Structure and Antibacterial Activity of Bi-cyclohexanone Pentaerythritol Ketal

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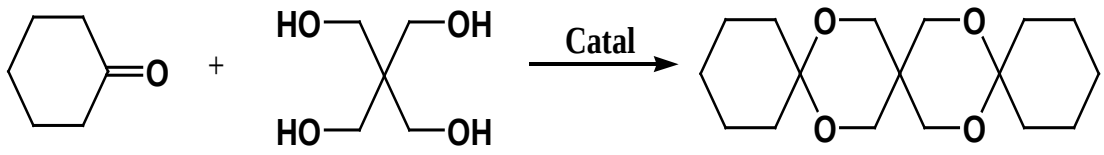
Abstract. Cyclohexanone pentaerythritol ketal was synthesized from cyclohexanone and pentaerythritol by condensation using $NaHSO_4$ as catalyst and characterized by NMR and MS spectrum. Furthermore, the structure of the tile compound was confirmed by single-crystal X-ray diffraction. It crystallizes in orthorhombic space group, P 21, with a unit cell dimensions of a = 11.1214(9) Å, b = 13.9216(6) Å and c = 11.6658(10) Å. In the crystal, there are two independent molecules with different conformation, varying both in bond lengths and angles. In each molecular, there are four six-membered cycles, two cyclohexyl groups and two 1,3-dioxane groups. The four six-membered cycles all display a typical stable boat conformation. The stacking interaction is responsible for the crystal's 1-D supra-molecular structure. The thermal gravimetric analysis (TGA) indicates the title compound is stable below 200°C, and the remaining weight ratio is less than 9% above 300°C. This compound was evaluated for their in vitro antimicrobial activity against six bacteria (*S. aureus, S. epidermidis, M. luteus, E. coli, K. pneumoniae, A. fumigatus*). It some anti-inflammatory activity against the tested bacteria and the inhibition is depending on the concentration.

Introduction

Acetals/ketals are the important compounds or intermediates in the steroid chemistry and synthetic carbohydrate [1,2]. In the synthesis, the acetals/ketals always need protection by 1,2- or 1,3-diols due to the high activity, which is commonly used in carbohydrate chemistry. Besides, the acetals/ketals are used as intermediates and/or end products, in the phyto pharmaceutical, fragrances and lacquers industries [3,4]. They also have been used as solvents in many fields, such as cosmetics, detergent and lacquer industries [5], fragrance industries [6], pharmaceuticals [7], synthesis of enantiomerical compounds and polymer [8,9], beverage additives and food [10]. Acetals and its derivatives have also been used as additives in motor lubricating oils, and water based fluids of drilling petroleum operations [11]. [2,2-bis(hydroxymethyl)propane-1,3-diol], pentaerythritol, is an important building block in thesynthesis of versatile compounds. Pentaerythritol can react with acetals/ketals to produce pentaerythritol acetals, which can be applied as vulcanizers and plasticizers, raw materials for production of valuable resins and lacquers [12]. In this article, we synthesized cyclohexanone pentaerythritol ketal (as shown in Scheme 1), studied its structure by single-crystal X-ray diffraction analysis and screened its antibacterial activity.



Scheme 1 Synthesis of cyclohexanone pentaerythritol ketal

Results and Discussion

Structure

The stereo structure of cyclohexanone pentaerythritol ketal was corroborated by single-crystal X-ray diffraction analysis. The main experimental data of the title compound is displayed in Table 1. The molecular structure is described in Fig. 1, and the packing of the compounds is depicted in Fig. 2, which were drawn with ORTEP-3. The structure of the title compound confirmed by X-ray is consistent with its structure determined by NMR and MS spectra data. All the geometric parameters of the title crystal are in the usual ranges. It crystallizes in triclinic space group, P_{21}, and the unit cell dimension is: a = 11.1214(9) Å, b = 13.9216(6) Å and c = 11.6658(10) Å.

