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David C. French
Loyola University Chicago

Marlon R. Lutz Jr.
Regis Technology

Chichi Lu

Matthias Zeller

Daniel Becker
Loyola University Chicago, dbecke3@luc.edu

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A Thermodynamic and Kinetic Characterization of the Solvent Dependence of the Saddle-Crown Equilibrium of Cyclotriveratrylene (CTV) Oxime

David C. French[a,*], Marlon R. Lutz Jr., [a] Chichi Lu, [a] Matthias Zeller,[b] and Daniel P. Becker [a,*]

[a]Loyola University Chicago, Department of Chemistry, 6525 North Sheridan Road, Chicago, IL 60626; [b]Youngstown State University, Department of Chemistry, 1 University Plaza, Youngstown OH 44555

Abstract

The equilibration of the saddle conformer of CTV oxime to the corresponding crown conformer was followed by ^{1}H NMR in five separate solvents, and kinetic and thermodynamic parameters were determined from the NMR data. The oxime saddle conformers of **3** are favored in $CDCl_3$ (K_{eq} = [saddle]/[crown] = 1.4), whereas the CTV oxime crown conformer **3a** is favored in three more polar solvents studied (DMSO-d_6, acetonitrile-d_3, acetone-d_6). Surprisingly, the CTV oxime crown conformer is also slightly favored in the non-polar solvent 1,4-dioxane-d_8. These behaviors are discussed in terms of hydrogen bonding, entropy, and possible host–guest considerations. An X-ray crystal structure was obtained for CTV monoketone, and structures of the different conformers of CTV, CTV ketone, and CTV oxime were calculated with semi-empirical AM1 methods for direct comparison of their ground-state energies.

Introduction

Within the realm of nanotechnology, the area of supramolecular chemistry includes the formation of molecular scaffolds that have the capacity to participate in specific intermolecular recognition of guest molecules,[1, 2] a phenomenon that has gained widespread attention since Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen were jointly awarded the Nobel Prize for Chemistry in 1987 in recognition of their work on host-guest assemblies. Host-guest chemistry emulates receptor-ligand interactions in living systems and strives for exquisite selectivity with applications in analytical detection, communication, and signaling. Cyclophanes are supramolecular structures comprised of aromatic units with bridging chains forming cage-like structures[3] and have found applications in molecular recognition and synthetic receptors, as building blocks for organic catalysts, in the preparation of crown ethers and cryptands[4] and as specific host molecules in the design of new pharmaceuticals.[5-8]

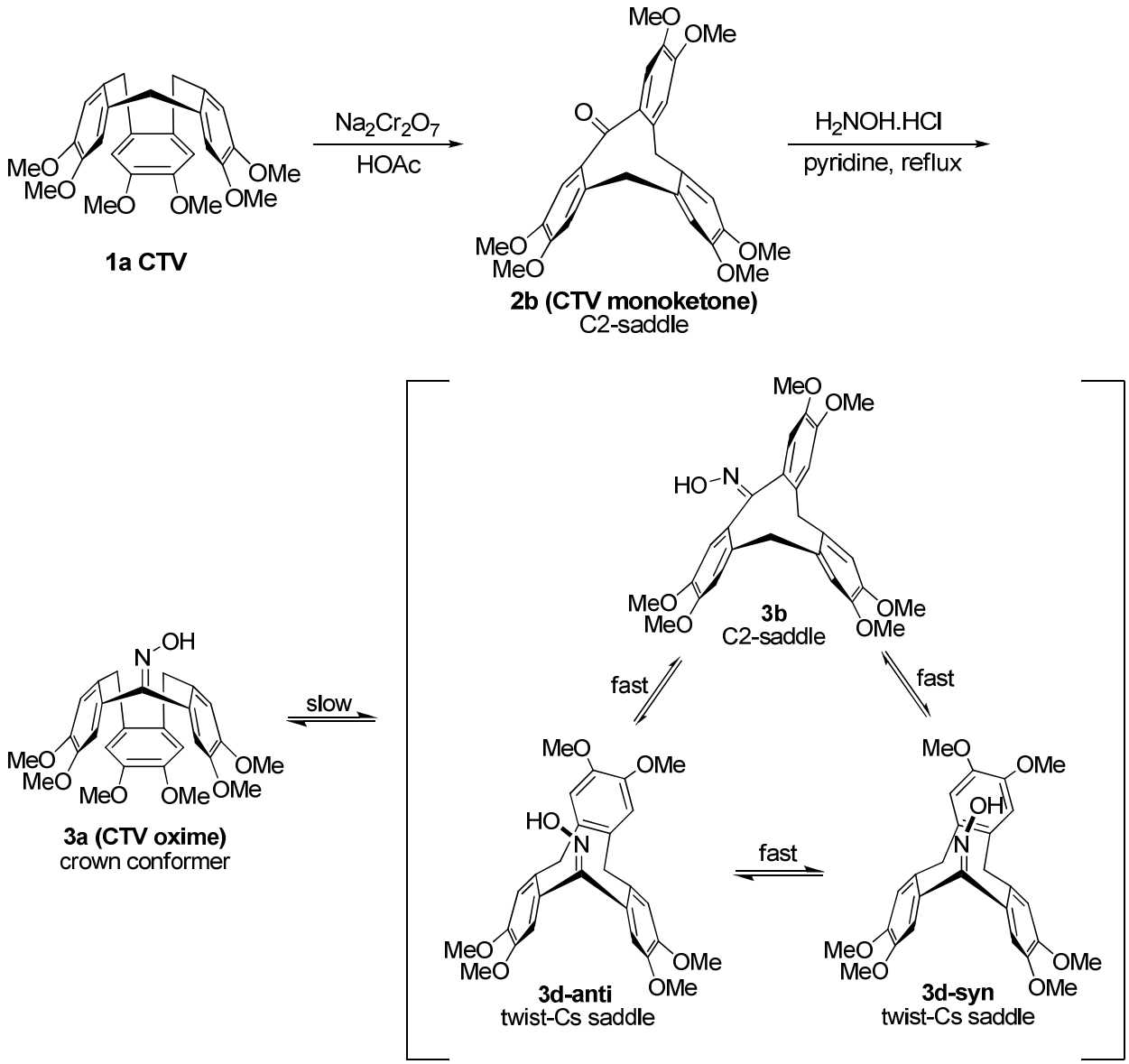
The often-cited trimeric crown-shaped cyclophane cyclotriveratrylene (CTV, **1**, hexamethoxy tribenzocyclononene,),[9] is a [1.1.1]orthocyclophane that is readily prepared via the trimerization of veratryl alcohol in acidic solution. CTV has been widely studied for its capability to act as a host for a variety of small organic and organometallic guests within its bowl-shaped cleft.[10-12] Many clathrates of CTV have been structurally characterized, including DMSO and ethanol[13], chlorinated organics[14], xenon[15], lanthanides[16] organometallic complexes,[17] C60,[18] and anionic C70 dimers.[19] Furthermore, CTV has also been used for

selective anion sensing.[20] Suitably substituted derivatives exhibit mesomorphic properties.[21] Elegant cryptophanes have been contructed by tethering CTV moieties in a face-to-face fashion employing linker chains attached to the peripheral phenolic oxygens.[9,22,23]

