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Isolation of the saddle and crown conformers of cyclotriveratrylene (CTV) oxime

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Abstract—The oxime of cyclotriveratrylene (CTV) has been prepared and the individual crown and saddle conformers were isolated and characterized. The equilibrium constant was measured in $CDCl_3$ and in DMSO-d_6 and was shown to favor the crown conformer by an order of magnitude in DMSO-d_6, relative to an approximately equal mixture at equilibrium in $CDCl_3$. The time course for interconversion of the saddle to the crown was measured by ^{1}H NMR and the $t_{1/2}$ of the saddle was determined to be 2.45 h in $CDCl_3$ at 25 °C, and 3.71 h in DMSO-d_6.

Supramolecular chemistry involves the formation of complex molecular entities that have the capacity to participate in specific molecular recognition of guest molecules.[1] Cyclophanes are supramolecular structures comprised of aromatic units with bridging chains forming cage-like structures[2] and have found applications in molecular recognition as synthetic receptors, as models for intercalation, as building blocks for organic catalysts, and in the preparation of crown ethers and cryptands.[3] Cyclophanes have been utilized as molecular scaffolds in the design of new pharmaceuticals[4–7] including use as cholesterol shuttles to modulate cholesterol metabolism[8] as potent human choline kinase (ChoK) inhibitors,[9] and as inhibitors of HIV protease.[10]

An archetypal cyclophane scaffold commonly employed in supramolecular chemistry is the trimeric crown-shaped molecule cyclotriveratrylene (CTV, **1,** hexamethoxy tribenzocyclononatriene,),[11] a [1.1.1]orthocyclophane that is readily prepared from the trimerization of veratryl alcohol in acid. CTV has been extensively studied for its capability to bind a variety of small organic and organometallic guests within its bowl-shaped cleft.[12–14] Many clathrates of CTV have been structurally characterized, including DMSO and ethanol,[15] chlorinated organics,[16] xenon,[17] lanthanides[18] organometallic complexes,[19] C60,[20] and anionic C70 dimers.[21] CTV has also been used for selective anion sensing,[22] and thioether derivatives of CTV have recently been employed as hosts to immobilize C60 onto gold surfaces.[23,24] CTV has been employed as a supramolecular building block to construct more complex cage-like cryptophanes,[25] and as a crystal engineering tecton giving network structures of unusual topology.[26]

CTV derivatives have also been studied for their mesomorphic properties[27] and are capable of forming liquid crystals by themselves[28] and as complexes with C60.[28]

We are interested in the preparation of novel apex-functionalized derivatives of CTV. Toward this end we synthesized the oxime derivative of CTV via the CTV ketone **2** (Scheme 1). Ketone **2** was prepared utilizing a modification of Steven's method[29] for oxidation of CTV with sodium dichromate in acetic acid under reflux. The conversion of **2** to the corresponding oxime was quite sluggish, presumably due to the aryl hydrogens ortho to the ketone hindering the approach of the nucleophilic hydroxylamine. The ortho hydrogen atoms are almost at contact distance, with 2.5 Å between their centers.[11] Complete conversion to the oxime required overnight heating under reflux in neat pyridine, which afforded two major products by thin-layer chromatography. Chromatographic separation yielded the desired oxime as two distinct conformers, which we have characterized. Indeed, the first clue to the conformational relationship was the fact that the individual components equilibrated back to a mixture of the two conformers upon standing in solution at room temperature over a

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Keywords: Cyclotriveratrylene (CTV); Tribenzocyclononatriene; Oxime; Conformers.