Table 1 Experimental Data

Empirical formula	$C_{34}H_{56}O_8$
Formula weight	592
Temperature	293(2)
Wavelength (Mo K□)	0.71088
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	11.1214(9),13.9216(6), 11.6658(10)
Volume	1593.8(2)
Z	4
Absorption coefficient	0.086
F (000)	654
Crystal size	0.41×0.32×0.24 mm^3
Theta range for data collection (°)	1.55 to 24.00
Index ranges	$-15 \le h \le 7$; $-18 \le k \le 9$; $-6 \le l \le 15$
Reflections collected	4504
Independent reflections	3880
Reflections theta (°)	3.50 to 28.78
Absorption correction transmission	0.9661 to 0.9834
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3880 / 1/ 380
Goodness-of-fit on F^2	0.927
Final R indices [I > 2s(I)]	R1 = 0.0657; wR2 = 0.1447
R indices (all data)	R1 = 0.0449; wR2 = 0.1241
Refine different density	-0.202 to 0.172

In the crystal, there are two independent molecules with different conformation varying in bond lengths and angles, as shown in Fig. 1 and Table 4. For example, the lengths of the main C-O bonds, C1-O1, C4-O2, C3-O3, and C5-O4 are 1.430, 1.425, 1.429, and 1.421 Å respectively, while, in the other molecular, the lengths of the main C-O bonds, C1'-O1', C4'-O2', C3'-O3', and C5'-O4' are 1.429, 1.417, 1.412, and 1.425 Å respectively. The main angles of C-O-O bonds, ∠C1-O1-C6, ∠C4-O2-C6, ∠C3-O3-C12, and ∠C5-O4-C12, are 114.4, 114.5, 114.2, and 113.4° respectively, while, in the other molecular, the main angles of C'-O'-O' bonds, ∠C1'-O1'-C6', ∠C4'-O2'-C6', ∠C3'-O3'-C12', and ∠C5'-O4'-C12', are 113.4, 114.3, 115.1, and 114.4° respectively. There are three quaternary carbons in each molecular. The bonds length related to C2 are very similar in the range from 1.518 Å to 1.532 Å, and the related angels are from 107.0 to 111.0°, which should be due

to the symmetry center role of C2. For other two quaternary carbons, C6 and C12, the related bonds length and the angle are in wider ranges.

In each molecular, there are four six-membered cycles, two cyclohexyl groups and two 1,3-dioxane groups. The four six-membered cycles all display the typical stable boat conformations, as shown in Fig. 1. There is no typical hydrogen bond in the two compound crystals for without hydrogen bond donor. As shown in Fig. 2, the stacking interaction is responsible for the crystal's 1-D supra-molecular structure, and the cyclohexyl groups and 1,3-dioxane groups incline to stack respectively. Besides, it is obviously that the two cyclohexyl groups stack in different directions one by one because of the fixed spiro structure.

