·5 Hz, and the smaller with

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[8] H. Finegold and H. Kwart, *J. Org. Chem.*, 1962, **27**, 2361.

τ 0·25, J 1·2 Hz; these are due to the *a* protons in (I; $n = 1$) and (II; $n = 1$) respectively and the appearance of two triplets clearly demonstrates the presence of the acyclic monohydrate in the system. Bands *B* and *D* are very similar in appearance to the multiplets at τ 5·24 and 5·54 in the spectrum of (VI) and are ascribed to the methine protons (*b* and *d*) in the *trans*- and *cis*-isomers, respectively, of the cyclic monohydrate (IV; $n = 1$), although the presence of some cyclic hemihydrate (V; $n = 1$) cannot be excluded (see below). The relative areas of the two bands in 17·5% solution vary little with temperature (2—62 °C) and the *trans*-isomer forms *ca.* 50% of the mixture; the larger proportion of *cis*-isomer in (IV; $n = 1$) than in (VI) is presumably due to its stabilisation by hydrogen bonding of axial OD groups. Band *C* consists of a triplet (τ 4·98; J 5 Hz) with a smaller triplet, slightly upfield, superimposed on it; it is ascribed to the *c* protons of (II; $n = 1$) and (III; $n = 1$), the latter being the major component. The presence of two triplets in this band is good evidence for the presence of both the acyclic mono- and di-hydrate. Band *E* consists of two triplets of doublets, the larger with τ 7·38, J_1 6·5, J_2 1·5 Hz, and the smaller with τ 7·40, J_1 6·5, J_2 1·0 Hz. These two triplets correspond to the methylene protons (*e* and *f*) in (I; $n = 1$) and (II; $n = 1$); once more, the presence of two triplets demonstrates the presence of the acyclic monohydrate (II) in the mixture. Decoupling band *E* from the aldehyde protons, *a*, simplifies it to two unsplit triplets, of which the major, downfield one decreases in size relative to the other as the temperature is reduced from 32 to 15 °C; by analogy with succinaldehyde, in which the proportion of free aldehyde to acyclic monohydrate decreases at lower temperatures, the larger triplet in ascribed to the *e* protons of (I) and the smaller to the *f* protons of (II). Although it was not possible to make any accurate assessment of the relative areas of these two triplets, it is clear that that due to (II) is much smaller than that due to (I) at temperatures above 35 °C. The complex multiplet *F* is due to the remaining methylene protons (*g* and *h*) in (I)—(IV). The 60 MHz spectra (Figure 3) of solutions of glutaraldehyde in deuterium oxide are deceptive; band *B* appears to be a rather distorted triplet and bands *C* and *D* merge to give a multiplet, partly obscured at 33·5 °C by the DOH peak. In our preliminary communication[3] we mistakenly assigned band *B* to the *b* + *d* protons of (IV) and band *CD* to the *c* protons of (II) and (III); in consequence the amount of cyclic monohydrate was grossly underestimated.

In a preliminary communication, Korn *et al.*[7] interpret their ^{1}H n.m.r. spectra for solutions of glutaraldehyde in water on the basis that the solutions contain only the free aldehyde (I), the cyclic monohydrate (IV), the cyclic hemihydrate (V), and higher polymers analogous to the latter. They assign band *C* to the methine (*b* + *d*) protons of (IV) and (V) and their polymeric analogues, and band *D* to hydroxy-protons. For the reasons given above we cannot accept this interpretation. In particular, the dual nature of the triplets in bands *A*, *C*, and *E* is, in our opinion, overwhelming evidence for the presence of the acyclic hydrates (II) and (III); the statement of Korn *et al.*[7] that ' the absorption in the amounts that the presence of these species would require is simply missing from the spectra measured on the sample above room temperature ' is not true. However Korn *et al.* are correct in maintaining that it is impossible to distinguish between (IV) and (V) by n.m.r. spectroscopy alone and we cannot, therefore, exclude the possibility that both are present (see below).

