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Unique trifurcated hydrogen bonding in a pseudopolymorph of tricyclohexane triperoxide (TCTP) and its thermal studies

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ABSTRACT

Tricyclohexane triperoxide (TCTP) was synthesized as a main by-product of tetraoxane synthesis and was characterized by spectroscopic techniques viz. ^{1}H NMR, ^{13}C NMR, FT-IR and Raman. The single crystal X-ray structure revealed the inclusion of solvent in 1:1 stoichiometric ratio involving a unique trifurcated C(sp^3)–H···O hydrogen bonding imparting remarkable symmetry to the molecule. The thermal stability of single crystal was determined by TG-DTA and DSC.

Cyclic peroxides are of interest because of their many potential applications. Their derivatives have been studied as radical initiators,[1] cetane number improvers,[2] improvised explosives[3] and antimalarials.[4] They are also interesting from the conformational point of view since their large rings can be stabilized in different conformations.[5] As a part of continuing research work in our laboratory on design, synthesis and characterization of new drug molecules[6] and X-ray crystal studies[7] of small organic molecules, we are extending our work to the design and synthesis of new cyclic peroxides to evaluate their antimalarial activity against drug resistant forms of malaria such as *Plasmodium falciparum* and also crystallizing them to study their crystal structure.

A naturally occurring sesquiterpene endoperoxide artemisinin has established the cyclic peroxides as potential antimalarial agents.[8] An exhaustive literature survey led us to speculate that by incorporating nitrogen[9] within the cyclohexyl ring, we could generate a new series of cyclic peroxides with improved antimalarial activity. We initially started with 4-piperidone monohydrate hydrochloride, which was alkylated with methyl bromoacetate in the presence of K_2CO_3 mixed in 1:2:2 ratios in acetone. The reaction mixture was refluxed for 15 h to yield methyl 2-(4-oxopiperidin-1-yl)acetate **1**. We followed previously reported procedures[2,10] with slight modifications[11] to synthesize piperidine-1,2,4,5-tetraoxane **3** for the first time. The progress of the reaction was monitored by ^{13}C NMR. The crude obtained after conventional work-up with $CHCl_3$ was a pale yellow viscous oil which solidified into an off white solid within two days. The solid was removed by simple filtration from the remaining yellow syrup and characterized by spectroscopic techniques viz. ^{1}H NMR, ^{13}C NMR, FT-IR and Raman (see Supplementary data). However, spectroscopic studies revealed the formation of a peroxide trimer, tricyclohexane triperoxide (TCTP) **4**, which is a main by-product of tetraoxane synthesis.[12] Raman spectrum recorded for TCTP (Fig. 1) shows

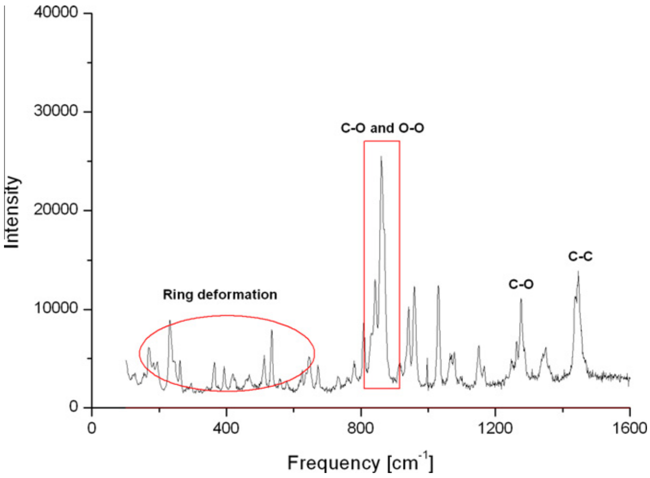

Figure 1. Raman spectrum of TCTP (200–600 cm^{-1}).

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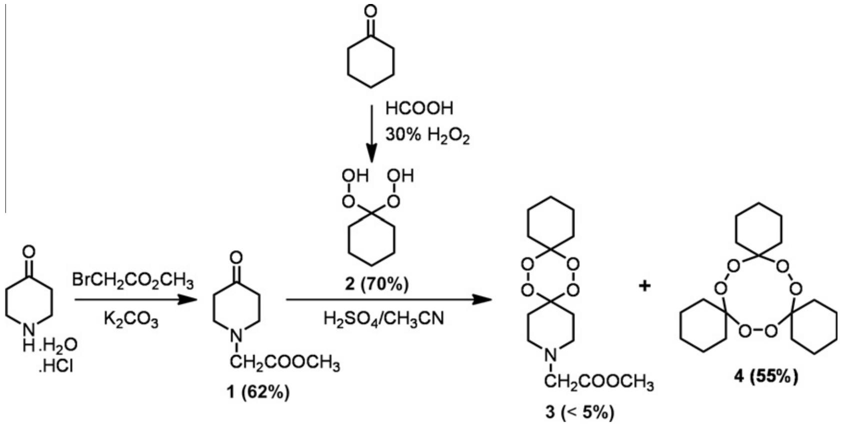

Scheme 1. Attempted tetraoxane synthesis.

peaks in the range of 800–1000 cm^{-1} corresponding to the combination of O–O and C–O stretching modes of hexaoxonane ring. Peaks at 1446 cm^{-1} and between 1200–1300 cm^{-1} can be attributed to C–C stretching mode and peroxide ring C–O stretching, respectively, which are well in agreement with the theoretically calculated spectrum reported by Oxley et al.[13] A schematic diagram depicting the above observation is shown in Scheme 1.[14]

Several attempts in our laboratory to isolate compound **3** in workable amounts from the reaction mixture were unsuccessful. Meanwhile, motivated by rich polymorphism shown by triacetone triperoxide (TATP), we started investigating the crystal structure of **4**. Herein, we report several interesting observations made from the crystal structure analysis of TCTP single crystal grown in chloroform.