CTV exists almost exclusively in its crown conformation (**1a**), and the saddle conformer of CTV was only recently isolated and characterized after preparation through high temperature melt and quench techniques by Zimmermann who also studied the thermodynamic and kinetic properties of the interconversion of the crown and saddle CTV conformers.[24] The intermediacy of the more flexible saddle conformation had been previously proposed in the umbrella-like inversion and racemization of an enantiopure d_9-CTV by Collet who followed the racemization to measure the barrier of interconversion to be 26.5 kcal/mol (111 kJ/mol)[9, 25] In contrast to CTV itself, CTV monoketone **2** has been reported to exist only in the saddle conformer based on equivalence of the methylene protons in proton NMR.[9, 26] The same is true for exocyclic methylenated derivatives of CTV.[26] Holman[22] as well as Huber[23] have identified topoisomeric cryptophanes containing blended crown and saddle CTV moieties; Holman's cryptophane undergoes a conformational crown to saddle "implosion" upon thermal liberation of its guest.

We are interested in the preparation of novel *apex*-functionalized derivatives of CTV and their unique chemistry,[27] ultimately in order to enable attachment to surfaces while displaying the concave cavity for interaction with guests for detection and signaling. Toward this end we recently reported[28] the synthesis of CTV oxime via the CTV ketone **2** (Scheme 1) and discovered that the oxime saddle and crown conformers were readily separable by column chromatography, but that re-equilibration of the conformers occurs within a matter of hours. Because the bowl-shaped crown conformer is essential for participation in host-guest chemistry that we wish to explore, we measured the equilibrium constant between the CTV oxime conformers and the kinetics of their interconversion. The more polar solvent DMSO-d_6 was shown to favor the crown conformer by nearly an order of magnitude, relative to an approximately equal mixture at equilibrium in the less polar $CDCl_3$. The time course for interconversion of the saddle conformer to the crown oxime conformer was measured by ^{1}H NMR, and the $t_{1/2}$ of the saddle was determined to be 2.45 ± 0.15 h in $CDCl_3$ at 25 °C, and 3.71 ± 0.07 h in DMSO-d_6. A similar solvent-dependence for the thermodynamic ratio and interconversion was observed by Zimmermann for the parent CTV, although the ratio of crown to saddle was an order of magnitude greater for CTV in $CDCl_3$ than for CTV oxime. For CTV itself, the saddle conformation is thermodynamically disfavored due to the steric crowding of the apical methylenes with the central aromatic ring at the back of the saddle,[24] whereas this steric interaction should be absent in the oxime twist-Cs saddle conformation of oxime **3d** (Scheme 1), as well as from CTV ketone twist-Cs saddle **2d** (cf. Scheme 2). Additionally, we hypothesized there may be a stabilizing π-π interaction between the central aromatic ring and the oxime itself in the twist-Cs saddle conformers of oxime **3**.

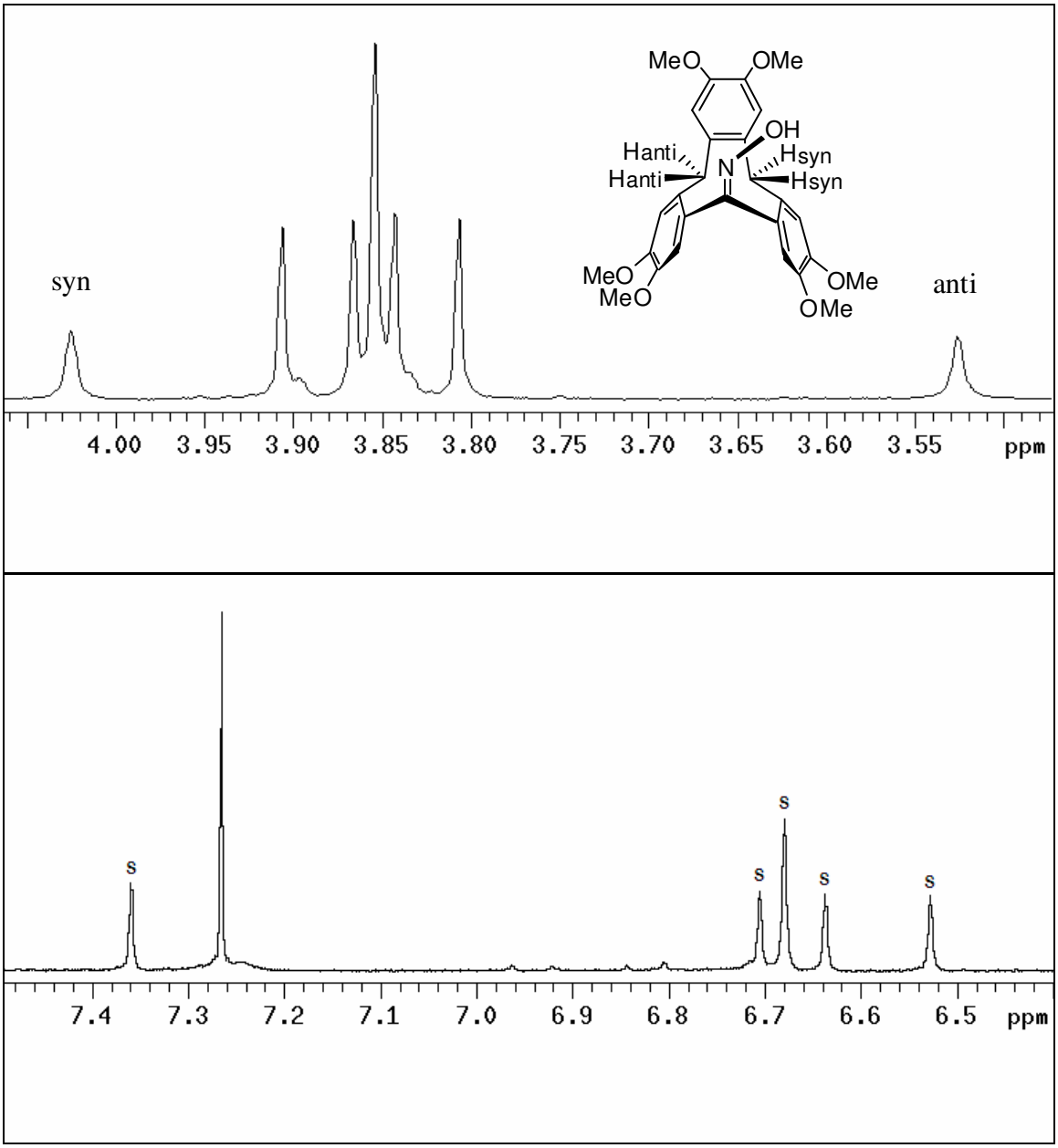
Scheme 1. Synthesis and conformers of CTV ketone and oxime.[a]