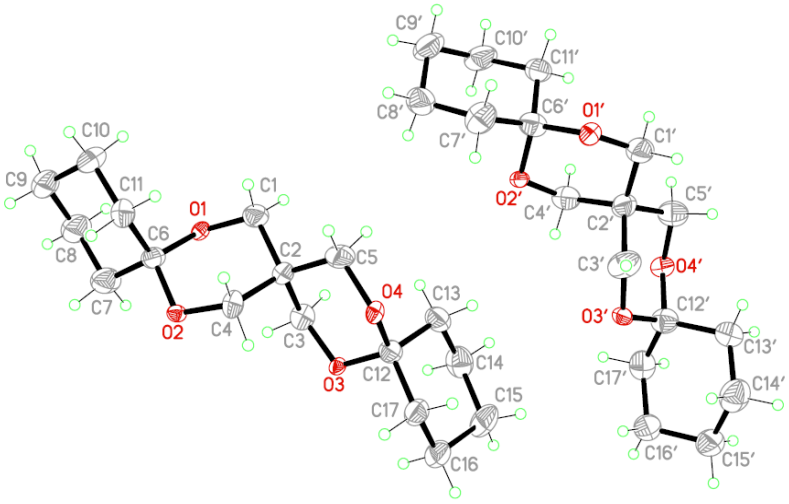


Fig. 1 The molecular structure of cyclohexanone pentaerythritol ketal

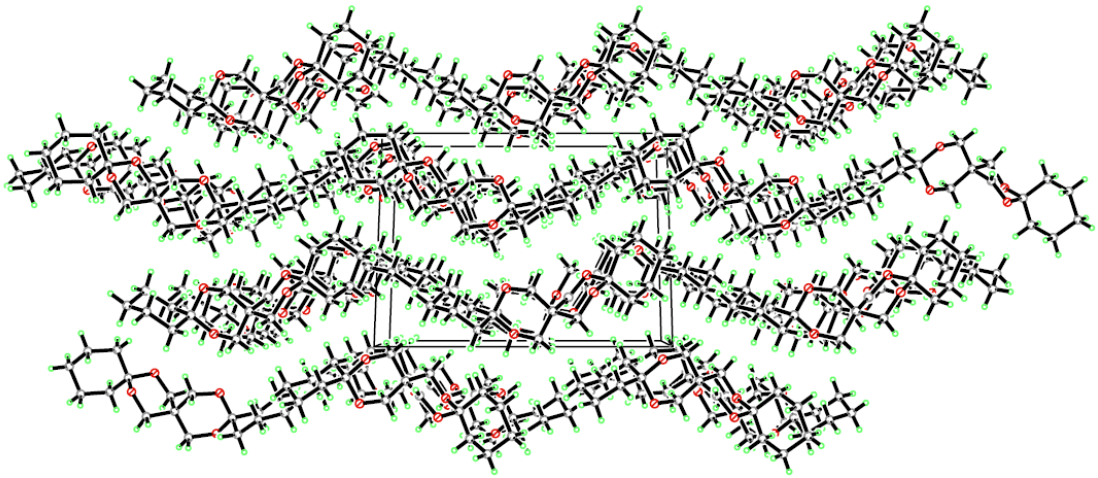


Fig. 2 The 1 D and 2D packing diagram of cyclohexanone pentaerythritol ketal

Thermal Gravimetric Analysis

The thermal character was studied by thermal gravimetric analysis and the TGA analysis was shown in Fig. 3. The TGA curve indicates that the title compound is stable below 200°C, and the compound starts to lose weight sharply as the temperature above 200°C. The first weight loss stage between 30°C and 200°C is only about 8%, which may correspond to the loss of absorbed solvent. The second weight loss stage is about 83% between 200 and 300°C, which should correspond to the decomposition of cyclohexanone pentaerythritol ketal. Above 300°C, there is less than 9% remaining, which may be due to the residue of carbon deposit.

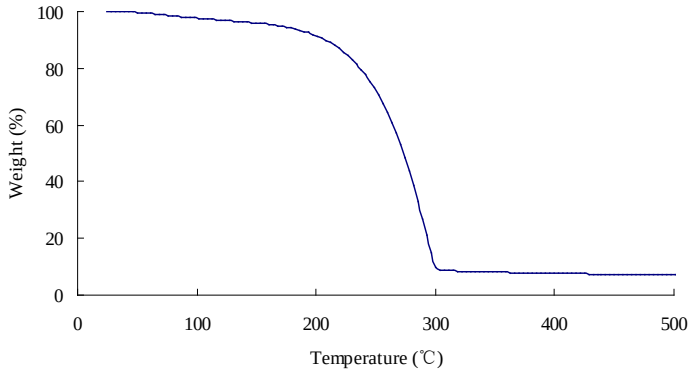


Fig. 3 The TGA curves of cyclohexanone pentaerythritol ketal

Anti-inflammatory Activity

In the daily sports and fitness (as shown in Fig. 4), there will be some small accidents, such as sprains, contusions, bleeding, etc., especially when injury wound contacts with the ground infiltrating some bacteria. Young people are generally infected gram-positive bacteria, and the physical weak elderly are inclined to be infected with gram-negative bacteria.