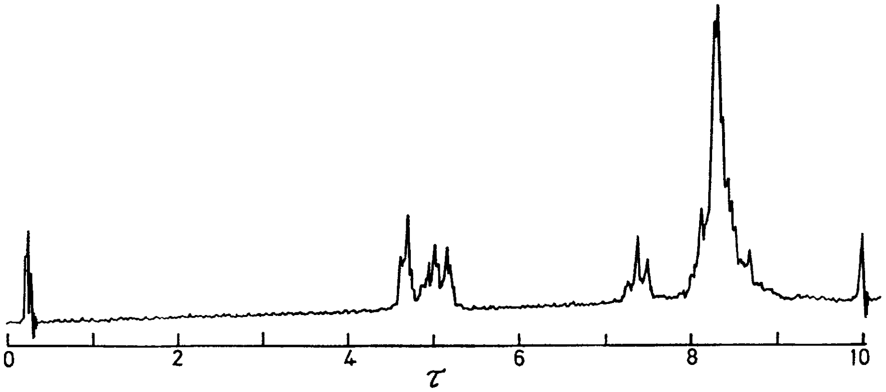

FIGURE 3 60 MHz ^{1}H n.m.r. spectrum of glutaraldehyde in D_2O (18·1%; 33·5 °C). The small singlet at the upfield end of the multiplet around τ 5 is due to DOH

Because the acyclic monohydrate (II; $n = 1$) is spectroscopically indistinguishable from an equimolar mixture of the free aldehyde (I; $n = 1$) and the acyclic dihydrate (II; $n = 1$), there are insufficient simultaneous equations relating the areas of bands *A*—*F* to the amounts of the components (I)—(IV) for complete analysis and some simplifying assumption has to be made. Since we have shown that the amount of (II) is less than that of either (I) or (III) we have assumed, for purposes of calculation, that (II) is absent, which may be true at the higher temperatures studied. The results summarised in Table 2 are based on this assumption; any (II) present will be included equally in the estimated amounts of (I) and (III) and this unavoidable error no doubt accounts in part for the notable drift in the equilibrium constants for solutions of different concentrations at 33·5 °C. Table 4 also includes values for $K_{\mathrm{I}\rightleftharpoons\mathrm{V}}$ calculated on the assumption that the equilibrium mixture contains (V) in place of (IV). It will be seen that $K_{\mathrm{I}\rightleftharpoons\mathrm{V}}$ shows a pronounced downward drift and $K_{\mathrm{I}\rightleftharpoons\mathrm{IV}}$ a smaller upward drift with increasing concentration; we believe that this is due to the presence of some cyclic hemihydrate (V) in the more concentrated solutions. In spite of these uncertainties, however, the general picture is clear. Glutaraldehyde, like succinaldehyde, exists in aqueous solution predominantly as the cyclic hydrate; as the temperature is raised the amount of free aldehyde increases greatly, mainly at the expense of the cyclic hydrate; a similar conclusion was reached by Korn *et al.*[7] Owing to the presence of the very strong water peak it is less easy to calculate the composition of the equilibrium mixture in solutions of glutaraldehyde in water; only the areas of bands *A*, *B*, *E*, and *F* can be measured at *ca.* 30 °C, and that of band *B* is subject to considerable inaccuracy. However, the mean of four concordant determinations on a 22·5% solution in H_2O at 33·5 °C gave 17 mol % of (I), 21 mol % of (III), and 62 mol % of (IV), not greatly different from the values determined in D_2O (Table 4).

