3-Hydroxy-2,2-dimethylpropionaldehyde: Equilibria and Structure of its Dimer

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The structure and stereochemistry of the dimer of 3-hydroxy-2,2-dimethylpropionaldehyde (1) has been deduced by i.r. and n.m.r. spectroscopy. Equilibria involved in solutions of (1) have been observed and discussed. It has been proved that the dimer is a mixture of two stereoisomers, of which the *cis* is more stable.

3-HYDROXY-2,2-DIMETHYLPROPIONALDEHYDE (1) is often used as intermediate in the synthesis of several organic products, mainly neopentyl glycol. Compound (1) was synthesized in aqueous solution from isobutyraldehyde and formaldehyde using NaOH as catalyst, an aldol-type reaction. Compound (1) is usually separated from the reaction mixture as a crystalline solid in the form of a dimer. It is well known [1] that (1) exists in equilibrium

$$HOCH_2{\cdot}CMe_2{\cdot}CHO$$

(1)

between monomer and dimer. The equilibrium depends on the physical state of the compound; for example the equilibrium is shifted to the monomeric form in the melted state and, after cooling, it slowly gives the dimer. In solution the equilibrium position also depends on the solvent. This kind of behaviour is similar to that of other hydroxy-aldehydes.[2]

The influence of various parameters on the equilibrium prevents the direct analysis of (1) in the reaction mixture. The monomer–dimer equilibrium can be ' quenched ' by acetylating and the acetylated products analysed by means of g.l.c. The chromatographic analysis shows two peaks in the region of the expected dimeric compound. The two peaks have been investigated by means of g.l.c.–mass spectrometry in order to gain further structural information. Both peaks show the same molecular weight and the same fragmentation pattern. The molecular weight corresponds to a dimeric form of (1) with two acetyl groups. We point out that the equilibrium state of (1) in solution is influenced by the presence of at least two dimeric isomers.

The purpose of this work is to establish the structure and stereochemistry of the dimeric forms by i.r. and n.m.r. spectroscopy, and to investigate the equilibria existing in solution.

EXPERIMENTAL

Techniques.—The i.r. spectra were obtained with a Perkin-Elmer model 457 spectrometer. The ^1H n.m.r. spectra were obtained with a Varian HA 100 instrument; chemical shifts (δ values, tetramethylsilane as internal standard) are accurate to ± 0.01 p.p.m. and coupling constants to ± 0.2 Hz. The solvents for the n.m.r. spectra were obtained commercially and used without further purification. Analytical g.l.c. was carried out with a glass column (1.1 m × 3 mm) packed (10%) with Silicone Rubber UCC W 982 (Hewlett–Packard) on HP Chromosorb W AW DMCS 80—100 mesh; temperatures were 85—230 °C (programmed at 6° min^{-1}). Mass spectra were obtained with a Varian CH7 instrument.

Preparation of the Dimer of 3-*Hydroxy*-2,2-*dimethylpropionaldehyde.*—Isobutyraldehyde (297 g), a 36% aqueous solution of formaldehyde (333 g), and water (1 986.5 g) were mixed; a 30% solution of sodium hydroxide (53.5 g) was added dropwise. The mixture was stirred for 1 h, keeping the temperature below 18 °C. The dimer precipitated after 2 h; it was separated, washed with water, and purified by recrystallization from ether several times, m.p. 89—90. 5 °C.

The i.r. spectrum of crystalline (1) in Nujol did not show any carbonyl absorption but showed strong absorption for hydroxy and ether linkages. On the other hand the i.r. spectrum of the melted product showed strong absorptions

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[1] E. Spath and I. Szilagyi, *Ber.* 1943, **76B**, 949.

[2] T. G. Bonner, E. J. Bourne, and J. Butler, *Chem. and Ind.*, 1961, 750; C. A. Armour, T. G. Bonner, E. J. Bourne, and J. Butler, *J. Chem. Soc.*, 1964, 301; M. Vogel and D. Rhum, *J. Org. Chem.*, 1966, **31**, 1775.

for formyl carbonyl and hydroxy-groups, in agreement with the formation of monomeric (1).

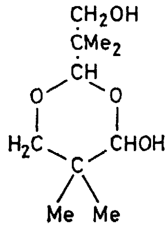
The diacetate derivative was prepared by acetylation of the dimer in pyridine. The product showed no hydroxy-absorption in the i.r. spectrum. The purity (>97%) was determined by g.l.c., *m/e* 288 (M^+, 0.1%), 287 ($M^+ - H$, 0.1), 245 ($M^+ - C_2H_3O$, 0.2), 229 ($M^+ - C_2O_3O_2$, 1.0), 173 (5), 145 (15), 85 (40), 56 (50), and 43 (100).