[a]Letters associated with oxime conformer structure numbers (eg. **a**, **b**, and **d**) correspond to analogous conformations of CTV ketone, **2** (cf. Scheme 2). Semi-empirical AM-1 calculations found no energetic minimum for oxime conformer **3c** corresponding to **2c**, hence **3c** is not represented. Saddle conformers depicted are based on new X-ray and computational data described herein, and thus differ slightly from saddle conformers previously depicted.[28]

Figure 1 shows the ^{1}H NMR spectrum in $CDCl_3$ at room temperature of the saddle conformer of CTV oxime, which was separated from the crown conformer by chromatography as described below. All six aromatic protons are chemically unique, due to the asymmetry of the oxime, and resonate at δ 6.96 (1H, s), 6.90 (1H, s), 6.86 (1H, s), 6.81 (2H, s), 6.71 (1H, s),

respectively. The two aliphatic methylene protons are either syn or anti to the oxime hydroxyl and thus appear at separate chemical shifts, [δ 4.02 (2H, s), 3.54 (2H, s)]; specific syn/anti assignments are tentative for the two methylenes. The geminal hydrogen atoms within one methylene group are equivalent on the NMR time scale. They display only one signal for both hydrogen atoms and show no geminal coupling. This is consistent with rapid interconversion of conformers (ie. pseudorotation), as known for CTV ketone **2**[26] and illustrated by the equilibrium between the saddle conformers of oxime **3** in Scheme 1 and as reported by Zimmermann for CTV.[24] The resonances in the region of 3.81 to 3.91 ppm are the methoxy moieties of the CTV-oxime saddle conformer. These five peaks for the six methoxy groups (3.91, 3.87, 3.85, 3.84 and 3.81 ppm) integrate 3:3:6:3:3, respectively.



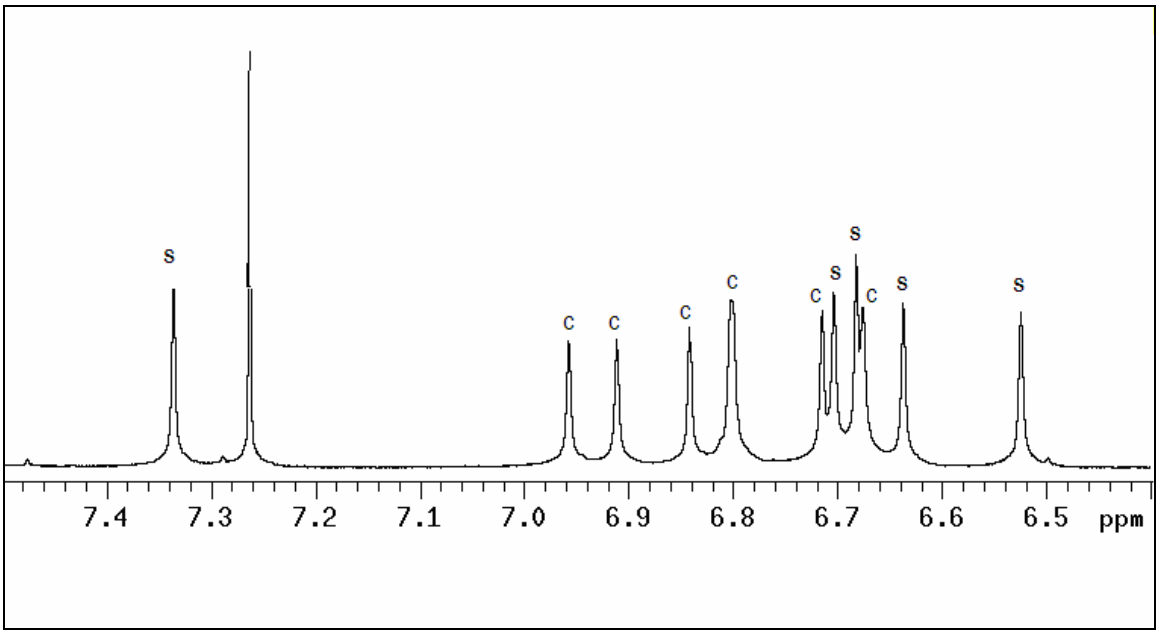


Figure 1. Top: The aliphatic region of the ^{1}H NMR spectrum of the saddle conformation of the CTV oxime dissolved in $CDCl_3$ at room temperature. Middle: The ^{1}H NMR spectrum of the saddle conformation of the CTV oxime dissolved in $CDCl_3$ at room temperature in the region of 6.4 to 7.5 ppm. The letter "s" denotes saddle, these peaks integrate 1:1:2:1:1, respectively. Chloroform is at 7.26 ppm, and the low intensity peaks between 6.80 and 6.98 ppm are due to the presence of a small amount of crown. Bottom: The ^{1}H NMR spectrum of the CTV oxime after saddle-crown equilibration at 25 °C. The letter "s" denotes saddle, "c" denotes crown.