TABLE 4

Composition of solutions of glutaraldehyde (I; $n = 1$) in deuterium oxide

t/°C	Initial aldehyde concn. (%)	Initial aldehyde concn. $(x_1)_0$	Composition of solute (mol %) (I)	Composition of solute (mol %) (III)	Composition of solute (mol %) (IV)	Equilibrium constant K_x $(I)\rightleftharpoons(III)$	Equilibrium constant K_x $(I)\rightleftharpoons(III)$	Equilibrium constant K_x $(I)\rightleftharpoons(V)$ *
33·5	1·89	0·0038	18·0	16·8	65·2	0·931	3·63	2629
33·5	18·05	0·0422	19·7	13·2	67·1	0·729	3·56	202·4
33·5	34·38	0·0949	18·9	9·7	71·4	0·636	4·21	102·7
33·5	51·08	0·1729	19·0	6·0	75·1	0·496	4·97	60·0
2	17·53	0·0408	4·4	17·8	77·8	4·48	18·7	
15	17·53	0·0408	6·6	17·2	76·2	2·86	12·1	
31·5	17·53	0·0408	16·7	16·9	66·4	1·11	4·16	
32	17·53	0·0408	15·6	18·5	65·9	1·29	4·40	
50	17·53	0·0408	34·1	18·9	47·0	0·606	1·44	
63	17·53	0·0408	53·1	18·5	28·4	0·380	0·559	
100	17·53	0·0408	80·2	10·3	9·5	0·138	0·124	

* Alternative to (IV), see text.

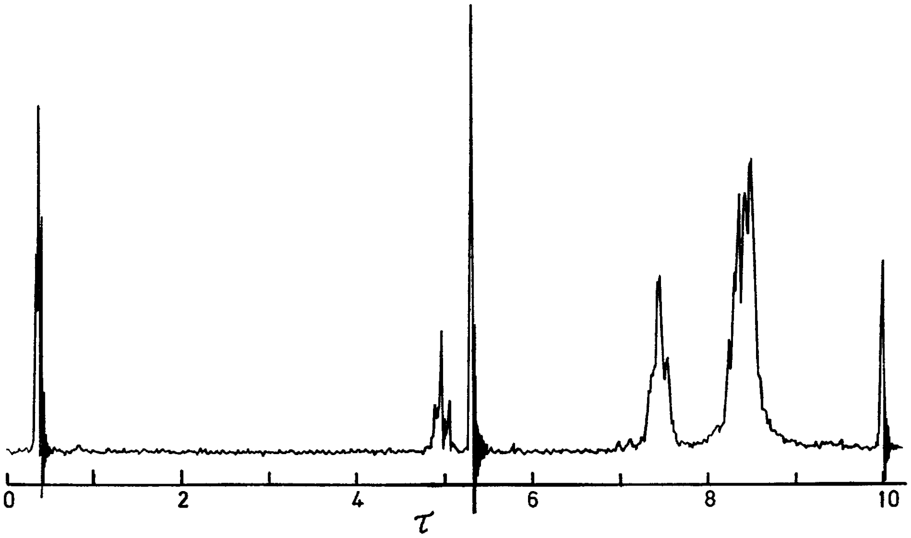

FIGURE 4 60 MHz ^{1}H n.m.r. spectrum of adipaldehyde in D_2O (9·1%; 33·5 °C). The singlet at τ 5·30 is due to DOH

The 60 MHz ^{1}H n.m.r. spectrum of adipaldehyde (I; $n = 2$) in deuteriochloroform shows three peaks, *viz.*, a triplet (τ 0·24, J 1·5 Hz) for the aldehyde protons, a multiplet (τ 7·53) for the *e* methylene protons, and another multiplet (τ 8·33) for the *h* methylene protons. The last two peaks approximate to an A_2B_2X system; the ratio of the areas is 1 : 2 : 2 as expected. The spectrum in deuterium oxide solution (Figure 4) divides into four bands as shown in Table 5. The spectrum is much simpler than those of succinaldehyde and glutaraldehyde; it contains no band corresponding to the cyclic monohydrate (IV) which is therefore not present in the

TABLE 5

Band	*A*	*B*	*C*	*D*
Chemical shift/τ	0·37	4·98	7·46	8·1—8·9
Protons	*a*	*c*	*e*	*g* + *h*

equilibrium mixture. Bands *A* and *B* are simple triplets, with *J* 1·8 and 4·8 Hz respectively; bands *C* and *D* form an A_2B_2X system, as in the spectrum in deuteriochloroform. The spectrum shows no evidence for the presence of both the monohydrate (II) and the dihydrate (III) and it is clear that only one of these is present in detectable amount. It is most reasonable to suppose that the two aldehyde groups react independently and we have therefore analysed the results on the basis of an equilibrium between (I) and (III) only. The results (Table 6) show that there is much more free aldehyde in solutions of adipaldehyde than in solutions of succinaldehyde and glutaraldehyde, as might be expected from its much lower solubility.

