Synthesis and identification of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one

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3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one by condensation of acetone with formaldehyde in the ratio of 1:4 in an alkaline medium at a temperature of 30-35°C (product yield 67.4%) was obtained. To determine the composition of obtained compound elemental analysis was used. Functional composition and structural elements were identified using IR spectroscopy. To prove the structure of the synthesized compound, ^{1}H and ^{13}C NMR spectra were taken on a JNN-ECA Jeol 400 spectrometer (at a frequency of 399.78 MHz and 100.53 MHz) with a $CDCl_3$ solvent. Quantum-chemical calculations of stable conformations of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one was performed using *ab initio* DFT B3LYP method and 6-31G (d) and 6-311+G(3df,2p) basis sets. It was found that the stable conformers obtained by calculations are in the "chair" conformation; the hydroxymethyl substituents in conformer I are located equatorially, in conformation II – axially and equatorially, in conformation III – axially. In the conformer III, as a result of spatial proximity, hydroxymethyl substituents form an intramolecular hydrogen bond. The total energies and dipole moments were calculated; a lower value of the dipole moment of the conformation II may indicate its preference over the others.

Keywords: tetrahydropyranone; acetone; formaldehyde; synthesis; condensation; conformational analysis; quantum-chemical calculations; Gaussian.

3,5-диметиленокситетрагидропиран-4-оны синтездеу және идентификациялау

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Ацетон мен формальдегидтің 1:4 қатынаста және 30-35°C температурада жүргізілген сілтілік ортадағы конденсациясынан 3,5-диметиленокситетрагидропиран-4-он синтезделініп алынды (шығымы 67,4%). Синтезделген қосылыстың элементтік құрамы элементтік талдау әдісімен анықталды. Функционалдық құрамы мен құрылымдық элементтері ИҚ спектрі нәтижелерімен идентификацияланды. Қосылыстың құрылысын дәлелдеу үшін JNN-ECA Jeol 400 спектрометрінде (жиілігі 399.78 және 100.53 МГц сәйкес) $CDCl_3$ еріткішінде ЯМР ^{1}H және ^{13}C спектрлері түсірілді. 3,5-диметиленокситетрагидропиран-4-онның мүмкін болатын тұрақты конформацияларын болжау үшін 6-31G(d) және 6-311+G(3df,2p) базалық жиынтығымен DFT B3LYP эмпирикалық емес әдісімен кванттық-химиялық есептеулерлер жасалынды. Нәтижесінде тұрақты құрылымдардың «орындық» конформациясында болатындығы анықталып, I-конформердегі гидроксиметилдік орынбасарлардың экваториальді, II-конформердің аксиальді және экваториальді, ал III-конформердің гидроксиметилдік орынбасарларының аксиальді орналасатындығы белгілі болды. Сондай-ақ III-ші конформердегі гидроксиметилдік орынбасарлардың кеңістіктік жақындасуының нәтижесінде молекулаішілік сутектік байланыс түзілетіндігі көрсетілді. Конформерлердің жалпы энергиясы мен дипольдік моменттерін есептеулер арқылы II-конформердің дипольдік момент мәнінің төмен болуы оның басқа орналасумен салыстырғандағы басым болу мүмкіндігін арттыратындығы анықталды.

Түйін сөздер: тетрагидропиранон; ацетон; формальдегид; синтез; конденсация; конформациялық талдау; кванттық-химиялық есептеулер; Gaussian.

