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Synthesis and structure of 2,4,6-tricyclobutyl-1,3,5-trioxane

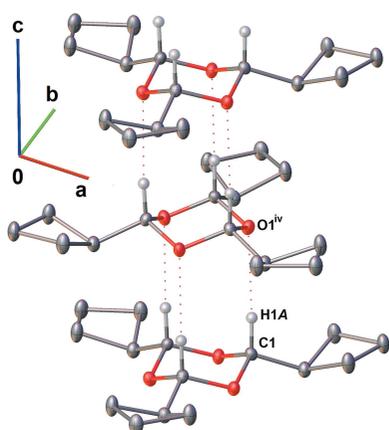
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The synthesis and structure of 2,4,6-tricyclobutyl-1,3,5-trioxane, C₁₅H₂₄O₃ **1**, is described. It was formed in 39% yield during the work-up of the Swern oxidation of cyclobutylmethanol and may serve as a stable precursor of the cyclobutane carbaldehyde. The molecule of **1** occupies a special position (*3,m*) located at the center of its 1,3,5-trioxane ring. The latter is in a chair conformation, with the symmetry-independent O and C atoms deviating by 0.651 (4) Å from the least-squares plane of the other atoms of the trioxane ring. All three cyclobutane substituents, which have a butterfly conformation with an angle between the two planes of 25.7 (3)°, are in the *cis* conformation relative to the 1,3,5-trioxane ring. Intermolecular C—H...O interactions between the 1,3,5-trioxane rings consolidate the crystal structure, forming stacks along the *c*-axis direction. The crystal studied was refined as a racemic twin.

1. Chemical context

Aliphatic aldehydes are well known to form trimers – derivatives of 1,3,5-trioxane. Some of these trimers are commercially-available, stable forms of the corresponding aldehydes, from which monomers can be regenerated by simple heating. Examples are trioxane and paraldehyde. For our research in the area of polymer chemistry, we need regular amounts of cyclobutane carbaldehyde. Besides this, cyclobutane carbaldehyde is a versatile synthetic building block for the incorporation of the cyclobutane ring into organic molecules in medicinal chemistry and drug discovery (Deaton *et al.*, 2008; Inagaki *et al.*, 2011). However, it is known to be unstable and prone to polymerization and decomposition by various routes (Slobodin & Blinova, 1953; Roquette & Walters, 1962; Funke & Cerfontain, 1976). Bearing all that in mind, we assumed that the trimeric form of cyclobutane carbaldehyde should have a long shelf life and might find application as a stable equivalent of cyclobutane carbaldehyde for long-term storage, with the possibility of performing a thermal breakdown back to the monomer once required. In this paper we describe our attempted synthesis of 2,4,6-tricyclobutyl-1,3,5-trioxane, **1**, the trimer of cyclobutane carbaldehyde.

One of the most straightforward routes to cyclobutane carbaldehyde is the oxidation of the commercially available cyclobutylmethanol (Yusubov *et al.*, 2007; Deaton *et al.*, 2008). Further treatment with calcium chloride (Slobodin & Blinova, 1953) should afford the desired trimer. By employing Swern oxidation conditions, we were able to obtain the desired



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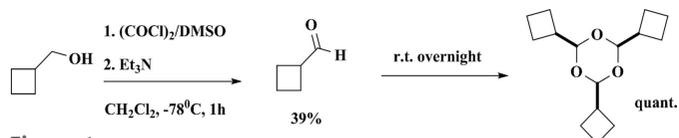
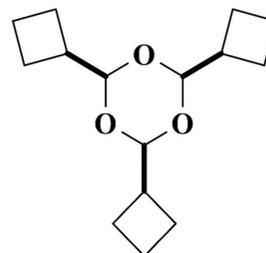


Figure 1
Synthesis of 2,4,6-tricyclobutyl-1,3,5-trioxane, **1**.