TABLE 6

Composition of solutions of adipaldehyde (I; $n = 2$) in deuterium oxide at 33·5 °C

Initial aldehyde concn.		Composition of solute (mol %)		Equilibrium constant K_x
(%)	$(x_I)_0$	(I)	(III)	(I) $\rightleftharpoons$ (III)
4·56	0·0083	58·5	41·5	0·720
9·12	0·0176	57·5	42·5	0·765
18·50	0·0398	60·4	39·6	0·715
	Mean	58·8	41·2	0·733

The individual equilibrium constants given in Tables 2, 4, and 6 are not well suited for comparison with the equilibrium constants for the hydration of aliphatic monoaldehydes. The overall hydration constants for the formyl group, $K_d = x_{CHO}/x_{O\cdot CH\cdot O} = (2x_I + x_{II})/x_{D_2O}\cdot(x_{II} + 2x_{III} + x_{IV})$, which do not vary with concentration for the three dialdehydes, are more suitable for this purpose; our values for K_d are given in Table 7, together with the values obtained by Gruen and McTigue[9] for the hydration of some aliphatic monoaldehydes in deuterium oxide. It will be seen that K_d for adipaldehyde is close to those for the monoaldehydes, whereas the constants for succinaldehyde and glutaraldehyde are much higher. This difference is clearly due to the ease with which succinaldehyde and glutaraldehyde, but not adipaldehyde, form cyclic hydrates. The thermodynamic parameters also recorded in Table 7 fully bear out this conclusion; $\Delta H°$ and $\Delta S°$ for the formation of the acyclic hydrates (II) and (III) are similar to those for the hydration of the monoaldehydes, whereas the enthalpy and entropy changes accompanying the formation of the cyclic hydrates (IV) from succinaldehyde and glutaraldehyde are substantially larger.

TABLE 7

Hydration of some aliphatic aldehydes and dialdehydes in D_2O

Aldehyde	$\Delta H°$/kcal mol^{-1}			$\Delta S°$/cal K^{-1} mol^{-1}			Hydration constant K_d
	(I) $\rightleftharpoons$ (II)	(I) $\rightleftharpoons$ (III)	(I) $\rightleftharpoons$ (IV)	(I) $\rightleftharpoons$ (II)	(I) $\rightleftharpoons$ (III)	(I) $\rightleftharpoons$ (IV)	
$OCH\cdot[CH_2]_2\cdot CHO$	−7·5	−8·6	−11·1	−23·0	−26·6	−30·7	9·19 (25 °C)
$OCH\cdot[CH_2]_3\cdot CHO$		−7·4	−10·9		−23·9	−33·3	4·30 (25 °C)
$OCH\cdot[CH_2]_4\cdot CHO$							0·73 (33·5 °C)
$CH_3\cdot CHO$		−5·5			−18·4		1·11 (25 °C)
$CH_3\cdot CH_2\cdot CHO$		−6·2			−21·3		0·80 (25 °C)
$CH_3\cdot[CH_2]_2\cdot CHO$		−6·9			−24·2		0·57 (25 °C)