Kinetic Procedure.—The dimer–monomer equilibrium was studied spectrophotometrically, using a Perkin-Elmer 450 spectrophotometer. Starting from the dimer the increase in absorption at 290 nm, due to the carbonyl of the monomer, was observed as a function of time in water (pH 7) and other solvents.

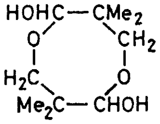
A number of aqueous solutions at equilibrium, with different initial concentrations of the dimer, were used to obtain the molar extinction coefficient ε of the monomer at $\lambda_{max.}$. The monomer : dimer equilibrium ratio in the above solutions was obtained by n.m.r. using a Varian T-60 spectrometer. The molar extinction coefficient was found to be 20.6 l mol^{-1} cm^{-1}; this value is in agreement with the coefficient reported for several aldehydes.[3] The same procedure was also carried out to obtain the molar extinction coefficient in other solvents.

RESULTS AND DISCUSSION

Structure of the Dimer.—On the basis of i.r. and mass spectral data, one can suggest the two cyclic structures (2) and (3) for the dimeric form of (1), in agreement with the literature for similar compounds.[2,4] The two structures (2) and (3) can be easily observed by n.m.r. spectroscopy. Structure (3) should give an intensity ratio of 1 : 3 for the methylene and methyl groups. Structure (2) should give instead three signals for the methyl groups in the ratio 1 : 2 : 1, an AB quartet for the ring methylene group, and also a signal for the methylene group outside the ring.



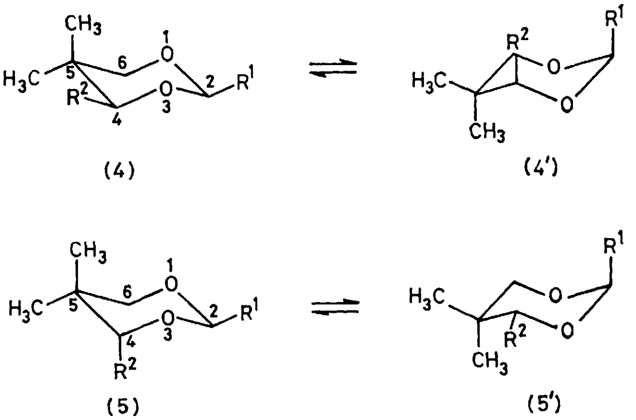
(2)



(3)

A solution of crystalline (1) freshly dissolved in $CDCl_3$, in which the monomer is practically absent, gave an n.m.r. spectrum which corresponds to structure (2). Also the acetylated product gave an n.m.r. spectrum which corresponds to acetylated (2). Furthermore, the n.m.r. spectrum of (1) dissolved in a strongly protic solvent (DMSO) showed the hydroxy-group coupled with vicinal protons. The spectrum definitely showed the presence of a CH_2OH group and a CHOH group ruling out the possibility of structure (3) * and confirming the 1,3-dioxan structure.

Isomers of the Dimer (2).—Steric analysis of 1,3-dioxan and its derivatives has been extensively performed.[5] It is now well established that the 1,3-dioxans exist in a chair conformation which is much more stable than any of the boat structures. Consequently the configurational and conformational isomers of the dimer (2) are those shown in the Scheme (only one mirror image is drawn in each case). Conformers (4) and (4′) are *cis*-structures since the substituents R^1 and R^2 lie on the same side, (5) and (5′) are *trans*-structures. It is also well known [6] that 2-alkyl-substituted 1,3-dioxan shows a large energy difference between axial and equatorial positions. The energetically preferred conformation (>95%) has the substituent in the equatorial position. Considering the nature of the substituent R^1 it can be deduced that the *cis*- and *trans*-isomers exist predominantly as (4) and (5), respectively. In agreement with this, n.m.r. investigations on the dimer and on the acetylated derivative in the temperature range from −100 to +80 °C do not give any indication of conformational equilibrium.



SCHEME $R^1 = C(CH_3)_2{\cdot}CH_2OH$, $R^2 = OH$

The presence of two isomers is confirmed by the n.m.r. spectra which show signals whose intensity increases with time. These signals which are clearly distinguished from those of the monomer must be attributed to an isomer. After some hours at room temperature the solution shows peaks of comparable intensity for the isomers and it was possible to determine the spectral parameters of both. Also the n.m.r. spectrum of the acetylated product clearly indicates a mixture of two isomers in agreement with the g.l.c. results. The chemical shifts and the coupling constants measured allow us to conclude that the dimer exists mainly in the

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* The multiplicity of the signals disappears when deuterium oxide is added to the DMSO solution.