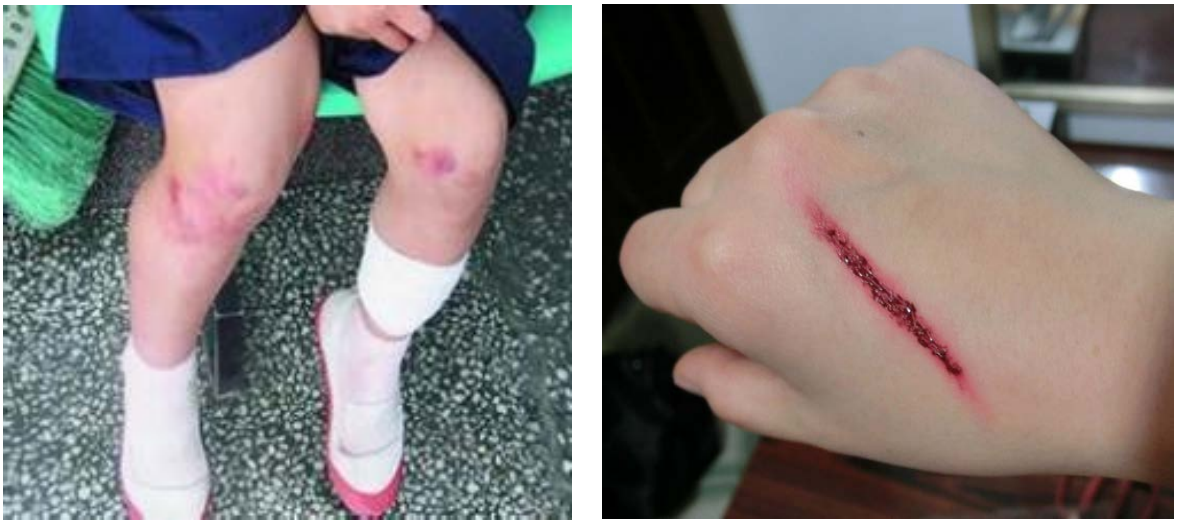
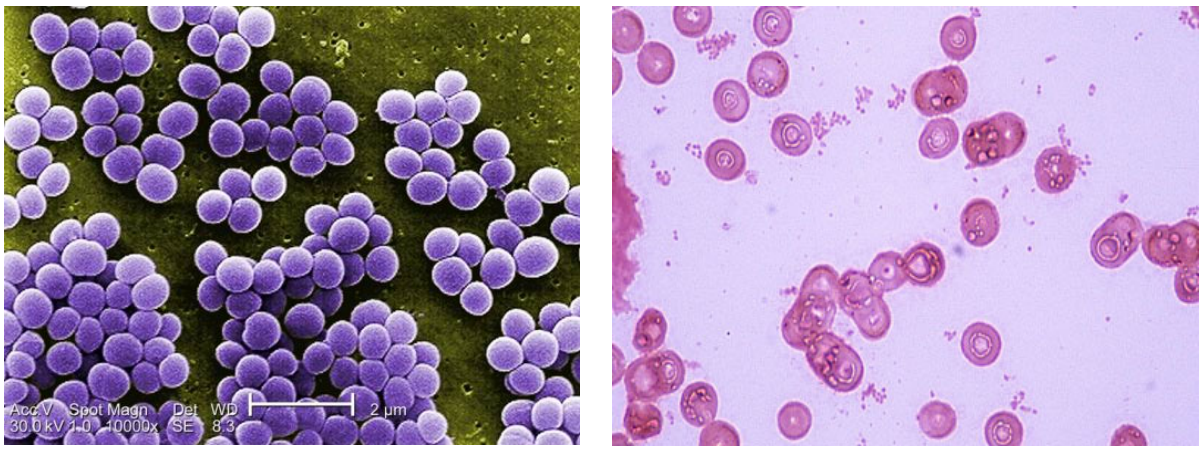