aldehyde monomer in 39% yield. (Fig. 1). It was found that freshly distilled cyclobutane carbaldehyde solidifies quickly upon short storage at room temperature, forming a colourless solid material readily soluble in organic solvents, especially non-polar ones. No calcium chloride was required for the trimerization, contrary to what was observed by Slobodin and co-workers. It should be noted that the melting point of our trimer was 391–393 K, close to that reported by Slobodin (391.5–393.5 K) while Funke and co-workers observed the melting to proceed at 397–398 K (Funke & Cerfontain, 1976). Analysis of the synthesized compound by means of ^1H and ^{13}C NMR spectroscopy revealed the presence of unchanged cyclobutane rings along with the absence of the aldehyde group [no downfield signals of the aldehyde proton (*ca* 9–12 ppm) in the ^1H NMR spectrum and no signals of the aldehyde carbon (*ca* 180–220 ppm) in the ^{13}C NMR spectrum]. The most downfield signal in the ^1H NMR spectrum was a doublet at 4.81 ppm and the most downfield signal in the ^{13}C NMR spectrum was observed at 103.3 ppm. The number of signals and their integral intensities (in the ^1H NMR spectrum) demonstrated that, aside from the disappearance of the aldehyde group, no further degradation of the parent molecule had taken place. We made an assumption that the desired trimer had formed. However, dimeric, trimeric, tetrameric and higher cyclic forms or a linear polymer could also form. It should be noticed that the NMR technique cannot distinguish between these forms, since all the integral intensities and coupling constants would be the same, unless a large macrocycle is formed, where conformational effects would make some equivalent signals become non-equivalent. The mass spectrum of **1** solved the question and proved the structure to be trimeric. However, neither NMR nor mass spectrometry can provide information about the assignment of the cyclobutyl groups with respect to the trioxane ring. It is known that paraldehyde – the trimer of acetaldehyde – exists in the form of two structural isomers: the *cis* isomer with all three methyl groups being in equatorial positions with respect to the trioxane ring and the *trans* isomer with one methyl group in an axial position and the two methyl groups in equatorial positions (Carpenter & Brockway, 1936; Kewley, 1970). These structures have the smallest 1,3-diaxial strain and are the only ones observed. In our case, with more bulky cyclobutyl groups, one might expect that only the *cis* isomer would be formed.

The molecular structure of 2,4,6-tricyclobutyl-1,3,5-trioxane, **1**, has been elucidated by X-ray diffraction analysis on single crystals grown from methanol. In summary, 2,4,6-tricyclobutyl-1,3,5-trioxane, **1**, was formed in 39% yield during the work-up of the oxidation reaction of cyclobutylmethanol with DMSO and oxalyl chloride (Swern oxidation). It is a

trimeric form of the cyclobutane carbaldehyde. The aldehyde itself is unstable and quickly polymerizes even at room temperature. The described trimer could probably serve as a stable form of the cyclobutane carbaldehyde. The compound is also of potential interest as a solid fuel.



2. Structural commentary

The molecule of **1** (Fig. 2) occupies a special position (*3.m*) occurring in the center of its 1,3,5-trioxane ring. The latter is in a chair conformation with the symmetry-independent atoms O1 and C1 deviating by 0.651 (4) Å from the least-squares plane of the other ring atoms. All three cyclobutane substituents, which show a butterfly conformation with an angle between the two planes of 25.7 (3)°, are in a *cis* conformation relative to the 1,3,5-trioxane ring.

3. Supramolecular features

Infinite stacks of molecules of **1** along the *c*-axis direction consolidate the crystal structure (Fig. 3) through C1–H1A⋯O1^{iv} interactions between adjacent 1,3,5-trioxane rings (Table 1).

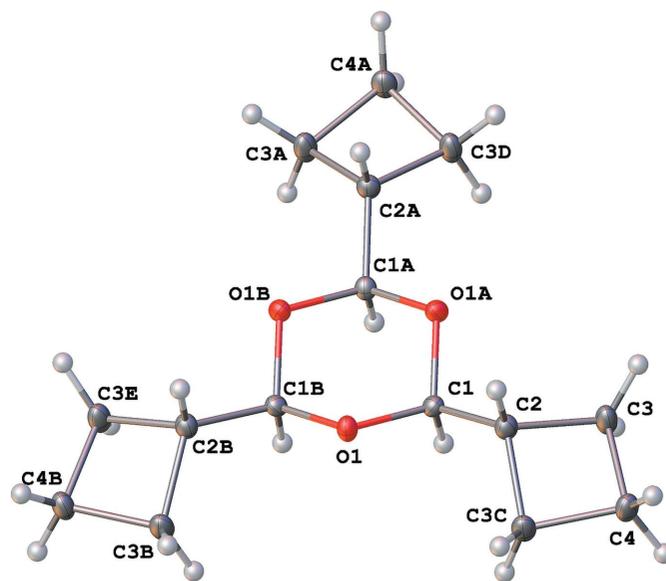


Figure 2
Molecular structure of **1** with displacement ellipsoids drawn at the 50% probability level. Symmetry codes: (A) $y - x, -x, z$; (B) $-y, x - y, z$; (C) y, x, z ; (D) $-y + x, -y, z$; (E) $-x, -x + y, z$.