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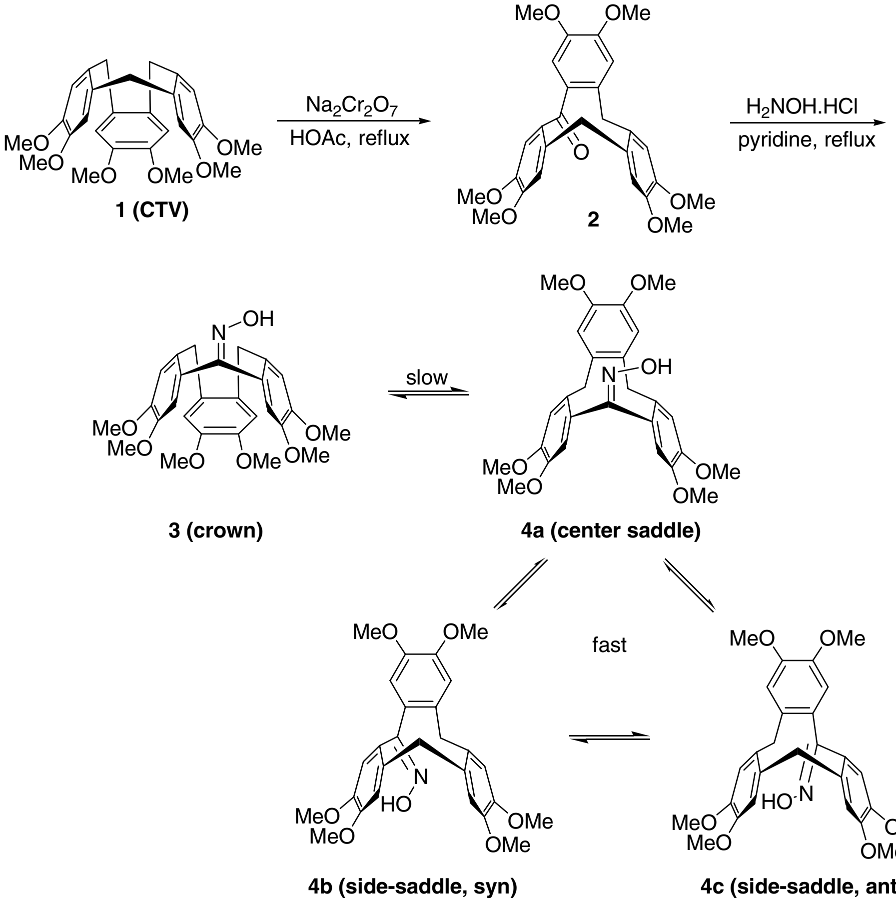

Scheme 1.

period of 1–2 days. The first-eluting crown conformer **3** was obtained in 70% yield, followed by 27% of the slower-eluting saddle conformation **4**. This isolated ratio reflects some interconversion during workup and chromatography at room temperature from an initial saddle to a crown ratio of 56:44 based on a proton NMR spectrum of the crude reaction mixture after 16 h in pyridine under reflux (115 °C). The methylene protons of crown oxime **3** are two separate AX quartets due to the asymmetry of the oxime [δ 4.77 (1H, d, $J = 13.8$ Hz), 4.38 (1H, d, $J = 13.5$ Hz), 3.58 (1H, d, $J = 13.8$ Hz), and 3.50 (1H, d, $J = 13.5$ Hz)], with the axial (internal) protons resonating at 1.2 ppm and 0.8 ppm downfield, respectively. For the saddle conformation, the two methylenes are either *syn* or *anti* to the oxime hydroxyl and are thus at two separate chemical shifts, [δ 4.02 (2H, s), 3.54 (2H, s)], and there is no geminal coupling due to equivalence resulting from rapid interconversion of conformers, as illustrated by the equilibrium between **4a**, **4b**, and **4c**, bearing in mind that each saddle conformer shown may exist as two twist conformers as for the parent CTV saddle.[30] Curiously, the *syn* and *anti* oxime saddle isomers **4b** and **4c** are interconverted through bond rotations. The CTV ketone is known to exist exclusively as the flexible saddle conformation, due to greater conjugation of the carbonyl with the phenyl rings, as evidenced by the equivalence of its four methylene protons [δ 3.77 (4H, br s)] due to pseudorotation that is rapid on the NMR time scale. Similar to the oxime, CTV 5-methylene and 5-isopropylidene derivatives are also equilibrium mixtures of saddle and crown conformations.[29] The absorbances for the C=N stretches of the crown and saddle oximes are essentially identical at 1606 and 1607 cm^{-1}, respectively, although we expected to see some difference due to greater conjugation in the saddle. The symmetry successively decreases from CTV, which has C_{3v} symmetry, to ketone **2**, which has C_s symmetry, to oxime **4**, which lacks symmetry elements except for identity. The oxime is a structurally chiral molecule, although lacking chiral tetrahedral carbon atoms.