Specifically, we are targeting apex-modified CTV derivatives as new host molecules, including the use of the oxime moiety as a linker unit for attachment of CTV to surfaces. The conformational dynamics of the parent CTV containing only sp^3 centers in the apex has been studied in detail, but the conformational dynamics are profoundly impacted by the presence of an sp^2 center in the apex. In order to better understand the conformational dynamics of new CTV derivatives containing sp^2 centers in the apex we have undertaken a study to characterize the thermodynamics and kinetics of the solvent dependence of the interconversion of the conformers of CTV oxime by NMR. To this end we have selected five deuterated NMR solvents for these studies of various polarities. Specifically, the chosen solvents were DMSO-d_6, acetonitrile-d_3, acetone-d_6, $CDCl_3$, and 1,4-dioxane-d_8.

The Saddle-Crown Equilibrium Thermodynamics

Experiments were conducted to determine the saddle-crown equilibrium constants (K_{eq}) and interconversion rates (k_1 and k_2) in solution as a function of temperature.

$$\text{crown} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{saddle}$$

$K_{eq} = k_1 / k_2$ = [saddle] / [crown] (1)

The equilibrium constant was measured at five temperatures on the interval of 25 °C to 45 °C. Freshly prepared samples of the saddle conformer were dissolved in a given NMR solvent and maintained at constant temperature for 16 to 48 hrs, depending upon the rate of equilibration. Then, the equilibrium was measured by ^{1}H NMR, where the [saddle] / [crown] ratio was taken as the ratio of the saddle to crown integrals in the aromatic region.

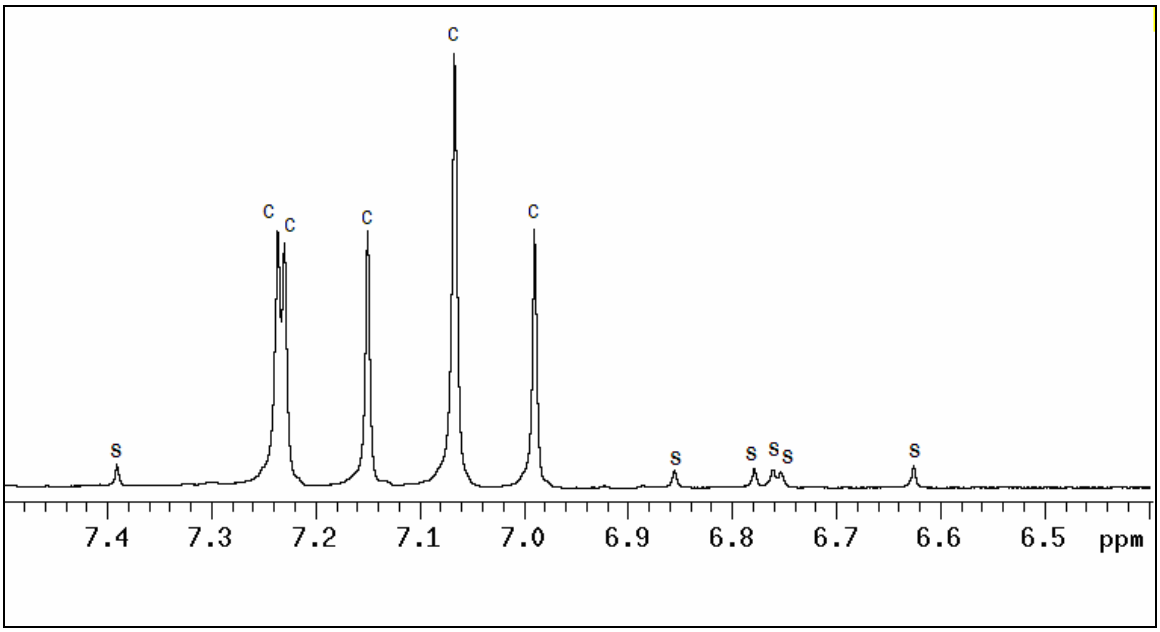


Figure 2. The ^{1}H NMR spectrum of an equilibrium mixture of CTV oxime crown and saddle dissolved in DMSO-d_6 at 25 °C in the range 6.4 to 7.5 ppm. The letter "s" denotes saddle, "c" denotes crown.

Figure 2 shows the aromatic region of the ^{1}H NMR spectrum of the of the CTV oxime dissolved in DMSO-d_6 after saddle-crown equilibration at 25 °C. Equilibrium constants at 25, 30, 35, 40, and 45 °C for the CTV oxime dissolved in DMSO-d_6, acetonitrile-d_3, acetone-d_6, $CDCl_3$, and 1,4-dioxane-d_8 were obtained from spectra of the type shown here. The enthalpy (ΔH) and entropy (ΔS) for the interconversion of the saddle and crown conformers are related to the equilibrium constant through,

$$\ln K_{eq} = -\Delta H / RT + \Delta S / R \quad (2)$$

Linear regression analysis of ln K_{eq} vs. 1000 / T (K) plotted in Figure 3 furnishes the thermodynamic parameters ΔH and ΔS, and a summary of the results appears in Table 1.