It has long been known that both succinaldehyde[10] and glutaraldehyde[11] polymerise readily in the presence of traces of water to give glassy polymers which revert quantitatively to the monomers on vacuum distillation; adipaldehyde polymerises much less readily.[12] Overberger *et al.*[13] suggested the tetrahydropyran structure (VIII) for the polymer of glutaraldehyde, but Aso and Aito[14] preferred a more complex structure containing 'pendant' aldehydo-groups; our n.m.r. studies are fully explicable on the basis of structure (VIII). During the polymerisation of liquid glutaraldehyde to the glassy polymer, the bands at τ 0·26, 7·45, and 8·08 due to the free aldehyde diminish in area and are partially replaced by broad bands at τ 4·9, 6·6, and 8·2 due to the polymer. After 7 h the areas of the bands show that the mixture contains *ca.* 25% of free aldehyde and 75% of polymer (VIII; $x = ca.$ 3); as the polymerisation progresses further the mixture becomes a glass and gives no observable n.m.r. signals. Trituration of the product after 36 h with water gave a solid; the ^1H n.m.r. spectrum of this, in deuteriochloroform, showed bands at τ 0·26 (s, C*H*O), *ca.* 4·9 (two broad overlapping bands, τ 4·8 and 5·0, methine protons of polymer), 7·50 (t, *J* 6 Hz, monomer α-CH_2) and 8·34 (broad s with some fine structure at downfield end, monomer α- and polymer α- and β-CH_2); the relative areas of the bands (2·5 : 22 : 5·5 : 70) indicate that the polymer contains *ca.* 4% of free aldehyde and the absence of any OH signal that the degree of polymerisation is very high. The polymer undergoes partial depolymerisation on storage at room temperature. The relative areas of the above n.m.r. bands in a specimen kept for 14 days were 8 : 15 : 17 : 56 and there was a new band (area = 4) at τ 6·55br (t, O*H* of polymer); these areas indicate the presence of 15% of occluded free aldehyde and a much reduced degree of polymerisation (*x ca.* 3), in agreement with the molecular weight (332) determined by vapour-pressure osmometry in carbon tetrachloride.

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[9] L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 1963, 5217.

[10] C. D. Harries, *Ber.*, 1902, **35**, 1183; C. D. Harries and P. Hohenemser, *ibid.*, 1908, **41**, 255.

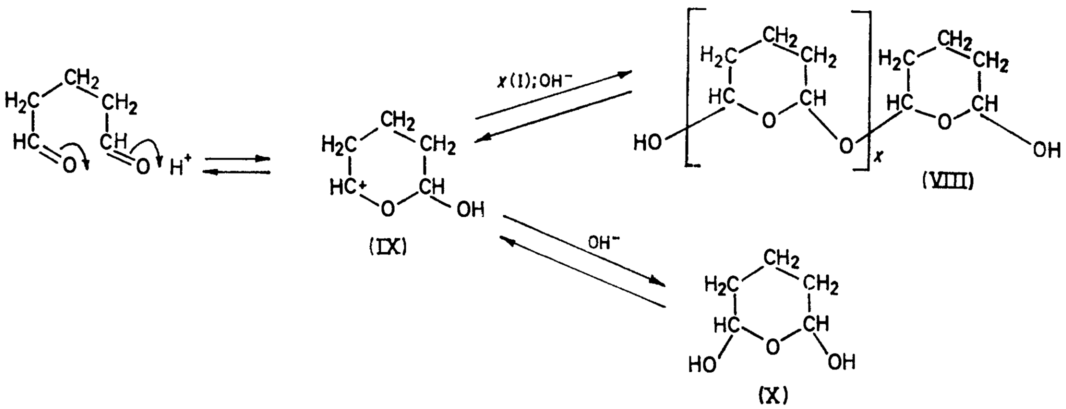
[11] C. D. Harries and L. Tank, *Ber.*, 1908, **41**, 1701.

[12] A. Wohl and H. Schweitzer, *Ber.*, 1906, **39**, 890.

[13] C. G. Overberger, S. Ishida, and H. Ringsdorf, *J. Polymer Sci.*, 1962, **62**, s1.

[14] C. Aso and Y. Aito, *Bull. Chem. Soc. Japan*, 1962, **35**, 1476; *Makromol. Chem.*, 1962, **58**, 195.