Синтез и идентификация 3,5-диметиленокситетрагидропиран-4-она

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Конденсацией ацетона с формальдегидом в щелочной среде в соотношении 1:4 при температуре 30-35°C получен 3,5-диметиленокситетрагидропиран-4-он (выход 67,4%). Состав полученного соединения установлен элементным анализом. Функциональный состав и структурные элементы идентифицированы с помощью ИК-спектроскопии. Для доказательства строения синтезированного соединения были сняты спектры ЯМР ^{1}H и ^{13}C на спектрометре JNN-ECA Jeol 400 (на частоте 399,78 МГц и 100.53 МГц) с растворителем $CDCl_3$. Выполнены квантово-химические расчеты устойчивых конформаций 3,5-диметиленокситетрагидропиран-4-она неэмпирическим методом DFT B3LYP с базисными наборами 6-31G(d) и 6-311+G(3df,2p). Установлено, что устойчивые структуры находятся в конформации «кресло»; гидроксиметильные заместители конформера I расположены экваториально, конформера II – аксиально и экваториально, конформера III – аксиально. В конформере III в результате пространственного сближения гидроксиметильные заместители образуют внутримолекулярную водородную связь. Рассчитаны полные энергии и дипольные моменты конформеров, более низкое значение дипольного момента конформации II может указывать на ее предпочтительность перед остальными.

Ключевые слова: тетрагидропиранон; ацетон; формальдегид; синтез; конденсация; конформационный анализ; квантово-химические расчеты; Gaussian.

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Synthesis and identification of 3,5-bis(hydroxymethyl) tetrahydro-*4H*-pyran-4-one

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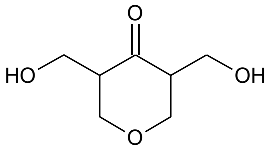
1. Introduction

Tetrahydropyranones, their derivatives and isomers, as well as other heterocyclic ketones with sulfur and nitrogen atoms in the ring, are widely used in medicine [1-4].

We investigated synthesis and identification of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one, which is a promising starting material for the synthesis of various heterocyclic compounds. The structural formula of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one:



Condensation of acetone with formaldehyde in an alkaline medium proceeds according to a complex scheme studied by Holmes and Morgan. The nature of the final products depends on the ratio of components taken for the reaction [5]. In his article [6], Morgan suggested 2 products of condensation of one mole of acetone and four moles of formaldehyde: 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one and 5-(*β*-oxipropionyl)-1,3-dixane.

As a result of identification and proving the structure of the products of this condensation using IR and NMR spectra, we were able to prove that the reaction product is 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one.

Being a heterocyclic ketone with symmetrically located substituents, which contain polar functional groups, the resulting compound can form various spatial structures, computer simulation of which may be of interest.

Six-membered alicyclic compounds have a large variety of forms and conformational effects. The nature and origin of these effects have been studied in many papers on heterocycles and their substituted analogues.

Zubkov et al. [7] based on the analysis of transition state conformations, explained the high chemoselectivity of intramolecular cycloaddition in substituted piperidine-4-ones. Mistryukov [8] has investigated the stereochemistry and the electrostatic, steric, and conformational factors of the hydride reduction of 4-piperidone derivatives. Diwischek et al. [9] observed the stereochemistry of 1,2,6-trimethyl-4-piperidone. Energy differences between chair conformations of the cis- and the trans-isomer of 1,2,6-trimethyl-4-piperidone and the potential energy surface of the equilibration process of the trans-isomer of 1,2,6-trimethyl-4-piperidone between its chair conformers were determined by quantum chemical calculations (BLYP/SVP approach).

Miranda and others [10] have performed high level ab initio quantum chemical calculations for tetrahydro-4-pyranone (B3LYP/6-311+G (3df,2p). The molecule has a "chair" conformation; the angles and lengths of bonds are given one the Figure 1 (in Å and in degrees respectively).