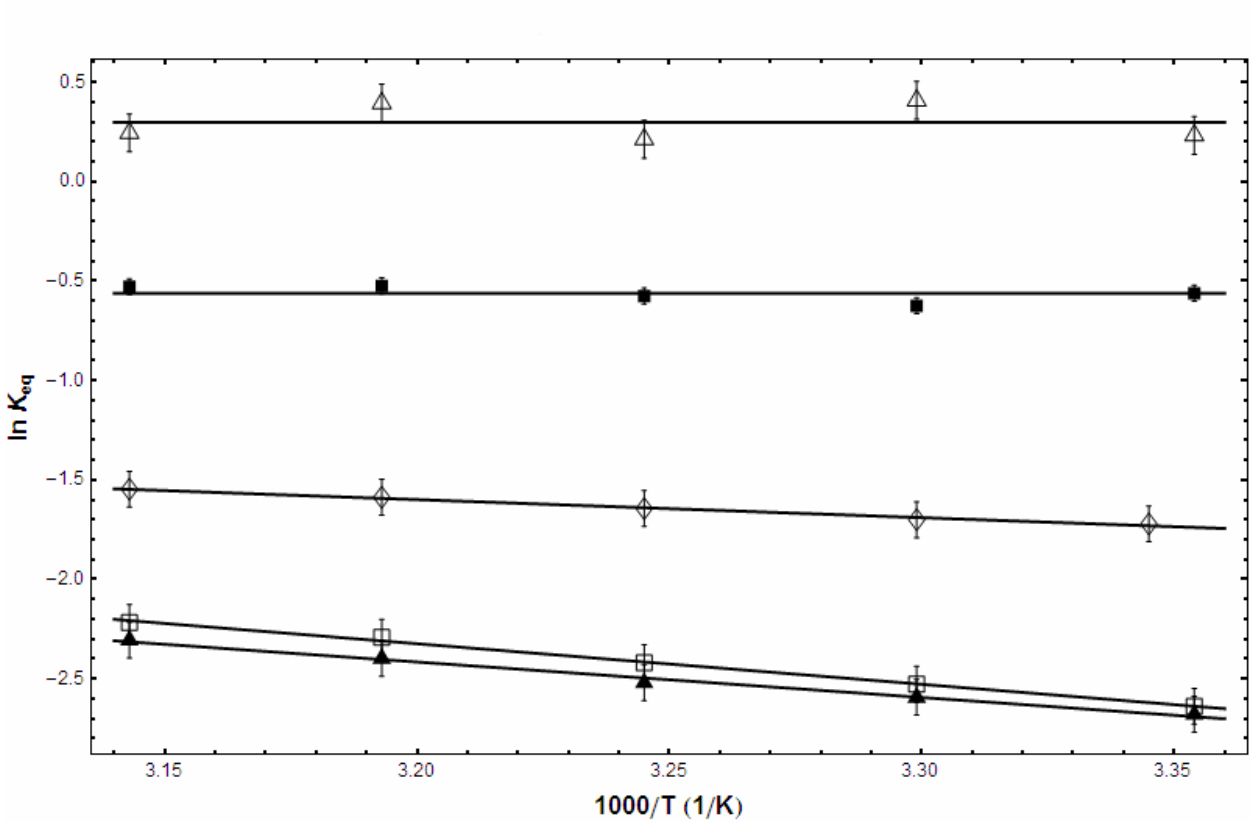


Figure 3. ln K_{eq} vs. 1000 / T (K): $CDCl_3$ (△), 1,4-dioxane-d_8 (■), acetone-d_6 (◊), acetonitrile-d_3 (□), DMSO-d_6 (▲).

Table 1: Thermodynamic parameters for the CTV oxime saddle-crown interconversion in different solvents.

Solvent	μ *(D)*[a]	K_{eq} *(298 K)*	ΔH*(kJ mol*$^{-1}$*)*	ΔS *(J mol*$^{-1}$ *K*$^{-1}$*)*	ΔG *(kJ mol*$^{-1}$*)*
1,4-dioxane-d_8	0.00	0.57	~ 0	− 4.6 ± 0.3	1.4 ± 0.1[b]
$CDCl_3$	1.04	1.4	~ 0	2.5 ± 0.8	− 0.7 ± 0.2[b]
acetone-d_6	2.88	0.18	7.6 ± 0.5	10.9 ± 1.5	4.4 ± 0.5[c]
acetonitrile-d_3	3.92	0.072	17.0 ± 0.6	35.0 ± 1.9	6.6 ± 0.6[c]
DMSO-d_6	3.96	0.069	14.8 ± 0.8	27.4 ± 2.7	6.6 ± 0.8[c]

[a]Dipole moments for corresponding protic solvents from the CRC Handbook of Chemistry and Physics 86th Edition. Editor David R. Lide, Copyright 2005 by CRC Press. [b]Calculated using Equation 4 and K_{eq} *(298 K)* determined by NMR. [c]Calculated using the linear regression results at 298 K.

Table 1 shows the thermodynamic parameters for the interconversion of the saddle and crown conformers of the CTV oxime dissolved in acetone-d_6, acetonitrile-d_3, and DMSO-d_6. The equilibrium constants for the CTV oxime dissolved in acetonitrile-d_3 and DMSO-d_6 are quite similar, while the K_{eq} determined in acetone-d_6 is over two times greater, thus the saddle is more favored in acetone-d_6 than in acetonitrile-d_3 or DMSO-d_6. Also, the values of ΔH determined for the interconversion of the saddle and crown conformers of the CTV oxime dissolved in acetonitrile-d_3, and DMSO-d_6 are similar, while the ΔH determined in acetone-d_6 is approximately half. The values of ΔS show a similar trend. The values of ΔG were calculated using the linear regression results at 298 K with Equation 3, and show the same solvent dependent trend as the other thermodynamic parameters.

$$\Delta G = \Delta H - T\Delta S \qquad (3)$$

The trends in these thermodynamic parameters suggest that the crown conformer is stabilized through solvation by acetonitrile-d_3 and DMSO-d_6, relative to the CTV oxime crown conformer dissolved in acetone-d_6. All three of these solvents are known to form hydrogen bonds, and the geometry of the crown should afford greater accessibility to the oxime hydroxyl group for hydrogen bonding with the solvent. Thus, solvation by DMSO-d_6 and acetonitrile-d_3 may increase the relative energy differences of the crown and saddle through stronger hydrogen bonding with the crown relative to acetone-d_6.

In $CDCl_3$, there was no change in the saddle-crown equilibrium constant with changing temperature for the CTV oxime. The line of zero slope drawn through the data in Figure 3 for $CDCl_3$ represents the average of the data for these five points with $\ln K_{eq} = 0.30$ and a standard deviation of 0.09. The average K_{eq} is 1.4 for the CTV oxime dissolved in $CDCl_3$ at all five temperatures, so that the saddle conformation is always slightly favored. The lack of a discernable non-zero slope in this case indicates that, within experimental error, $\Delta H \approx 0$. Also, the small, positive value determined for $\ln K_{eq}$ corresponds to the small, negative free energy, ΔG by Equation 4.

$$\Delta G = -RT \ln K_{eq} \qquad (4)$$

When these values are used to calculate the entropy change, a small, positive value for ΔS is obtained. This suggests that the conversion of crown to saddle, when dissolved in $CDCl_3$, is spontaneous and primarily entropy driven.

In 1,4-dioxane-d_8, there also was no change in the saddle-crown equilibrium constant with changing temperature. As in the case of $CDCl_3$, the line of zero slope drawn through the data in Figure 3 for 1,4-dioxane-d_8 represents the average of the data for these five points with $\ln K_{eq} = -0.56$ and a standard deviation of 0.04. The average K_{eq} is 0.57 here, so that in 1,4-dioxane-d_8 the crown conformation is always slightly favored. The lack of a discernable non-zero slope in this case also indicates $\Delta H \approx 0$. The small, negative value determined for $\ln K_{eq}$ corresponds to a small, positive free energy, ΔG.

