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Dihydroxyacetone dimers; Solution and Crystal Structure of Stereoisomers of 2,5-Diethoxy-1,4-Dioxane-2,5-Dimethanol

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Abstract: 1,3-Dihydroxy-2-propanone (dihydroxyacetone) in aqueous solution is an equilibrium remeniscent of the one in ketoses. When reacted with triethyl orthoformate and ethanol two stable diethyl ethers were isolated and their structures have been shown to be the *cis*- and *trans*-isomers of 2,5-diethoxy-1,4-dioxane-2,5-dimethanol. NMR spectroscopy and X-ray crystallography revealed that the *trans*-isomer adapts chair conformation while the *cis*-isomer is a twist-boat both in solution and crystalline state.

INTRODUCTION

1,3-Dihydroxy-2-propanone or dihydroxyacetone is the simplest member of the family of ketoses. Because of its importance in the metabolism of carbohydrates there has been a lot of interest in this molecule. In particular the monophosphate ester is important. It is well known that in nature the enzyme fructose 1,6-diphosphate aldolase is responsible for breakdown of C-6 molecules to yield C-3 species. More recently aldolases have been developed as a class of enzymes capable of forming carbon-carbon bonds with a great degree of stereoselectivity.[1] One limitation, however, is that dihydroxyacetone phosphate is necessary as one of the two substrates to be combined.[2] Our interest in monosubstituted derivatives of dihydroxyacetone is concerned with their possible use as substrates for baker´s yeast in stereoselective reductions.[3]

Hydroxyaldehydes and ketones have a greate tendency of forming internal cyclic hemiacetals and hemiketals provided the distance between the hydroxy group and the carbonyl group is suited for the formation of five or six-membered rings. Similar structures consisting of more than one molecule, are also formed in smaller hydroxy aldehydes and ketones. The equilibrium between the cyclic *p*-dioxane form and the open ketone form of dihydroxyacetone has been studied by spectroscopic methods.[4] To our knowledge derivatives of the different stereoisomers of the cyclic dimer have not been described.

RESULTS AND DISCUSSION

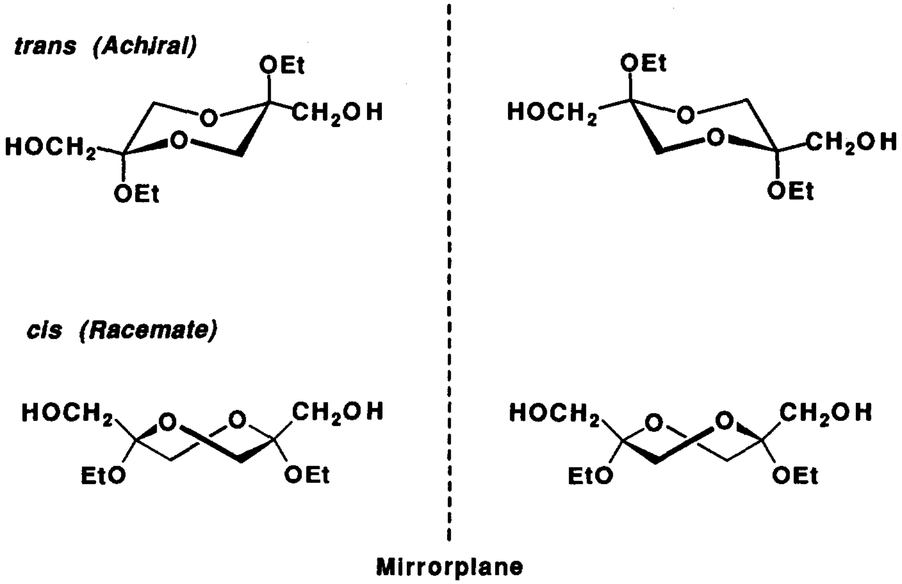

Figure 1. Structures of the *cis* and *trans* isomers of 2,5-diethoxy-1,4-dioxane-2,5-dimethanol with their mirror images. The figure shows that while the *trans*-form is achiral (the mirror image is the same molecule), the *cis*-form is chiral and produced as a racemic mixture.

2,5-Diethoxy-1,4-dioxane-2,5-dimethanol was synthesised from dihydroxyacetone, triethyl orthoformate and ethanol.[2] TLC showed two products ("upper" and "lower" spot) in almost equal amounts and they were easily separable by preparative layer chromatography (PLC). Both compounds crystallised readily from methanol.