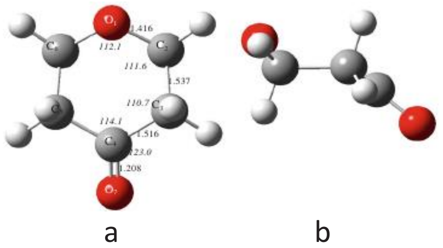


Figure 1 – Front (a) and side (b) views of the most stable conformation found for tetrahydro-4-pyranone

2. Experiment

We carried out the modified synthesis of acetone and formaldehyde at a ratio of 1:4 in an alkaline medium [11]. 11.2 g of acetone (0.2 mole), 24 g (0.8 mole) of formaldehyde, 3 g (0.02 mole) of K_2CO_3 were added to a device consisting of a round-bottom flask with a reflux condenser and a mechanical stirrer. The reaction mixture was stirred at a temperature of 30-35°C for 7 days. The course of the reaction was monitored by TLC in the benzene-alcohol system (6:4). The next day, the solution discolored, then turned yellow. After 7 days the mixture was placed in a separatory funnel, extraction was carried out 3 times with benzene and the upper layer is separated. The resulting benzene extract was dried with anhydrous magnesium sulfate. The next day, benzene was distilled off. After distilling off the benzene, a crystalline precipitate formed on the bottom of the flask. After placing the obtained precipitate on filter paper, it was washed several times with hexane, and recrystallization was performed in ethanol.

3. Results and Discussions

As a result, 21.5 g of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one were obtained in the form of a light yellow powder. Yield 67.4%, T_b=138-140°C. After synthesis, the physicochemical properties o+f the compound were studied. Physicochemical properties of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one are given in Table 1.

To determine the gross formula and elemental composition of the resulting product elemental analysis was performed. Results of elemental analysis of 3,5-bis(hydroxymethyl) tetrahydro-*4H*-pyran-4-one are given in Table 2.

Functional composition and structural elements were identified using IR spectroscopy. The results of the spectrum analysis of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one are shown in Table 3.

To identify the structure of the synthesized compound and confirm that the compound corresponds to the structure of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one, ^{1}H and ^{13}C NMR spectra were obtained. The ^{1}H NMR spectrum was recorded on a JNN-ECA Jeol 400 spectrometer (at a frequency of 399.78 MHz) with a solvent $CDCl_3$ (Table 4).

The ^{13}C NMR spectrum was recorded on a JNN-ECA Jeol 400 spectrometer (at a frequency of 100.53 MHz) with a solvent $CDCl_3$. The results of the spectral analysis are shown in Table 5.

Spectrum analysis shows that the structure of the obtained product is consistent with the structure of 3,5-bis(hydroxymethyl) tetrahydro-*4H*-pyran-4-one.

We carried out the conformational analysis of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one using the methods of quantum chemistry. Quantum-chemical calculations were performed in the GAUSSIAN 09 program with full geometry optimization. The most stable molecular structures were obtained from DFT calculations using the B3LYP density functional and the 6-31G(d) and 6-311+G(3df,2p) basis sets.

Due to the influence of the substituents, the conformation of the six-membered "chair" cycle differs from the conformation of the unsubstituted tetrahydropyranone calculated by the authors [10]. According to quantum chemical calculations, the conformers have a "slightly distorted chair" conformation;

Table 1 – Physicochemical properties of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one

Compound	T_b, °C	R_f (benzene-alcohol system 6:4)	Product yield, %
3,5-bis(hydroxymethyl) tetrahydro-*4H*-pyran-4-one	138-140	0.21	67.4

Table 2 – The percentage by mass of the elements included in the 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one (Gross formula $C_7H_{12}O_4$)

Element	Detected, %	Estimated, %
C	52.41	52.50
H	7.93	7.55
O	39.65	39.94

Table 3 – IR spectrum of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one

Compound	Frequency, ν, cm^{-1}				
	OH	CH_2	C=0	C-C	C-O-C
3,5-bis(hydroxymethyl) tetrahydro-*4H*-pyran-4-one	3432	2933.2872	1703	1657.1452	1101

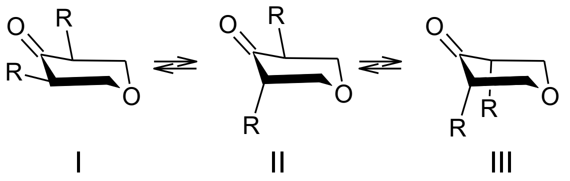
Table 4 – ^{1}H NMR spectrum of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one