As with acetone-d_6, acetonitrile-d_3, and DMSO-d_6, 1,4-dioxane-d_8 is known to form hydrogen bonds. However, 1,4-dioxane-d_8 is non-polar whereas the other solvents have

substantial dipole moments. Also, the positive ΔG determined for the CTV oxime dissolved in 1,4-dioxane-d_8, is of the same order of magnitude as the positive free energies determined in the case of the three most polar solvents. Therefore, it seems reasonable that the crown conformer is stabilized primarily by stronger hydrogen bonding in all of these solvents.

The Crown-Saddle Interconversion Kinetics

The interconversion kinetics were monitored by ^{1}H NMR. Freshly prepared samples of the saddle conformer dissolved in DMSO-d_6, acetonitrile-d_3, acetone-d_6, $CDCl_3$, or 1,4-dioxane-d_8, respectively, and were maintained at the same temperatures noted above. The decrease in the ^{1}H NMR saddle peak intensities ΔI(t) in the aromatic region were recorded at constant temperature over 3 to 24 hours, depending upon temperature. Non-linear curve fitting of the exponential decrease of the saddle peak intensity as a function of time furnished the time constant τ, which is equal to the inverse of the rate constant k. The approach to equilibrium is described by the equation,

$$\Delta I(t) = \exp(-kt) \qquad (5)$$

where $k = 1 / \tau$.

Here $k = k_1 + k_2 = k_1(1 + 1/ K_{eq})$, and ΔI(t) = [crown](t) – [saddle](t) is the difference in the concentration of the crown and saddle conformers at time (t). [24] Thus, k_1 for the conversion of crown to saddle can be found by determining τ by ^{1}H NMR, and the relation $k_1 = k/(1 + 1/ K_{eq})$.

According to Eyring's absolute rate theory, the activation energy (E_a), enthalpy ($\Delta H^{\ddagger}$), and entropy ($\Delta S^{\ddagger}$) of transition for the conversion of the crown to saddle conformer are related to the rate constant through

$$k_1 = A \exp(-E_a / RT) = (\kappa k_B T / h) \exp[-(\Delta H^{\ddagger} - T\Delta S^{\ddagger}) / RT] \qquad (6)$$

Linear regression analysis of ln k_1 vs. 1000 / T (K) yields the parameters E_a and ln A (s^{-1}). An Arrhenius plot of the data is shown in Figure 4, and a summary of these results appears in Table 2.

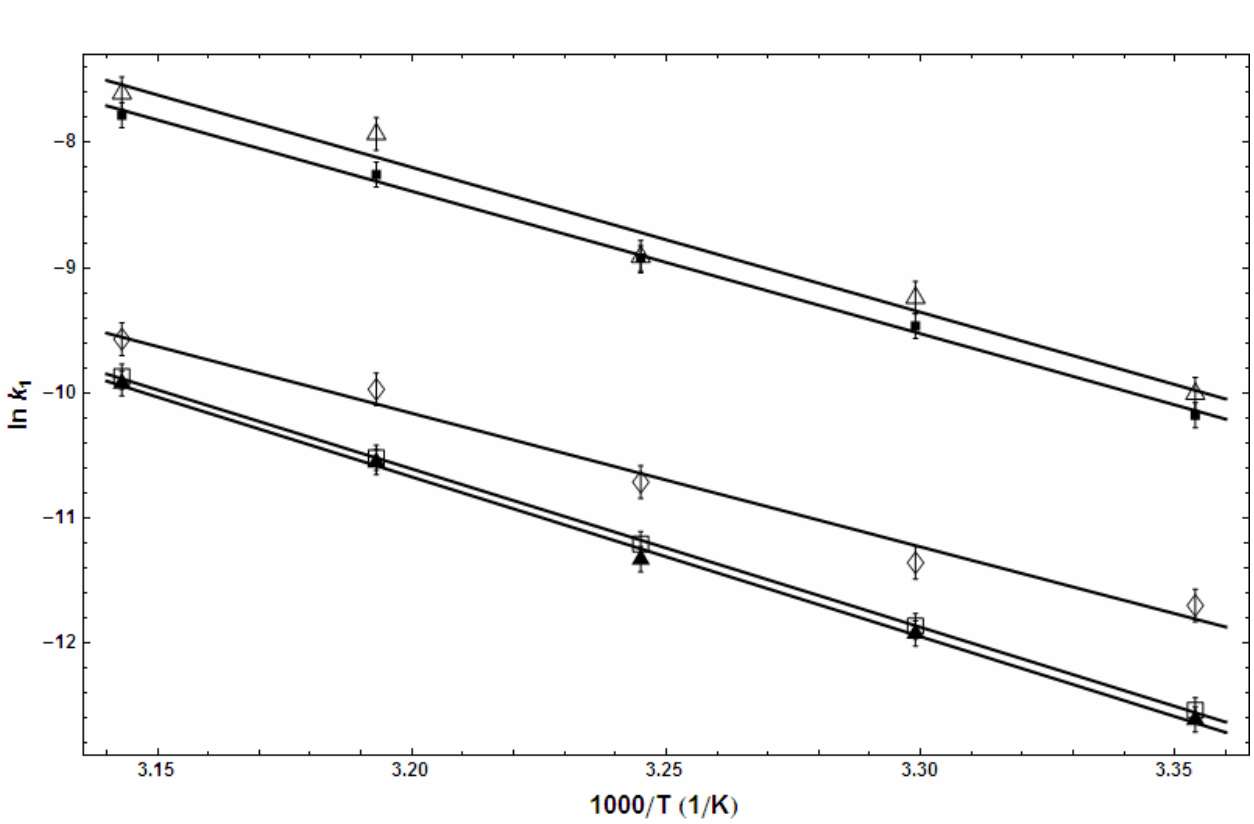


Figure 4. Arrhenius plot of the crown → saddle conversion rate k_1 determined from ^{1}H NMR spectra recorded in $CDCl_3$ (△), 1,4-dioxane-d_8 (■), acetone-d_6 (◇), acetonitrile-d_3 (□), and DMSO-d_6 (▲).

Table 2: Arrhenius and Eyring parameters.