Table 1
Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$C1-H1A\cdots O1^{iv}$	1.00	2.52	3.514 (3)	177

Symmetry code: (iv) $y, -x + y, z + \frac{1}{2}$.

4. Database survey

The *cis-cis-cis* configuration of the cyclobutane rings observed in **1** seems to be typical for 2,4,6-trisubstituted-1,3,5-trioxanes, as follows from the search for such compounds in the Cambridge Structural Database (CSD, Version 5.40, November 2018 update; Groom *et al.*, 2016). Indeed, only in 2,4,6-tris(trichloromethyl)-1,3,5-trioxane (refcode PRCHLA; Hay & Mackay, 1980) out of the 31 entries found, is one of the three substituents in a *trans* conformation with the other two are in a *cis* conformation. Another compound (MUKCEC; Arias-Ugarte *et al.*, 2015) consists of as a superposition of both *cis-cis-cis* and *trans-cis-cis* conformations as a result of the disorder of one of the substituents. In the latter conformation, the central ring is in a boat conformation as the equatorially oriented cyclobutane rings become axially oriented.

5. Synthesis and crystallization

General experimental remarks

The synthesis of **1** was carried out under a purified argon atmosphere. The ^1H and ^{13}C NMR spectra were recorded on a

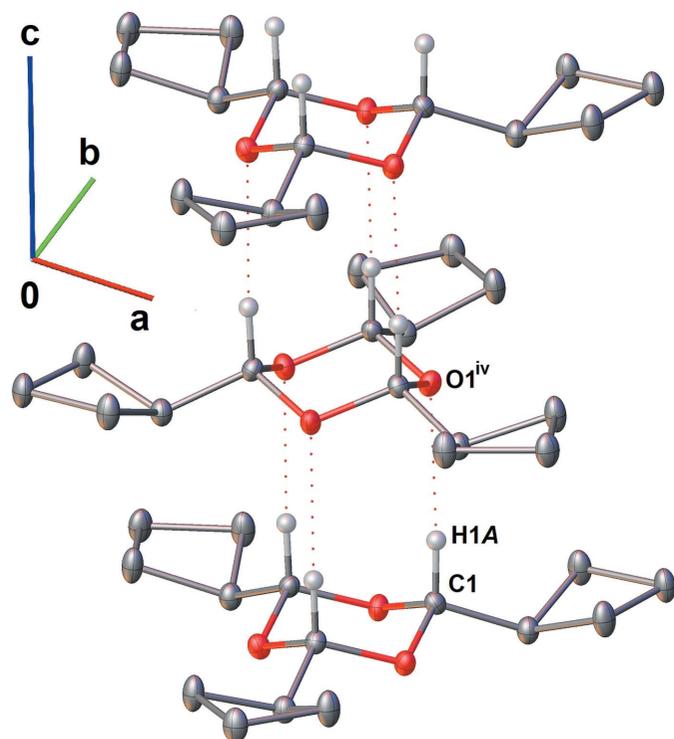


Figure 3
A fragment of the infinite stacks formed by molecules of **1** along the c -axis direction. Hydrogen atoms except those of the 1,3,5-trioxane rings are omitted for clarity. Red dashed lines represent intermolecular $C-H\cdots O$ interactions (Table 1).

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{15}H_{24}O_3$
M_r	252.34
Crystal system, space group	Hexagonal, $P6_3cm$
Temperature (K)	120
a, c (Å)	9.9966 (12), 7.9461 (10)
V (Å ³)	687.68 (19)
Z	2
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.08
Crystal size (mm)	$0.30 \times 0.25 \times 0.20$
Data collection	
Diffractometer	Bruker APEXII DUO CCD area detector
Absorption correction	Multi-scan (SADABS; Bruker, 2008)
T_{min}, T_{max}	0.701, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	7859, 671, 645
R_{int}	0.026
$(\sin \theta/\lambda)_{max}$ (Å ⁻¹)	0.681
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.041, 0.108, 1.03
No. of reflections	671
No. of parameters	35
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}, \Delta\rho_{min}$ (e Å ⁻³)	0.36, -0.22
Absolute structure	Refined as an inversion twin

Computer programs: APEX2 and SAINT (Bruker, 2008), SHELXT (Sheldrick, 2015a) and SHELXL2014/6 (Sheldrick, 2015b).