Despite the fact that CTV and its derivatives have been studied for decades, the saddle conformation of the parent CTV was only recently isolated and characterized after preparation by high temperature melt and quench by Zimmerman, who also studied the thermodynamic and kinetic interconversion of the crown and saddle conformers.[30] The intermediacy of the more flexible saddle conformation in CTV crown-umbrella inversion was proposed by Collet,[31] who demonstrated that the barrier to crown-to-crown inversion via racemization of chiral CTV-d_9 is 26.5 kcal/mol, the process most likely proceeding via the saddle conformation.[11] Zimmerman also studied the mesomorphic properties of nonasubstituted tribenzocyclononatriene derivatives,[27] wherein the

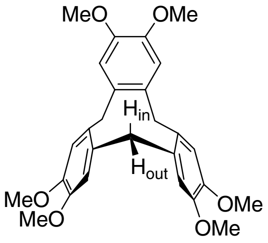

Figure 1.

crown conformation is destabilized relative to the saddle form due to nonbonding interactions of the substituents with neighboring aryl rings.[11] For the parent CTV, the saddle conformation is thermodynamically disfavored due to the negative steric crowding of proton H$_{in}$ (Fig. 1) with the face of the central aromatic ring at the back of the saddle.[30] This destabilizing steric interaction is absent in oxime conformation **4a**, and although there may be a stabilizing π–π interaction between the central aromatic ring and the oxime in **4a**, the side-saddle conformations may enjoy some stabilization due to greater conjugation.

We observed that the rigid oxime crown conformer **3** and the more flexible saddle conformers **4** slowly interconvert at room temperature over 1–2 days to a mixture of conformers. The equilibrium ratio of conformers is highly solvent-dependent, with the crown conformer favored in DMSO-d_6 with an equilibrium constant at 25 °C K_{eq} = [saddle]/[crown] = 0.087 for the 8:92 ratio of saddle to crown at equilibrium. A nearly equal molar ratio is obtained in $CDCl_3$ at 25 °C, with a 48:52 ratio obtained at equilibrium (K_{eq} = saddle]/[crown] = 0.92). The ratio of crown conformer is an order of magnitude higher in the more polar solvent DMSO-d_6 than in $CDCl_3$ as was the case with CTV; Zimmerman showed that for CTV, the crown conformation is favored by an order of magnitude in the more polar solvent dimethylformamide (DMF) versus chloroform [K (300 K) = [saddle]/[crown] = 0.1 in chloroform, K (300 K) = 0.008 in DMF],[30] although the percentage of saddle was an order of magnitude less for CTV than for the oxime in both solvents, respectively. Differences in solvation and particularly H-bonding between the oxime functionality in the two conformers and the DMSO solvent may play a role in the equilibrium, and possibly a favorable host–guest interaction between crown host and solvent guest. For CTV the preference for crown in DMSO-d_6 was attributed to the higher dipole moment of crown versus saddle, as the saddle lacks a net dipole moment due to pseudorotaton. For CTV the saddle is the faster running conformer, but the elution order for the oxime is reversed, with the crown as the faster-running conformer. We expected a greater preference for oxime saddle relative to CTV based on the steric arguments provided above, and the fact that the ketone exists exclusively in the saddle conformation. The fact that the oxime prefers the crown conformation impacts the potential host–guest chemistry of the oxime, since the CTV nucleus can interact with guests within the bowl-shaped crown structure.

We monitored the interconversion kinetics by ^{1}H NMR. Freshly prepared samples of the saddle conformer were dissolved in $CDCl_3$ and in DMSO-d_6 and were maintained at 25 °C in the NMR for 18 h and 20 h, respectively. The decrease in the ^{1}H NMR saddle peak intensities in the aromatic region was recorded as a function of time. Non-linear curve fitting of the exponential decrease of the saddle peak intensity furnished the time constant $\tau = 1.275\text{e}+04$ s ($t_{1/2} = 2.45$ h; $k = 7.84 \times 10^{-5}\ \text{s}^{-1}$) for the conversion of saddle to crown dissolved in $CDCl_3$ at 25 °C, and $\tau = 1.926\text{e}+04$ s ($t_{1/2} = 3.71$ h; $k = 5.19 \times 10^{-5}\ \text{s}^{-1}$) for the conversion of saddle to crown dissolved in DMSO-d_6 at 25 °C. Thus, the interconversion of oxime conformers is significantly faster than the parent CTV ($t_{1/2}$ = 1 day[30]), and is faster in $CDCl_3$ than in DMSO-d_6, which may be due to the greater microviscosity of dimethylsulfoxide relative to chloroform.

Utilization of the CTV oxime in the preparation of novel apex-modified CTV derivatives is underway and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.004.

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