Solvent	E_a *(kJ mol^{-1})*	*ln A (s^{-1})*	$\Delta H^{\ddagger}$ *(kJ mol^{-1})*	$\Delta S^{\ddagger}$ *(J mol^{-1} K^{-1})*
1,4-dioxane-d_8	94.65 ± 2.7	28.0 ± 1.1	92.1 ± 2.7	37.1 ± 8.9
$CDCl_3$	96.2 ± 8.5	28.8 ± 3.3	93.7 ± 8.5	43.9 ± 27.7
acetone-d_6	88.8 ± 6.4	24.0 ± 2.5	86.2 ± 6.4	3.5 ± 20.7
acetonitrile-d_3	105.1 ± 1.4	29.9 ± 0.4	102.6 ± 1.1	52.2 ± 3.7
DMSO-d_6	106.1 ± 2.8	30.2 ± 1.1	103.6 ± 2.8	54.8 ± 8.9

Taking a transmission coefficient of $\kappa = 1$, and setting $A = (\kappa k_B T / h)$ in Equation 6 produces Equation 7.

$$\ln [k_1 / A] = - \Delta H^{\ddagger} / RT + \Delta S^{\ddagger} / R \qquad (7)$$

Linear regression analysis of ln [k_1 / A] vs. 1000 / T (K), furnishes the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

The energy barrier to the crown-saddle interconversion is large in all solvents studied, ranging from ca. 89 to 106 kJ/mole. All of the activation energies in Table 2 are of the same order of magnitude found by Zimmermann for CTV dissolved in $CDCl_3$.[24] Also, all of the activation energies are of the same relative magnitude. Therefore, in contrast to the strong solvent dependence found for ΔH of the interconversion, there seems to be a lack of any substantial solvent effect upon the energy barrier to the crown-saddle interconversion. Furthermore, the values determined for the enthalpy of activation in Table 2 do not appear to show the type of solvent dependence as the thermodynamic parameter ΔH.

Conformational Analysis via Molecular Modeling Compared With the Crystal Structure of CTV Ketone 2

In order to better understand the structure of the saddle conformer and its implications for the thermodynamic preference for the saddle relative to the crown conformer we have obtained a single-crystal X-ray structure of the CTV ketone **2** (Figure 5). Repeated attempts to crystallize the CTV oxime were unsuccessful. Whereas the monoketone molecule itself is achiral, CTV ketone **2** crystallized in a chiral conformation in crystals that are enantiomerically pure, as a conglomerate. The conformation in the crystal structure of CTV monoketone **2** is a nearly C_2-symmetric side-saddle conformer (carbonyl on the *side* of the saddle as depicted, rather than in the center), with an approximate C_2 axis passing directly through the carbonyl double bond.

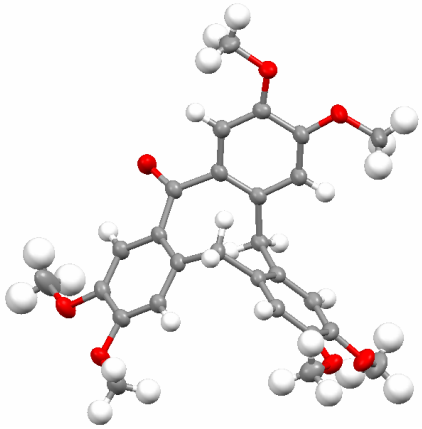


Figure 5. Single Crystal X-Ray Structure of CTV Monoketone **2** (Thermal Ellipsoids, 50% Probability)

The X-ray crystal structure of CTV ketone **2** was compared with the calculated energy-minimized equilibrium geometries of the ketone, parent CTV and the oxime using semi-empirical AM1 methods. Although the CTV ketone has long been known to exist in the saddle conformation based on NMR evidence, [26] semi-empirical AM1 calculations that we performed suggest that the crown conformer should be more stable than the saddle conformers by at least 13.2 kJ/mole. Furthermore, energy minimizations identified three distinct saddle conformational minima for the CTV ketone in addition to the crown conformation **2b** (Scheme 2): a C_2 symmetric saddle (**2b**) almost identical to the nearly-C_2 symmetric X-ray structure; a pseudo C_s saddle (**2c**) that would have a vertical mirror plane of symmetry except for the

carbonyl on the left and methylene on the right (as drawn); and another conformer (**2d**) which is twisted from a perfect C_s symmetry. However, there are actually *six* unique saddle conformational minima upon consideration of the mirror images of each of the three chiral saddle conformers. In addition, the saddle conformers are each significantly more flexible than the rigid crown, hence entropic contributions seem to be determinant, and the CTV ketone exists – based on the NMR evidence – exclusively as the saddle conformers undergoing rapid pseudorotation. To further validate this assumption we examined the ^{1}H NMR of the CTV ketone **2** in DMSO-d_6 at 100°C hoping to increase the rate of interconversion of the saddle conformers with the putative crown conformer, but no new peaks indicative of the crown conformer appeared in the spectrum, nor shifts in peaks indicative of a new species in the equilibrium.

Interestingly, our calculations identified the C_2-saddle **2b** as the most thermodynamically stable of the three saddle conformations of ketone **2** (Scheme 2), which is essentially identical to the saddle conformation observed in the X-ray crystal structure (Figure 5). The crystal structure is more distorted from perfect C2 symmetry as evidenced by the unequal dihedral angles (20.8° and 41.6°, respectively), relative to the nearly-perfect C_2 AM1 structure (30.9° and 31.8°, respectively; Table 3). This disparity may be due to crystal packing forces in the X-ray structure relative to the gas-phase calculations, particularly in light of the asymmetry of the enantiomeric crystal, or it could be due to an unequal mesomeric effect of the carbonyl with one aryl in preference to the other.