The 60 MHz ^{1}H n.m.r. spectra of 22% solutions of glutaraldehyde in either water or deuterium oxide are completely unchanged after 90 days at room temperature, there being no sign of polymerisation. Addition of a drop of DCl to such a solution in deuterium oxide, however, causes rapid polymerisation and after 48 h the spectrum is essentially that of the high polymer. Both the polymerisation and hydration of glutaraldehyde clearly involve, as the first step, protonation to the cyclic carbonium ion (IX) (*cf.* Overberger *et al.*[13]); this may then react either with more aldehyde, leading to the polymer (VIII), or with hydroxide ion, leading to the cyclic monohydrate (X). In the presence of a large excess of aldehyde (as in the undiluted liquid) or in the absence of hydroxide ion (as in the presence of added acid) the polymer will preponderate, whereas in dilute, neutral aqueous solution the cyclic monomer will be the main product. In more concentrated aqueous solution a mixture of cyclic monohydrate and polymer will be formed, the average value of x in (VIII), *i.e.*, the degree of polymerisation, depending on the initial aldehyde concentration. Our experiments suggest that substantial formation occurs only when the initial aldehyde concentration is considerably higher than that of the commercially available solutions (25%) used for protein cross-linking.



SCHEME

The 60 MHz ^{1}H n.m.r. spectrum of a deuteriochloroform solution of the glassy polymer obtained by keeping undiluted succinaldehyde at room temperature for several days showed bands at τ 0·20 (s, C*H*O of monomer), 4·55br (s, methine protons of polymer), 5·95br (t, O*H* of polymer), 7·25 (s, methylene protons of monomer), and 7·4—8·4br (m, methylene protons of polymer); the relative areas of these bands (6 : 25 : 3 : 14 : 52) indicate the presence of 25% of free aldehyde and 75% of a polymer analogous to (VIII) with a degree of polymerisation of 8 ($x = 7$). The 60 MHz spectra of solutions of succinaldehyde (6—55%) in deuterium oxide were completely unchanged after 21 days at room temperature.

EXPERIMENTAL

Succinaldehyde.—The following procedure gave a purer product than that of Fakstorp *et al.*[15] The ethanol–water azeotrope was distilled from a mixture of 2,5-diethoxytetrahydrofuran (100 ml) and 0·1M-acetic acid (100 ml) through a column (9 × 1 cm) packed with gauze Dixon rings. Distillation was stopped when the reflux temperature reached 98 °C. The residue was saturated with sodium chloride and extracted continuously with ether for 5 days. The extract was dried ($MgSO_4$) and evaporated; distillation of the residue gave succinaldehyde (23·8 g; 43%), b.p. 59—60 °C at 12 mmHg; n_D^{26} 1·4229; $\nu_{max.}$ 2880 (CH str), 2820 (CH str), 2720 (CH str), 1725 (CO str), 1405, 1382, and 1350 cm^{-1}, which rapidly polymerised to a glassy solid, $\nu_{max.}$ (C_6H_6) 3500 (OH str), 2900 and 2800 (CH str), and 1730w (CO str) cm^{-1}.

Glutaraldehyde and Derivatives.—The commercial 25% aqueous solution (150 ml) was concentrated to 50 ml under reduced pressure, 1·5 g of aldehyde being lost in the distillate. The concentrate was saturated with sodium chloride and extracted with ether (3 × 100 ml). Distillation of the dried extract gave glutaraldehyde (25 g), b.p. 77—79 °C at 15 mmHg, $\nu_{max.}$ 2900 (CH str), 2870 (CH str), 2820 (CH str), 2720 (CH str), 1730 (CO str), 1440, 1410, 1390, and 1360 cm^{-1}. On being kept at room temperature for 24 h the mobile liquid polymerised to a glassy solid, $\nu_{max.}$ (C_6H_6) 3400 (OH str), 2920 (CH str), 2800 (CH str), and 1730w (CO str) cm^{-1}, from which the monomeric aldehyde could readily be regenerated by distillation under reduced pressure.