Fig. 4 The wound in the daily sports and fitness

The most common infective bacteria are such gram-positive bacteria as *Staphylococcus aureus* (Fig 5 A), *Streptococcus pneumoniae*, *Streptococcus pyogenes* and such Gram-negative as *Escherichia coli*, *Haemophilus influenzae* (Fig 5 B). In vivo infection by pathogenic microorganisms will cause acute systemic infection, especially for the children, the elderly, immunocompromised or with chronic diseases, and without timely treatment there will be some complications and even sepsis or sepsis.



(A) (B)

Fig. 5 The photograph of *Staphylococcus aureus* and *Haemophilus influenzae*

In this work, we investigated the anti-inflammatory activity of the title compound under the concentration of 20mg/L and 200 mg/L. and the results were summarized in Table 2. From the results, it was found that the title compound shows some anti-inflammatory activity against the tested bacteria and the inhibition is depending on the concentration. The title compound are more active against *S. aureus*, *S. epidermidis*, and *E. coli* under both concentration with the inhibition effect more than 50% under 20 mg/L and the highest inhibition effect of 88.6% under 200 mg/L against *S. epidermidis*. But it is not so active against other three bacteria, *M. luteus*, *K. pneumoniae*, and *A. fumigatus*, with much lower inhibition effects.

Table 2 The anti-inflammatory activity of the title compound

Bacteria	S. aureus	S. epidermidis	M. luteus	E. coli	K. pneumoniae	A. fumigatus
Inhibition effect /% (20mg/L)	56.8	85.1	45.2	77.8	39.2	45.3
Inhibition effect /% (200mg/L)	81.2	88.6	59.3	80.1	29.9	52.5

Experimental

Materials

All chemicals were purchased from Xi'an Chemical Companies. All yields refer to isolated products. The NMR spectrum was recorded on a Bruker Drx-400 spectrometer, operating at 400 MHz for ^{1}H; δ values are reported in ppm and *J* values in hertz, and the mass spectrum were recorded on a Micromass Platform Ⅱ spectrometer, using the direct-inlet system operation with the electron impact (EI) mode at 75 eV.

Synthesis of Cyclohexanone Pentaerythritol Ketal

Cyclohexanone and pentaerythritol were added in a flask with the molar ratio of 2:1, and the toluene was added as the water carrier and the solvent. 5%(wt) solid acid, $NaHSO_4$ was added as catalyst. The mixture was refluxed until no water can be carried out, and the mixture was cooled to room temperature. Then $NaHSO_4$ was filtrated, and the toluene was evaporated out to produce crude product. Colorless crystals of cyclohexanone pentaerythritol ketal were obtained in ethanol by recrystallization with the yield of 75.9%, mp 115.5-116.2°C; ^{1}H-NMR (D_6-DMSO, 400 MHz), δ: 3.62 (4H, s), 1.76 (4H, t, *J* = 7.2 Hz), 1.55 (4H, td, *J* = 7.6, 1.2 Hz), 1.35 (2H, t, *J* = 7.6 Hz); MS (EI) *m/z*: 296 (M^+).

X-ray Data Collection and Structure Refinement

All H atoms were positioned geometrically, with C–H = 0.93-0.98 Å, and refined with a riding model, with *U*iso(H) = 1.2*U*eq(carrier). Data collection: SMART; cell refinement: SAINT; data reduction: SAINT; program (s) used to solve structure: SHELXS97; program (s) used to refine structure: SHELXL97; molecular graphics: Ortep-3 for Windows; software used to prepare material for publication: WinGX.

Thermal Analysis

Thermal analysis was performed on a TGA/SDTA851e Thermal Analyzer, where the heating rate was 10 K min^{-1} in the range of 298-773 K.

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