[3] 'Organic Electronic Spectral Data' Interscience, New York, vol. 1-6.

[4] S. Patai, in 'The Chemistry of the Ether Linkage,' Interscience, New York, 1967, pp. 332—334.

[5] E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, 1968, **90**, 3444; F. G. Riddell, *Quart. Rev.*, 1967, 364; O. H. Ellestad, P. Klaboe, and G. Hagen, *Spectrochim, Acta*, 1972, **28A**, 137.

[6] H. Booth, *Progr. N.M.R. Spectroscopy*, 1969, **5**, 149.

cis-form immediately after dissolving the crystalline form.

The chemical shifts of 2*ax*-H agree with those in the literature,[5] the *trans*-isomer having the absorption at slightly lower field because of the position of the OH group (δ 4.41 and 4.90, respectively); a similar effect is known for cyclohexanols.[6] The chemical shift of the methyl and methylene groups of the substituent at position 2 agree with those predictable from correlation tables [7] and there is not a large difference between the two isomers as the substituent should be equatorial in both isomers. The proton in position 4 is distinguished from that in position 2 because its coupling with the hydroxy-group splits or broadens the signal. It is known that the equatorial protons in 1,3-dioxans absorb at lower field that the corresponding axial protons, and the *trans*-isomer (5) has the signal produced by the equatorial proton in position 4 at lower field than that of the *cis*-isomer (4) (δ 4.80 and 4.59, respectively).

The *cis–trans* attribution is further supported by the observed chemical shifts of the hydroxy-group and by the $^3J_{\mathrm{H.OH}}$ coupling constants observed in the two isomers. In fact the axial hydroxy-proton has the resonance at higher field than the corresponding equatorial proton and also the coupling constant $^3J_{\mathrm{H.OH}}$ is greater when the hydroxy-group is equatorial (*J* 5.5 and 3.5 Hz, respectively). This is in agreement with results for similar compounds.[5]

Also important for the assignment is conformity with the W rule for the coupling constant. It is known [6,8] that $^4J_{\mathrm{H.H}}$ in 1,3-dioxans is *ca.* 0.5 Hz, but $^4J_{2eq\text{-H},6eq\text{-H}}$ and $^4J_{4eq\text{-H}.6eq\text{-H}}$ have a value of 1—2 Hz. The *cis*-isomer (4) does not have a W type coupling, as opposed to the *trans*-isomer which has the proton in position 4 equatorial. Consequently the AB quartet of the *trans*-isomer (4) does not have a W type coupling, as opposed 6*eq*-H) broader than the two signals at higher field (produced by 6*ax*-H). So all the evidence is completely consistent with the two suggested structures for the dimer. In addition to the absorptions ascribed to (5), other signals corresponding to the monomer (1) gradually develop.*

The ratio of the amounts of isomers (4) and (5) in equilibrium conditions is *ca.* 1.65 ± 0.05 at room temperature in the solvents used. From this value is derived the free energy difference of 0.30 ± 0.02 kcal mol^{-1} between the two stereoisomers. This destabilization of (5) compared to (4) must be attributed to the axial hydroxy-group of (5).

Equilibrium of Dimer and Monomer.—In order to test the reversibility of the dissociation process, a solution of the dimer in water (the solvent used in the synthesis process) was kept at 24 °C until the absorbance value at $\lambda_{\mathrm{max.}}$ (290 nm) was constant. The same solution was heated at 80 °C and a higher absorbance value obtained. On cooling the solution to 24 °C the absorbance value slowly reverted to the former value.

The dissociation reactions of the two diastereoisomeric dimers to the monomeric form can be described as (4) $\rightleftharpoons$ (1) $\rightleftharpoons$ (5). The equilibrium constants for the dissociation reactions are given by (1) and (2) where *C* is

$$K_{(4)} = \frac{2(1 + a)C^2}{a(2p - C)} \tag{1}$$

$$K_{(5)} = \frac{2(1 + a)C^2}{2p - C} \tag{2}$$

the equilibrium concentration of the monomer, *a* the equilibrium molar ratio between (4) and (5), and *p* the total weighted dimer. By using an *a* value of 1.65, the $K_{(4)}$ and $K_{(5)}$ values obtained at 24 °C are 0.43 and 0.71 mol l^{-1}; this shows higher dissociation for the *trans*-diastereoisomer as expected.