Varian MercuryPlus 300 (300 MHz) spectrometer using $CDCl_3$ as solvent. Dichloromethane, triethylamine and DMSO were distilled over calcium hydride. Methanol was distilled over magnesium turnings. Oxalyl chloride was distilled over phosphorus pentoxide. Cyclobutylmethanol is commercially available and was used without further purification.

Synthesis of compound **1**

To a stirred solution of oxalyl chloride (13.5 g, 0.11 mol) in 110 ml of dry dichloromethane was added dropwise at 195 K the solution of dry dimethylsulfoxide (16.5 g, 0.21 mol) in 30 ml of dry dichloromethane followed by the solution of cyclobutylmethanol (8.1 g, 0.09 mol) in 110 ml of dry dichloromethane. The reaction mixture was stirred at 195 K for 1 h and then neat triethylamine (48.2 g, 0.47 mol) was added. The cooling bath was removed and when the reaction mixture had returned to room temperature, 100 ml of water was added and the reaction mixture was further stirred for 10 min. The flask content was then transferred to a separatory funnel, the bottom organic phase was collected and the aqueous phase was extracted with dichloromethane (2×100 ml). The combined organic phase was washed with 10% HCl (3×100 ml), water (2×100 ml), dried with anhydrous magnesium sulfate, filtered and the solvent was removed on the rotary evaporator. The residue was distilled under atmospheric pressure and the fraction boiling in the range 399–393 K was collected. The yield was 3.09 g (39%) and the product solidified after standing at room temperature overnight, quantitatively forming compound **1**. ^1H NMR (300 MHz, $CDCl_3$): δ

1.65–2.16 (6H, *m*), 2.55 (1H, *dt*, $J = 15.7; 7.7$ Hz), 4.81 (1H, *d*, $J = 5.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 18.5; 22.4; 38.1; 103.3. Mass spectrum m/z : 252 ($[M^+]$), 169, 85, 67.

Colourless crystals of **1** suitable for X-ray analysis were obtained by dissolving the crude solid material (0.05 g) in 5 ml of warm methanol and keeping the resulting solution in a vial tightly stoppered with a plug of cotton wool for two days at room temperature.

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. The hydrogen atoms were positioned geometrically ($\text{C}-\text{H} = 1.00$ and 0.99 Å for CH and CH_2 groups, respectively) and refined using a riding model with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$. The crystal studied was refined as a racemic twin with a BASF of 0.146.

Acknowledgements

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Synthesis and structure of 2,4,6-tricyclobutyl-1,3,5-trioxane

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Computing details

Data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT* (Bruker, 2008); program(s) used to solve structure: *SHELXT* (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2014/6* (Sheldrick, 2015b); molecular graphics: *SHELXL2014/6* (Sheldrick, 2015b); software used to prepare material for publication: *SHELXL2014/6* (Sheldrick, 2015b).

2,4,6-Tricyclobutyl-1,3,5-trioxane

Crystal data

$C_{15}H_{24}O_3$

$M_r = 252.34$

Hexagonal, $P6_3cm$

$a = 9.9966$ (12) Å

$c = 7.9461$ (10) Å

$V = 687.68$ (19) Å³

$Z = 2$

$F(000) = 276$

$D_x = 1.219$ Mg m⁻³

Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å

Cell parameters from 7859 reflections

$\theta = 3\text{--}30^\circ$

$\mu = 0.08$ mm⁻¹

$T = 120$ K

Prism, colorless

$0.30 \times 0.25 \times 0.20$ mm

Data collection

Bruker APEXII DUO CCD area detector
diffractometer

phi and ω scans

Absorption correction: multi-scan
(*SADABS*; Bruker, 2008)

$T_{\min} = 0.701$, $T_{\max} = 0.746$

7859 measured reflections

671 independent reflections

645 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.026$

$\theta_{\max} = 29.0^\circ$, $\theta_{\min} = 2.4^\circ$

$h = -13 \rightarrow 13$

$k = -13 \rightarrow 13$

$l = -10 \rightarrow 10$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.041$

$wR(F^2) = 0.108$

$S = 1.03$

671 reflections

35 parameters

1 restraint

Hydrogen site location: inferred from
neighbouring sites

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0819P)^2 + 0.1148P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} < 0.001$

