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Chemistry of Keto Acetals: III.* Stereochemical Features of the Addition of Triethyl Orthoformate to 6-(Diethoxymethyl)-1-trimethylsiloxycyclohexene

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Abstract—Stereochemistry of the addition of triethyl orthoformate to 6-(diethoxymethyl)-1-trimethylsiloxycyclohexene has been studied. The reaction yields a mixture of isomeric 2,6-bis(diethoxymethyl)cyclohexanones with diequatorial and axial/equatorial orientations of the acetal fragments, the latter prevailing. The stereochemistry of the addition is determined by the transition state structure rather than by thermodynamic stability of the resulting keto diacetal.

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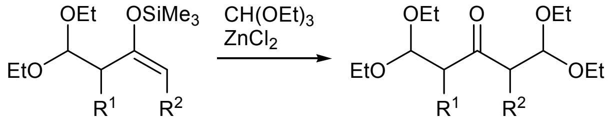
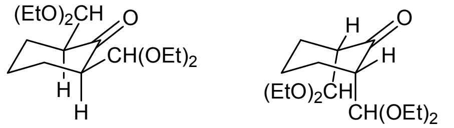
Keto diacetals are interesting but still difficultly accessible polyfunctional intermediate products in fine organic synthesis. Keto diacetals were used to obtain numerous heterocyclic compounds [1, 2] and hydroxy diacetals as starting materials for the synthesis of cyanine dyes [3, 4]. The synthesis of keto diacetals was described in several publications [5–7]. The most general procedure for the synthesis of β,β′-keto diacetals is based on the addition of triethyl orthoformate to silyl enol ethers containing an acetal fragment (Scheme 1).

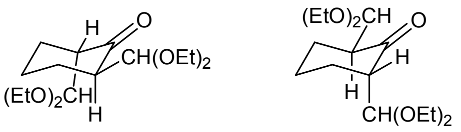
Scheme 1.



$R^1 = R^2 = H, R^1R^2 = (CH_2)_3.$



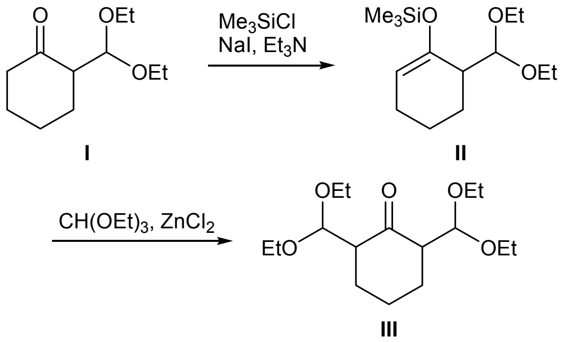
cis Isomers



trans Isomers

2,6-Bis(diethoxymethyl)cyclohexanone can be formed as optically inactive *cis* isomer and two optically active *trans* isomers, and the *cis* isomer can exist as diequatorial (*ee*) and diaxial (*aa*) conformers. Unfortunately, stereochemistry of the above reactions remained beyond the scope of all relevant publications. We decided to explore this problem in the present work. Scheme 2 illustrates the general scheme of synthesis of 2,6-bis(diethoxymethyl)cyclohexanone (**III**).

Scheme 2.



Initial 2-(diethoxymethyl)cyclohexanone (**I**) was prepared by condensation of 1-(trimethylsiloxy)cyclohexene with triethyl orthoformate [8]. As expected, the addition of diethoxymethyl group was stereoselective, and the product was a single isomer with equatorial orientation of the acetal fragment (according to the ^{1}H NMR data). The ^{1}H NMR spectrum of **I** contained only one one-proton signal at about δ 4.8 ppm (d, 1-H).

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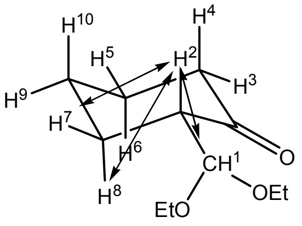
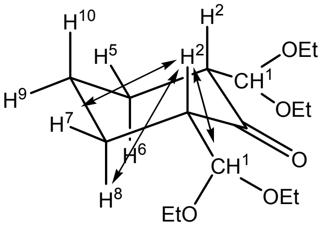
* For communication II, see [1].

The 2-H proton also appeared as a single signal at δ 2.64 ppm (broadened doublet of triplets with coupling constants of 10.2 and 6 Hz). The coupling constant 10.2 Hz corresponds to diaxial interaction between 2-H and 8-H. The coupling constants of 2-H with 7-H and 1-H are approximately equal (J = 5.9 Hz). These findings suggest axial orientation of 2-H and equatorial orientation of the acetal fragment.