Compound	Chemical shift, σ, ppm ($CDCl_3$)			
	$CH_2(C^{3,5})$	CH ($C^{2,6}$)	$CH_2(C^{7,8})$	OH(^{9,10})
3,5-bis(hydroxymethyl) tetrahydro-*4H*-pyran-4-one	3.61 (dd)	2.19 (tp)	3.53 (tp)	5.15 (tp)

Table 5 – ^{13}C NMR spectrum of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one

Compound	Chemical shift, σ, ppm			
	$CH_2(C^{2,6})$	CH ($C^{3,5}$)	$CH_2(C^{7,11})$	C^4
3,5-bis(hydroxymethyl) tetrahydro-*4H*-pyran-4-one	66.18	50.39	62.02	215.19

hydroxymethyl substituents in position 3 and 5 of the ring occupy the equatorial position (I), axial and equatorial (II), axial position (III) (Figure 2).



Note: R = $-CH_2OH$

Figure 2 – Representation of the proposed conformational equilibrium for 3,5-bis(hydroxymethyl) tetrahydro-*4H*-pyran-4-one

The conformer (III) has a "chair" conformation; both hydroxymethyl substituents occupy the axial position (Figure 3).

As it shown in the Figure 3, the substituents of conformer III are spatially close together and form an intramolecular hydrogen bond. The bond lengths and dihedral angles for the substituents of conformers are given in Table 6.

According to the calculations the difference in the total energy of the conformers does not exceed 18 kJ/mol. The low energy of transition of both substituents from the equatorial position to unfavorable axial position (conformer III) may possibly be explained by the formation of a hydrogen bond between the hydroxyl groups of the substituents. For a more detailed study of the spatial structure of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one, we intend to obtain 2D NMR spectra of the compound.

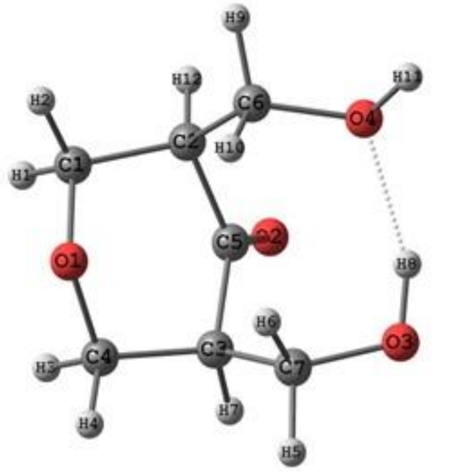


Figure 3 – View of conformer (III) found for 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one

Table 6 – The bond lengths, dihedral angles, total energy, total dipole moment of conformations for 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one

Conformation	Dihedral angle (O^1-C^1-C^2-C^6)	Dihedral angle (O^1-C^4-C^3-C^7)	r (O^4-H^8), Å	Total energy, Hartrees	Total dipole moment, D
I	179	178	7.21	-574.808	2.22
II	175	72	7.38	-571.372	1.68
III	75	70	1.89	-574.801	4.88

4. Conclusion

The synthesis of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one was performed by condensation of acetone and formaldehyde in the ratio of 1:4 in an alkaline medium at a temperature of 30-35°C (product yield 67.4%). The structure of the synthesized ketone was determined and identified by IR spectroscopy, elemental analysis and one-dimensional NMR spectroscopy.

The stable conformations of the obtained ketone were studied by ab initio methods of quantum chemical calculations. The cycle in the molecule has the form of a "slightly distorted chair". As a result of the calculations, three stable conformers were obtained. The low conformational transition energy indicates that the molecule can exist in conformational equilibrium between them. The axial conformer III can be stabilized by an intramolecular hydrogen bond. However, a lower value of the dipole moment of the conformer II may indicate its preference over the axial one.

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