The freshly redistilled aldehyde (14·6 g, 0·146 mol) was kept for 18 h at room temperature in methanol (23·7 ml, 0·584 mol) containing finely powdered calcium chloride (8·25 g, 0·073 mol) and a few drops of concentrated hydrochloric acid. A few pellets of sodium hydroxide were added and the liquid poured off and evaporated. The residue was dissolved in ether (60 ml), washed with water (3 × 20 ml), dried ($MgSO_4$), and distilled through a column (15 × 1·5 cm) packed with gauze Dixon rings. The fraction of b.p. 52—54 °C at 12 mmHg (5·61 g, 26%), $\nu_{max.}$ 2900 (CH str) cm^{-1}, was pure 2,6-dimethoxytetrahydropyran (VI), and the fraction of b.p. 72—76 °C at 2 mmHg (4·29 g, 15%), $\nu_{max.}$ 2900 (CH str) cm^{-1}, pure glutaraldehyde bis(dimethyl acetal) (VII); the intermediate fractions contained substantial amounts of glutaraldehyde [$\nu_{max.}$ 1730 cm^{-1} (CO str)].

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[15] J. Fakstorp, D. Raleigh, and C. E. Schniepp, *J. Amer. Chem. Soc.*, 1950, **72**, 872.

Adipaldehyde.—*trans*-Cyclohexane-1,2-diol[16] (5·0 g, 43 mmol) in water (25 ml) was treated with a solution of sodium periodate (9·2 g, 43 mmol) in water (100 ml) and the mixture kept overnight at room temperature. Extraction with ether (4 × 100 ml) and distillation of the dried extract gave adipaldehyde (1·71 g, 49%), b.p. 65—69 °C at 2 mmHg, $\nu_{max.}$ 2900 (CH str), 2800 (CH str), 2700 (CH str), and 1725 (CO str) cm^{-1}; the aldehyde polymerised slowly on being kept.

Measurements.—The 60 MHz n.m.r. spectra were recorded on a Perkin-Elmer R10 spectrometer and the 100 MHz spectra on a JEOL JNM-MH-100 spectrometer. To avoid polymerisation the dialdehyde solutions were made up immediately from the freshly redistilled compounds.

Succinaldehyde in deuterium oxide. The following equations relate the areas, $a_A \ldots a_E$, of the n.m.r. bands in arbitrary units to the areas, $a_I \ldots a_{IV}$, attributable to the components of the equilibrium mixture: $a_A = 2a_I + a_{II}$; $a_B = 2a_{IV}$; $a_C = a_{II} + 2a_{III}$; $a_D = 4a_I$; $a_E = 4a_{II} + 4a_{III} + 4a_{IV}$; whence: $a_I = a_D/4$; $a_{II} = a_A - a_D/2$; $a_{III} = (a_C - a_{II})/2$; $a_{IV} = a_B/2$. The relationship $a_E = 2a_A + 2a_B + 2a_C - a_D$ was used as a check. By use of these equations and the known initial mol fractions, $(x_I)_0$ and $(x_{D_2O})_0$, the mol fractions, $x_I \ldots x_{IV}$ and x_{D_2O}, of the components of the equilibrium mixture are readily calculated. The measured band areas are given in Table 8.

TABLE 8

60 MHz ^{1}H N.m.r. spectra of solutions of succinaldehyde (I; $n = 0$) in D_2O

			Band areas					
t/°C	$(x_I)_0$	No. of expts.	a_A	a_B	a_C	a_D	a_E	$\frac{2a_A + 2a_B + 2a_C - a_D}{a_E}$
33·5	0·0144	4	3·80	34·3	5·25	3·98	88·9	0·93
33·5	0·0266	4	4·10	38·7	6·58	4·40	97·2	0·97
33·5	0·0545	4	4·58	37·5	6·10	4·38	92·9	0·99
33·5	0·1207	4	5·53	46·8	7·88	6·25	118·1	0·97
33·5	0·2192	4	5·70	44·2	6·00	5·68	109·7	0·97
65	0·0266	1	14·0	32·4	7·5	23·0	89·5	0·95
75	0·0266	1	16·0	29·0	8·9	26·1	75·0	1·09
85	0·0266	1	19·0	19·0	7·0	32·0	71·0	0·82