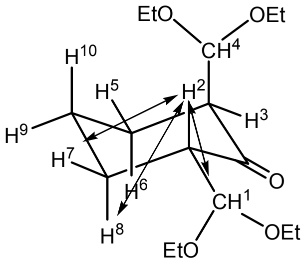


Keto acetal **I** was subjected to silylation with chloro(trimethyl)silane in the presence of triethylamine and sodium iodide in pentane–acetonitrile at –10 to –0°C (5 h; TLC monitoring). After appropriate treatment, we isolated 6-(diethoxymethyl)-1-trimethylsiloxycyclohexene (**II**). In this reaction the acetal fragment remained intact, and its conformation did not change. Compound **II** should be characterized by a high boiling point and should be thermally unstable (thermal elimination of alcohol should produce cyclic analog of Danishefsky's diene [3]). Poorly reproducible yields were obtained previously [7]. Therefore, in the present work the product, after washing from sodium chloride and triethylamine (which could bind the catalyst in the next step), was neither distilled nor purified by chromatography but was brought into the condensation with triethyl orthoformate immediately after removal of the solvent.

2,6-Bis(diethoxymethyl)cyclohexanone (**III**) was synthesized by condensation of silyl enol ether **II** with triethyl orthoformate at 10°C (48 h) in the presence of 20% zinc chloride in ethyl acetate as catalyst. The product was purified by chromatography on silica gel. We thus isolated two fractions with R_f 0.8 and 0.74. The fraction with R_f 0.8 was a mixture of isomeric 2,6-bis(diethoxymethyl)cyclohexanones with diequatorial (**A**) and axial–equatorial (**B**) orientation of the substituents.

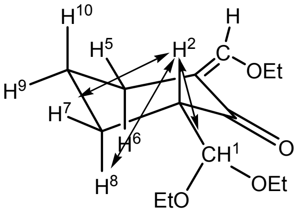


A

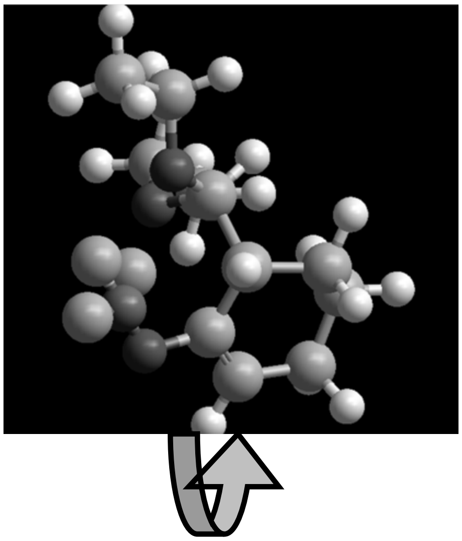


B

The more mobile fraction contained 64% of the *ee* isomer and 36% of the *ae* isomer. This followed from the intensity ratio (4.7:1) of the 2-H and 3-H signals at δ 2.58–2.68 and 2.69–2.77 ppm, respectively. The 2-H signal was a broadened doublet of triplets with the coupling constants $J_{2,8}$ = 10.2 Hz and $J_{2,18} \approx J_{2,18} \approx$ 6 Hz. The coupling constant $J_{2,8}$ = 10.2 Hz indicates axial position of the 2-H proton and hence equatorial orientation of the diethoxymethyl substituent. The 3-H signal of stereoisomer **B** was a doublet of triplets with coupling constants of 5.6 and 6.9 Hz. The latter constant corresponds to the 3-H–4-H coupling, and the former, to 3-H–5-H and 3-H–6-H. Their values suggest equatorial position of 3-H and axial position of the diethoxymethyl group. The acetal CH protons gave rise to two doublets at 4.83 and 4.86 ppm at a ratio of 14:86. The singlet at δ 8.58 ppm with an intensity of 0.05H was assigned to the CHO proton in the corresponding aldehyde formed as impurity as a result of partial hydrolysis of the acetal group. Furthermore, a triplet at δ 7.31 ppm (0.1H, J = 2 Hz) was observed, which is likely to belong to proton at the double bond generated by dealkoxylation of the keto diacetal. Elimination of ethoxy group is also supported by the presence of a quartet at δ 4.0 ppm due to OCH_2 protons. The increased intensity of the equatorial acetal proton signal as compared to ring methylene protons (5-H–10-H) indicates more facile elimination of alcohol from the axial acetal group, i.e., with predominant formation of structure **C**.



C



Structure of the energetically most favorable conformer of 6-(diethoxymethyl)-1-trimethylsiloxycyclohexene (**II**) and direction of electrophilic attack thereon.

The fraction with the lower R_f value (0.74) contained only one 2,6-bis(diethoxysimethyl)cyclohexanone (**III**) isomer with axial–equatorial orientation of the acetal substituents (structure **B**). This follows from the equal intensities of the 2-H and 3-H signals in the region of δ 2.7 ppm and of the doublet acetal proton signals at δ 4.8 ppm.