For the present study X-ray quality single crystals were grown in a thin tube of 5 mm diameter by the slow evaporation solution growth technique at room temperature. X-ray structure revealed solvated chloroform in 1:1 stoichiometric ratio in the crystal lattice of TCTP resulting in a pseudopolymorph of TCTP, which is the first example of solvated TCTP (sTCTP).[15] The sTCTP crystallized in a trigonal cell and R3c space group with the following lattice parameter: $a = 14.3252(3)$ Å, $b = 14.3252(3)$ Å, $c = 18.4732(5)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 120°$, $V = 3283.02(13)$ Å^3 and $\rho = 1.4015$ gcm^{-3}. Comparison of geometrical parameters between TCTP and sTCTP[5b] (Table 1) showed no significant difference, which is consistent with the earlier reported observations.[5a,15]

Six different polymorphic crystals of TATP were reported by Reany et al.[5a] and TCTP is also known to possess two separable conformers at room temperature,[5b] however without any solvent inclusion in any of the polymorphs. Thus, sTCTP is the only known example of a solvated cyclic triperoxide.[15]

Crystal packing suggests a dominant role of C–H···O interactions in determining molecular conformation and stability of solvated crystal as there were no other intermolecular contacts in the crystal lattice of sTCTP, although C–H group of C(sp^3)–H is a reluctant hydrogen bond donor. However, three chlorine atoms activate 'C–H' of $CHCl_3$ for hydrogen bonding.[16] A rare trifurcated hydrogen bond[17] C(sp^3)–H···O ($d_{H-O} = 2.661$ Å) was observed between the hydrogen atom (H19) of chloroform and three oxygen atoms (O2, O4 and O6) of the nine-membered hexaoxonane ring contributing to the symmetry of the complex, imparting C_3-symmetry. The oxygen atoms in hexaoxonane ring are arranged in two parallel planes separated by a distance of 1.076 Å (Fig. 2a). As a consequence of hydrogen bonding the three oxygen atoms (O2, O4 and O6) converge[18] towards H19. The packing diagram shows an intricately stacked picturesque floral pattern along the crystallographic C-axis and molecules appeared to be arranged in parallel layers along the B-axis (Fig. 2).

The thermal stability[19] of single crystal was determined by TG-DTA and DSC (Fig. 3). TG-DTA measurements were performed in an open ceramic pan in flowing nitrogen on 4.79 mg of sample and DSC was done in a sealed aluminium pan. DTA and DSC measurements gave consistent results. An endothermic peak occured at 92.24 °C corresponding to the melting point[5b] of sTCTP and the exothermic peak at 193.27 °C corresponding to sharp weight loss in the DTA curve that can be attributed to the decomposition process. However, we could not ascertain the thermolysis products in DTA curve and another endothermic peak at 378.81 °C. Nevertheless, thermal studies clearly indicate the stability of the compound till its meting point at 92.24 °C after which it decomposes above 120 °C.

Following these observations, sTCTP can be tried for peroxide based explosives[20] or as a propellant.[21] Crystallization of new polymorphs or pseudopolymorphs of TCTP and analogues (TATP) may be attempted in future using different solvents and mixture of solvents, which will enable us to evaluate the inclusion property of the crystal lattice of TCTP for discriminative selectivity[22] towards the solvent ($CHCl_3$) inclusion which till date is shown only by cyclodextrin and large ring (30-membered) hexalactam hosts.[23]

In conclusion, the reaction procedure needs further optimization to synthesize compound **3** in good yield which was formed in traces. Compound **3** can be a precursor for the synthesis of diversified tetraoxane libraries, which can be screened for antimalarial and anticancer activities. Nevertheless, the synthesis of compound **1** offers a convenient synthetic entry to a variety of intermediates used in the synthetic medicinal chemistry. TCTP, a main by-product of tetraoxane synthesis was synthesized and its crystals were grown in chloroform resulting in inclusion of chloroform in a pseudopolymorph (sTCTP). H-atom of $CHCl_3$ projects into the centre of the molecular cavity formed by hexaoxonane ring and resulted in a rare trifurcated hydrogen bond imparting C_3 symmetry to the molecule and stabilizing the resultant sTCTP.

Table 1
Comparison of geometric parameters between TCTP and sTCTP

Geometric parameter	sTCTP [°/Å]	TCTP[a] [°/Å]
C–O	1.417 (2)	1.4176 (18), 1.418 (2), 1.4271 (19)
O–C	1.419 (2)	1.4284 (18), 1.431 (2), 1.4187 (18)
O–O	1.473 (2)	1.4747 (14), 1.475 (2), 1.4678 (15)
O–C–O	111.96 (1)	112.76 (12), 112.76 (12), 112.05 (11)
C–O–O–C	135.75	135.0, 136.2, 134.2

[a] As reported by Denekamp et al. Org. Lett. 2005.