Both the ^1H and ^{13}C NMR spectra of the two products were very similar with respect to shifts and coupling constants. The most significant feature in both spectra was that they showed resonances due to half of the total number of nuclei, *i.e.* 5 ^{13}C resonances and 10 protons. This could be due to either symmetry or time averaged processes. Spectra recorded at different temperatures (+50 to -80 °C) in acetone solutions of both compunds showed very small changes only, indicating that latter possibilty was unlikely. The only significant changes were due to a downfield shift of the OH-protons of about 1 ppm on going to low temperature.

When examining the two forms as presented in Figure 1, it is evident that the *trans*-form contains a centre of symmetry. Moreover, the *cis*-form in the twist-boat conformation has a two-fold symmetry axis. In a chair conformation this would not have been the case.

In the ^1H NMR spectrum of the *cis*-form there was observed a small coupling of 2.2 Hz between the axial ring proton (3.532 ppm) and one of the methylene protons in the $-CH_2OH$ group (3.734 ppm). This must be due to a long range coupling since the two protons are joined by four bonds forming a uniplanar W-structure. (Figure 2) This coupling will take place when the conformation is a twist-boat. It may be argued that one of the protons of the axial $-CH_2OH$ group in the chair conformation also may show a similar coupling. However, due to interchange between the two equal chair conformations, this coupling would become small or negligible in this case. A similar coupling was not observed between the corresponding protons of the *trans*-isomer. It should also be remarked that an important contribution in favour of the conformations observed both in the crystalline state and in solution, is that both the *cis*- and the *trans*-isomer have nearly maximum anomeric effect.[5]

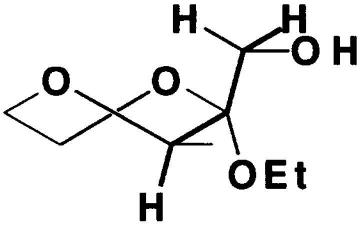

Figure 2. A part of the structure of the *cis*-isomer showing the W-arrangement (heavy lines) of the bonds joining the two protons which show long range coupling.

The equilibrium composition of dihydroxyacetone in DMSO solution has been studied previously.[6] On the basis of an observed long range coupling between one ring proton and the OH proton it was suggested that the 1,4-dioxane ring had adapted a chair conformation.

The absolute configurations of the *cis*- and *trans*-isomer are visualised in Figure 1. While the *trans*-isomer is achiral, the *cis*-isomer is a pair of enantiomers.

The X-ray crystal structures of the two isomers are shown in Figure 3. Both structures reveal the symmetry elements present, a center of symmetry in the *trans*-isomer and a two-fold symmetry axis of the *cis*-isomer. Also other structural features that are indicated on the basis of the NMR spectra, such as the conformations and the W-structure element are evident.

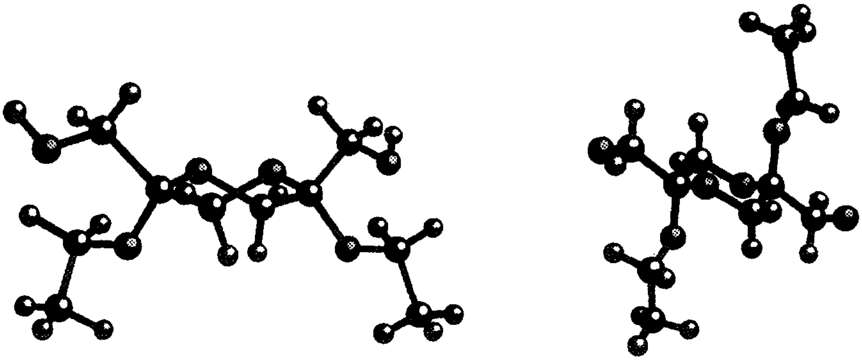

Figure 3. X-ray crystal structures of *cis*- (left) and *trans*-2,5-Diethoxy-1,4-dioxane-2,5-dimethanol (right).

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Chemicals. Triethyl orthoformat was purchased from Aldrich Chemical Co. and 1,3 - dihydroxyacetone (Dimer) from Janssen Chimica.

NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded in acetone-d_6 solutions using TMS as internal reference with shift values in ppm. The instrument was Bruker AM 500 operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. All assignements are confirmed by ^{1}H-^{13}C correlation, DEPT and double-quantum filtrated(DQF), phase-sensitive (TPPI) COSY.[7] The temperature of the sample was adjusted to 276K to avoid overlap of the hydroxyl proton with other resonances in the 3 - 3.5 ppm region. In low temperature work the temperature of the sample was measured with an ethylene glycol thermometer. The 2D DQF-COSY sweep-width in the directly observed dimension was 3332 Hz (2x oversampling), aquiring 600 ms. In the inderectly detected dimension a sweep width of 1666 Hz was used, with 680 points giving an aqusition time of 204 ms.