The weight ratio of the fractions with R_f 0.80 and 0.74 is 1:0.57, i.e., the major product in the reaction of 6-(diethoxymethyl)-1-trimethylsiloxycyclohexene (**II**) with triethylorthoformate is 2,6-bis(diethoxymethyl)-cyclohexane (**III**) with axial–equatorial orientation of the acetal substituents (stereoisomer **B**). The ratio of the *ae* and *ee* isomers was 59:41. Prevalence of the isomer with “unfavorable” axial orientation of one acetal group was rationalized with the aid of quantum chemical calculations. As might be expected, semiempirical PM3 calculations of the optimal configuration of 2,6-bis(diethoxymethyl)cyclohexanone predicted diequatorial orientation of the acetal substituents in the most energetically favorable conformer. Therefore, the factor determining the formation of the *ae* conformer is not its thermodynamic stability but kinetic features of the reaction of silyl enol ether **II** with triethyl orthoformate. Figure shows the most energetically favorable configuration of 6-(diethoxymethyl)-1-trimethylsiloxycyclohexene (**II**) according to quantum chemical calculations. Analysis of the given structure indicates that *trans*-attack by electrophile on the double bond leading to the *ae* isomer should be preferred from the steric viewpoint; in fact, this was observed experimentally.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker MSL-300 spectrometer at 300 MHz) using tetramethylsilane as internal reference. The progress of reactions was monitored, and the products were identified, by TLC on Silica gel 60 F_{254} plates using hexane–ethyl acetate (6:1) as eluent; spots were visualized by treatment with iodine vapor. The products were isolated by column chromatography on Merck Silica gel 60 (eluent hexane–ethyl acetate, 100:1 to 6:1). Zinc(II) chloride was heated to the melting point, cooled, ground, and dissolved in anhydrous ethyl acetate to a concentration of 20%; sodium iodide was calcined for 1 h at 250°C; triethylamine was preliminarily kept over potassium hydroxide and distilled under atmospheric pressure, a fraction with bp 89–90°C being collected; chloro(trimethyl)silane was distilled under atmospheric pressure (bp 57°C); ethyl acetate, acetonitrile, pentane, and hexane (of dried or ultrapure grade) were used without additional purification. 2-(Diethoxymethyl)cyclohexanone (**I**) was synthesized as described in [8].

6-(Diethoxymethyl)-1-trimethylsiloxycyclohexene (II). A mixture of 200 mL of acetonitrile, 200 mL of pentane, 59 g (0.39 mol) of sodium iodide, 55 mL (0.39 mol) of triethylamine, and 50 mL (0.39 mol) of chloro(trimethyl)silane was cooled to –10°C, 40 g (0.2 mol) of 2-(diethoxymethyl)cyclohexanone (**I**) was added to the resulting solution, and the mixture was stirred for 3.5 h at a temperature not exceeding –10°C. The mixture was then allowed to warm up to 0°C and, after 1.5 h, to 13°C. After 1 h, the acetonitrile layer was separated from the pentane layer, and the former was extracted with pentane (3×50 mL). The combined extracts were washed with 2% aqueous HCl (2× 50 mL) cooled to 0°C, a cold saturated solution of sodium carbonate (2×50 mL), and water (2×100 mL), and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue (40 mL) was brought into further transformations with additional purification.

2,6-Bis(diethoxymethyl)cyclohexanone (III). Compound **II** prepared as described above, 18 mL (0.06 mol), was added over a period of 1 h to a mixture of 40 mL (0.08 mol) of a 20% solution of $ZnCl_2$ in ethyl acetate and 12 mL (0.1 mol) of triethyl orthoformate, cooled to 10°C. The mixture was kept for 48 h at that temperature and treated with a saturated solution of sodium carbonate to pH 9. The abundant precipitate was filtered off and washed on a filter with diethyl ether (3×50 mL). The aqueous layer was extracted with diethyl ether (2×25 mL), the extracts were combined with the organic phase, dried over sodium sulfate, and evaporated, and the residue was subjected to column chromatography.

***ae* Isomer.** Yield 3.7 g (20%), n_D^{20} = 1.4565. ^{1}H NMR spectrum, δ, ppm: 1.17 t (6H, CH_3, *J* = 7 Hz), 1.19 t (6H, CH_3, *J* = 7 Hz), 1.50–2.50 m (6H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.64 br.d.t (1H, 2-H, *J* = 10.2, 6 Hz), 2.70 d.t (1H, 3-H, *J* = 5.6, 7 Hz), 3.48–3.61 m (4H, CH_2), 3.62–3.78 m (4H, CH_2), 4.83 d (1H, 1-H, *J* = 6.3 Hz), 4.86 d (1H, 4-H, *J* = 6.9 Hz). Found, %: C 63.71; H 9.95. $C_{16}H_{30}O_5$. Calculated, %: C 63.55; H 10.00.

Mixture of *ae* and *ee* isomers (36:64). Yield 6.48 g (35%), n_D^{20} = 1.4569. Found, %: C 63.83; H 9.96. $C_{16}H_{30}O_5$. Calculated, %: C 63.55; H 10.00. ^{1}H NMR spectrum of the *ee* isomer (from the spectrum of *ae*/*ee* isomer mixture), δ, ppm: 1.17 t (6H, CH_3, *J* = 7 Hz), 1.19 t (6H, CH_3, *J* = 7 Hz), 1.50–2.50 m (6H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.64 br.d.t (1H, 2-H, *J* = 10.2, 6 Hz), 3.48–3.61 m (4H, CH_2), 3.62–3.78 m (4H, CH_2), 4.83 d (1H, 1-H, *J* = 6.3 Hz).

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