TABLE 9

100 MHz ^{1}H N.m.r. spectra of solutions of glutaraldehyde (I; $n = 1$) in D_2O; initial mol fraction of (I) = 0·0408 in all cases

		Band areas						
t/°C	No. of expts.	a_A	a_B	a_C	a_D	a_E	a_F	$\frac{a_A + 3a_B + 3a_C + 3a_D}{a_F}$
2	1	2·5	24·4	10·8 *	22·5	5·5	167	1·05
15	3	3·27	23·6	9·66 *	19·1	8·2	160·4	1·00
31·5	4	9·03	18·6	9·45	18·3	19·1	146·6	1·01
32	3	8·93	19·7	11·0	19·5	19·3	155·7	1·02
50	1	19·5	14·3	11·0	13·0	40·2	135	1·00
63	1	32·2	9·4	11·0	7·5	61·8	114	1·02
100	1	45·0	2·3	5·8	3·1	91·0	88·0	0·89

* Corrected for DOH.

TABLE 10

60 MHz ^{1}H N.m.r. spectra of solutions of glutaraldehyde (I; $n = 1$) in D_2O at 33·5 °C

		Band areas					
$(x_I)_0$	No. of expts.	a_A	a_B	a_{CD} *	a_E	a_F	$\frac{a_A + 3a_B + 3a_{CD}}{a_F}$
0·0038	4	3·5	7·0	10·6	8·5	57·0	0·99
0·0422	4	7·1	12·0	16·7	14·0	95·5	0·98
0·0949	4	8·1	15·5	19·7	16·7	117·0	0·97
0·1729	4	9·2	19·5	22·6	21·0	139·5	0·97

* Corrected for DOH.

Glutaraldehyde in deuterium oxide. (a) 100 MHz. The following equations apply on the assumption that no (II) is present (see p. 2274): $a_A = 2a_I$; $a_B + a_D = 2a_{IV}$; $a_C = 2a_{III}$; $a_E = 4a_I$; $a_F = 2a_I + 6a_{III} + 6a_{IV}$; whence: $a_I = (2a_A + a_E)/8$; $a_{III} = a_C/2$; $a_{IV} = (a_B + a_D)/2$; $a_F = a_A + 3a_B + 3a_C + 3a_D$. The measured band areas are given in Table 9.

(b) 60 MHz. The following equations apply, it being assumed that no (II) is present and that $a_B = a_D$ (see Table 9): $a_A = 2a_I$; $a_B = a_{IV}$; $a_{CD} = 2a_{III} + a_{IV}$; $a_E =$

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[16] A. Roebuck and H. Adkins, *Org. Synth.*, 1955, Coll. Vol. 3, 217.

TABLE 11

60 MHz ^{1}H N.m.r. spectra of solutions of adipaldehyde (I; $n = 2$) in D_2O at 33·5 °C

$(x_I)_0$	No. of expts.	Band areas a_A	a_B	a_C	a_D	$\frac{2a_A + 4a_B}{a_D}$
0·0083	3	10·8	8·23	24·9	61·5	0·89
0·0176	4	18·0	14·2	40·8	101·6	0·91
0·0398	5	18·5	12·7	40·7	94·9	0·93

$4a_I$; $a_F = 2a_I + 6a_{III} + 6a_{IV}$; whence: $a_I = (2a_A + a_D)/8$; $a_{III} = (a_{CD} - a_B)/2$; $a_{IV} = a_B$; $a_F = a_A = 3a_B + 3a_{CD}$. The measured areas are given in Table 10.

Adipaldehyde in deuterium oxide. The following equations apply, since only (I) and (III) are present (see p. 2275): $a_A = 2a_I$; $a_B = 2a_{III}$; $a_C = 4a_I$; $a_D = 4a_I + 8a_{III}$; whence: $a_I = (2a_A + a_C)/8$; $a_{III} = a_B/2$; $a_D = 2a_A + 4a_B$. The measured areas are given in Table 11.

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