X-ray crystallography. Diffraction data were collected on a CAD-4 diffractometer using graphite monochromated Cu-Ka radiation (l = 1.54184Å). The structures were solved by direct methods and refining using the integrated computerprogram package MoLEN (Ref: MoLEN, An Interactive Structure Solution Procedure, Enraf-Nonius, Delft, The Netherlands, 1990).

2,5-Diethoxy-1,4-dioxane-2,5-dimethanol. In an oven dried flask was mixed anhyd EtOH (250 mL), conc H_2SO_4 (0.5 mL) and triethyl orthoformate (17.5 mL). The solution was refluxed for 30 min under N_2, cooled to 4 ^{o}C and dry dihydroxyacetone dimer (0.714 g) was added every 12h for 72h. The solution was stirred for an additional 24 h at 4 ^{o}C, water (2 mL) was added and the mixture stirred for 30 min, pH was adjusted to 8 with NaOH (2N) and excess EtOH was removed under reduced pressure. The white precipitate was triturated with Et_2O (2 x 50 mL), the Et_2O fractions were combined and extracted with satd NaCl (10 mL). The combined aqueous fraction was extracted with Et_2O (3 x 20 mL) to recover more product. The combined Et_2O fractions were dried over anhyd Na_2SO_4 and evaporated under reduced pressure. The product was crystallized from EtOAc/heptane to produce 0.90 g of the tittle compound as a mixture of *cis* and *trans* isomers. Further trituration (250 mL) and crystallization afforded additional 1.50g, total yield 2.40g (55%). The isomers were separated by PLC (1 : 2 : 16, MeOH : hexane : EtOAc, Rf 0.66 and 0.60), and crystallized from MeOH.

cis -2,5-Diethoxy-1,4-dioxane-2,5-dimethanol (Upper fraction, Rf 0.66). mp: 141-146 ^{o}C, ^{1}H NMR (276K) 3.884, H_{eq}, 3.532, H_{ax}, J_{gem} -11.96 Hz, 3.734, -CHHOH, J_W 2.20 Hz (to H_{ax}), 3.505, -CHHOH, J_{gem} -12.00 Hz, 4.049, (temp shift -8.2 ppb/K) -CHHOH, J_{vic} 7.3, and 4.9 Hz, (-CH_2OH), 3.665 and 3.746, -OCH_2CH_3, J_{gem} -8.97 Hz, -OCH_2CH_3 1.230, J_{vic} 7.0 Hz. ^{13}C NMR 61.66 (t) and 99.35 (s), ring carbons, 56.63 (t) and 15.55 (q), -OCH_2CH_3, 61.04, -CH_2OH. X-ray data: Monoclinic space group $P2_1/c$ with a=8.392(2), b=14.617(2), c=10.545(1) Å, b=105.00(1)^{o}, V=1249 Å^3 and one molecule of

$C_6H_{20}O_6$ in the asymmetric unit. The structure was refined to R=0.046 and R_W=0.06 using 2369 reflections.

trans -2,5-Diethoxy-1,4-dioxane-2,5-dimethanol (Lower fraction, Rf 0.60). mp: 126-131 °C, ^{1}H NMR (276K) 3.792 H_{eq}, 3.555 H_{ax}, J_{gem} -11.4 Hz, 3.631 and 3.367, $-CH_2OH$, J_{gem} -12.0 Hz, 3.867,$-CH_2OH$, J_{vic} 7.1 (-CHHOH) and 5.6 (-CHHOH), 3.512 and 3.575, $-OCH_2CH_3$ J_{gem} -9.14 Hz, $-OCH_2CH_3$ 1.162, J_{vic} 7.1 Hz. ^{13}C NMR 64.35 (t) and 95.93 (s), ring carbons, 56.32 (t) and 15.76 (q), $-OCH_2CH_3$, 62.74, $-CH_2OH$. X-ray data: Orthorhombic space group Pbca with a=15.846(1), b=15.052(4), c=10.468(2) Å, V=2501 Å^3 and one molecule of $C_6H_{20}O_6$ in the asymmetric unit. The structure was refined to R=0.067 and R_W=0.115 (the crystal was of poor quality) using 2566 unique reflections.

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