$\Delta\rho_{\max} = 0.36$ e Å⁻³

$\Delta\rho_{\min} = -0.22$ e Å⁻³

Absolute structure: Refined as an inversion twin

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.0000	0.13467 (13)	0.4774 (2)	0.0133 (4)
C1	0.13482 (17)	0.13482 (17)	0.5351 (3)	0.0120 (5)
H1A	0.1384	0.1384	0.6609	0.014*
C2	0.2745 (2)	0.2745 (2)	0.4645 (3)	0.0149 (4)
H2A	0.2716	0.2716	0.3387	0.018*
C3	0.43522 (17)	0.31060 (18)	0.5281 (3)	0.0198 (4)
H3A	0.4938	0.2852	0.4462	0.024*
H3B	0.4334	0.2667	0.6403	0.024*
C4	0.4839 (2)	0.4839 (2)	0.5319 (4)	0.0192 (5)
H4A	0.5420	0.5420	0.4310	0.023*
H4B	0.5377	0.5377	0.6365	0.023*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0101 (7)	0.0122 (6)	0.0170 (7)	0.0050 (3)	0.000	0.0017 (5)
C1	0.0113 (7)	0.0113 (7)	0.0135 (9)	0.0057 (6)	-0.0016 (7)	-0.0016 (7)
C2	0.0123 (7)	0.0123 (7)	0.0193 (8)	0.0056 (7)	0.0002 (7)	0.0002 (7)
C3	0.0118 (6)	0.0142 (7)	0.0339 (8)	0.0068 (6)	-0.0022 (7)	-0.0008 (8)
C4	0.0124 (7)	0.0124 (7)	0.0304 (9)	0.0044 (7)	-0.0014 (10)	-0.0014 (10)

Geometric parameters (\AA , $^\circ$)

O1—C1	1.4229 (13)	C2—H2A	1.0000
O1—C1 ⁱ	1.4230 (13)	C3—C4	1.548 (2)
C1—O1 ⁱⁱ	1.4229 (13)	C3—H3A	0.9900
C1—C2	1.505 (3)	C3—H3B	0.9900
C1—H1A	1.0000	C4—C3 ⁱⁱⁱ	1.548 (2)
C2—C3	1.545 (2)	C4—H4A	0.9900
C2—C3 ⁱⁱⁱ	1.545 (2)	C4—H4B	0.9900
C1—O1—C1 ⁱ	110.23 (18)	C2—C3—C4	88.62 (11)
O1 ⁱⁱ —C1—O1	110.03 (17)	C2—C3—H3A	113.9
O1 ⁱⁱ —C1—C2	108.66 (11)	C4—C3—H3A	113.9
O1—C1—C2	108.66 (11)	C2—C3—H3B	113.9
O1 ⁱⁱ —C1—H1A	109.8	C4—C3—H3B	113.9
O1—C1—H1A	109.8	H3A—C3—H3B	111.1
C2—C1—H1A	109.8	C3—C4—C3 ⁱⁱⁱ	88.39 (15)
C1—C2—C3	117.97 (13)	C3—C4—H4A	113.9

C1—C2—C3 ⁱⁱⁱ	117.97 (13)	C3 ⁱⁱⁱ —C4—H4A	113.9
C3—C2—C3 ⁱⁱⁱ	88.59 (16)	C3—C4—H4B	113.9
C1—C2—H2A	110.2	C3 ⁱⁱⁱ —C4—H4B	113.9
C3—C2—H2A	110.2	H4A—C4—H4B	111.1
C3 ⁱⁱⁱ —C2—H2A	110.2		
C1 ⁱ —O1—C1—O1 ⁱⁱ	58.4 (3)	O1—C1—C2—C3 ⁱⁱⁱ	67.9 (2)
C1 ⁱ —O1—C1—C2	177.20 (10)	C1—C2—C3—C4	-139.29 (18)
O1 ⁱⁱ —C1—C2—C3	-67.9 (2)	C3 ⁱⁱⁱ —C2—C3—C4	-18.09 (19)
O1—C1—C2—C3	172.39 (15)	C2—C3—C4—C3 ⁱⁱⁱ	18.05 (19)
O1 ⁱⁱ —C1—C2—C3 ⁱⁱⁱ	-172.39 (15)		

Symmetry codes: (i) $-y, x-y, z$; (ii) $-x+y, -x, z$; (iii) y, x, z .

Hydrogen-bond geometry (Å, °)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
C1—H1A \cdots O1 ^{iv}	1.00	2.52	3.514 (3)	177

Symmetry code: (iv) $y, -x+y, z+1/2$.