Since the entropy of mixing and symmetry number terms [9] are the same in the two diastereoisomers, it is possible to assume that there is no entropy difference between (4) and (5). In this way one can calculate the equilibrium molar ratio *a* in the range 24—80 °C and thereby, the equilibrium constants for both dissociations. The results are shown in Table 1.

TABLE 1

Dissociation equilibrium constants and free energy differences for diastereoisomers (4) and (5)

T/°C	$K_{(4)}$/ mol l^{-1}	$\Delta G°_{(4)}$/ kcal mol^{-1}	$K_{(5)}$/ mol l^{-1}	$\Delta G°_{(5)}$/ kcal mol^{-1}
24	0.43	0.50	0.71	0.2
35	0.82	0.12	1.34	−0.18
42	1.25	−0.14	2.02	−0.44
50	1.71	−0.34	2,25	−0.64
61	2.44	−0.60	3.83	−0.90
77	7.46	−1.40	11.48	−1.7

The temperature dependence of the equilibrium constants gives a heat of reaction $\Delta H°_{(4)}$ of 10.5 ± 0.1 and $\Delta H°_{(5)}$ of 10.2 ± 0.1 kcal mol^{-1} and a free entropy change for both dissociations $\Delta S°$ of 34 ± 0.3 cal mol^{-1} K^{-1}.

The parameters of a least-squares fitting of the data are $\ln K_{(4)} = -5\,300/T + 17.04$ (*r* 0.99, *s* 0.1) and $\ln K_{(5)} = -5\,150/T + 17.08$ (*r* 0.99, *s* 0.1). The equilibrium temperature data reveal the lower stability of the *trans*-diastereoisomer (5), mild endothermicity for both dissociations, and a large entropy change in agreement with the passage from the compact dimeric structure to the more disordered monomeric form.

Due to the low solubility of the dimer in water (*ca.* 4%), we have not been able to carry out concentration determinations of *cis*- and *trans*-dimers by n.m.r.; therefore we have referred the kinetics to the simplified equilibrium D $\longrightarrow$ 2M where D is the ' total ' dimer and M the monomer, determined by u.v. measurements.

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* Detailed n.m.r. results are given in Supplementary Publication No. SUP 22159 (4 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index Issue.

[7] J. W. Robinson, in ' Handbook of Spectroscopy ', C.R.C. Press, Columbus, 1974, vol. II.

[8] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 693.

[9] E. Eliel, N. Allinger, S. Angyal, and G. Morrison, ' Conformational Analysis ' Interscience, New York, 1965.

Using the standard solution[10] of this rate law, we obtain data which agree with a good straight line, the least-squares fitting parameters of which are $K_dt = 1.05 \times 10^{-3}\,t + 0.04$ (r 0.99, s 0.05) where K_d is the rate constant for the dissociation in min^{-1}. This gives support to the use of a simplified description of the equilibrium.

Table 2 collects the results for the dissociation constant rate K_d in various solvents. It should be noted that (a) equilibrium is achieved slowly (in water it needs about two days) and no dissociation takes place in solvents with a low dielectric constant; (b) the dissociation rate constant increases with the dielectric constant; (c) in methanolic solution the kinetic equation adopted does not hold because of solvent interaction with the monomer to give a hemiacetal.[11] This agrees with the low value obtained for the molar extinction coefficient.

TABLE 2

Dissociation constant rate (at 24 °C) in several solvents

Solvent	Dielectric constant D (at 25 °C)	Molar extinction coefficient ε/l mol^{-1} cm^{-1}	k_d [a]/min^{-1}	$t_{\frac{1}{2}}$ [b]/h
H_2O	78.5	20.6	1.05×10^{-3}	6
$(CH_3)_2SO$	46.7	24.2	5.6×10^{-4}	10
CH_3OH	32.6	13.3		
$CH_3OCH_2CH_3OH$	16.9	20.3	4×10^{-3}	60
Tetrahydrofuran	7		No dissociation	
Dioxan	2		No dissociation	

[a] See text. [b] Observed time for 50% reaction D $\rightleftarrows$ 2M.

[7/002 *Received, 4th January,* 1977]

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[10] W. J. Moore, ' Physical Chemistry ', 5th edn., Longman, Harlow, Essex, 1972, p. 340.

[11] See ref. 4 pp. 312—313.