Scheme 2. Conformers of CTV Ketone **2** as calculated with AM1

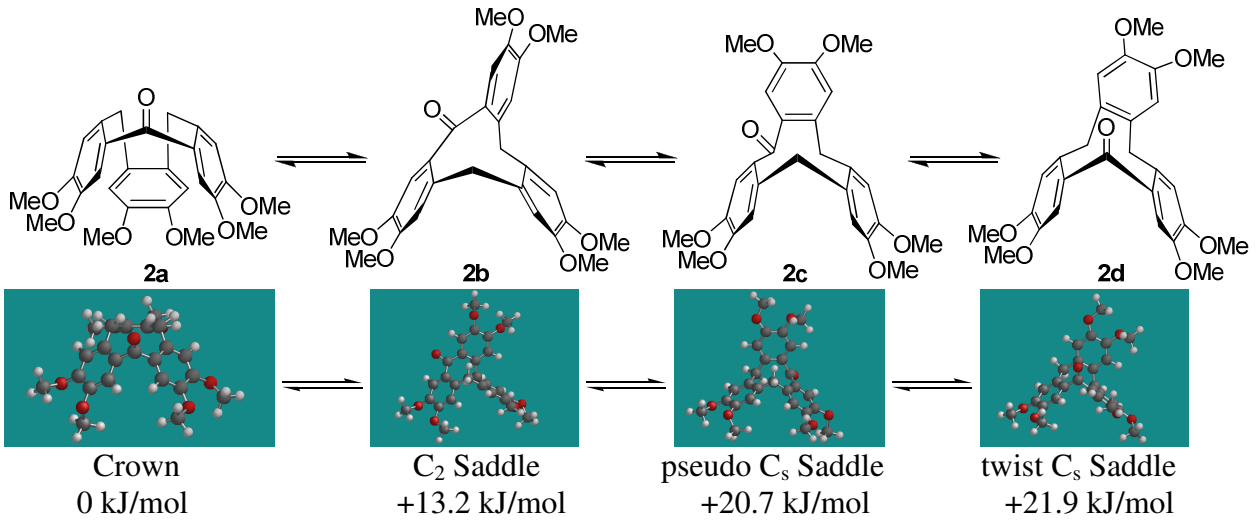
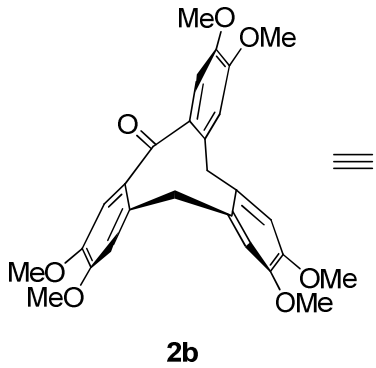
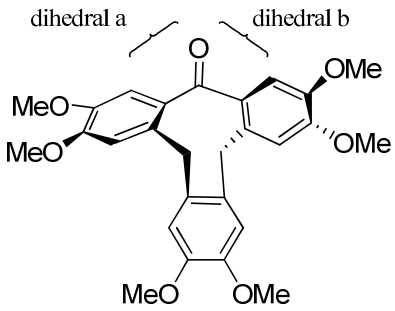


Table 3: CTV Ketone C_2-Saddle Conformer **2b**: Comparison of X-Ray and Calculated Structures



2b



2b

structure	dihedral a	dihedral b
X-ray	20.8	41.6
AM-1	30.9	31.8

A summary of calculated energies, dihedral angles (as defined in Table 3), and dipole moments for the conformers of CTV (**1**), CTV ketone (**2**), and CTV oxime (**3**) are included for direct comparison in Table 4. The dihedral angles involving the carbonyl or the oxime moiety, respectively, may indicate enthalpic resonance stabilization. The calculated dipole moments of the conformers may impact solvent-influenced conformational preferences and were therefore also included in this comparison.

The parent CTV is known to exist almost exclusively in the crown conformer[24] which is consistent with the calculated difference in heats of formation favoring the crown conformer by 16.7 kJ/mole. Whereas Zimmermann has argued that the saddle CTV conformer may have a lower effective (average) dipole moment due to rapid pseudorotation, the dipole of an individual saddle conformer **1b** is somewhat larger (4.0 D) than the corresponding crown conformer (3.1 D).

As noted above, the CTV ketone saddle conformers **2b**-**2d** were calculated to be 13.2 to 21.9 kJ/mole higher in energy than the crown conformer **2a**. The actual preference for saddle in solution (NMR) may again be attributable to entropic factors, for although resonance delocalization provides some stabilization of the saddle conformers relative to the crown conformer **2a** that does not enjoy coplanarity of the carbonyl with the aryl rings (dihedral angles = 79.1° and 80.8°), the crown conformer remains nonetheless lower in its calculated heat of formation. Furthermore, the orientation of the methoxy substituents can play a role in the relative energies of the conformers, as higher-level computational methods have demonstrated that ortho-dimethoxybenzenes with both methoxy groups coplanar with the ring are 4.4 to 9.9 kJ/mol more stable than conformers with one or two methoxyls out of plane, respectively; this is due to a substantial contribution of the mesomeric effect and is dependent upon additional substitution around the ring.[29] The enthalpic preference for the CTV ketone C_2 symmetric saddle **2b** over the two other saddle conformers is however consistent with greater conjugation of the carbonyl with the aryl rings as evidenced by the torsional angles (31.0° and 31.8°) for the C_2 saddle, relative to the two other saddle conformers where the carbonyl is further from co-planarity with the two more conjugated aryl rings (25.7° and 61.7°, respectively) while nearly

orthogonal with the other aryl rings (87.3° and 82.5°, respectively). The CTV ketone saddle conformers are all significantly more polar (μ = 5.5 D, 5.3 D, and 4.2 D) than the crown (2.8 D).

For CTV oxime, the crown **3a** is again calculated to be the most stable conformer relative to each individual saddle conformer, despite lack of conjugation of the C=N bond with the two attached aryl rings, as evidence by virtually orthogonal dihedral angles (86.9° and 86.7°, respectively). For the oxime, the energy of the C_2 saddle conformer **3b** is increased relative to the twist Cs saddle **3d**, presumably due to nonbonding interaction of the oxime hydroxyl with the adjacent ortho aryl hydrogen resulting in a larger dihedral angle (38.6°), relative to the ketone (31.8°). A corresponding pseudo-Cs saddle was not identified for the oxime; when minimizing the oxime by starting with a pseudo-Cs conformation, the twist Cs saddle conformer **3d** was consistently obtained. Similar to the CTV ketone, the flexibility of the saddle oxime conformers is greater, and the saddle exists as several energetically-accessible pseudorotamers. CTV oxime crown exists as two enantiomers, whereas there are a total of six conformers for the oxime due to the asymmetry of the oxime (two enantiomeric C2-saddle conformers; plus syn and anti oxime isomers, each as an enantiomeric pair). As with the ketone, the oxime saddle conformers exhibit significantly higher dipole moments (4.1 D and 3.3 D, respectively) as compared to the oxime crown conformer (1.3 D). This suggests that simple dipole dominated interactions between the molecule and the solvent are *not* the driving force for the thermodynamic equilibrium constants observed by NMR as the most polar solvents all favor the less polar crown conformers over the saddle conformers. Thus other reasons, such as potential host-guest interactions between the oxime and the solvents, or a preference to form stronger hydrogen bonds between the oxime and the solvent molecules for one of the conformers must be the decisive factor for the preference of the crown conformer observed in all solvents except $CDCl_3$.

Table 4: Comparison of calculated energies, dihedral angles, and dipole moments for ketone and oxime conformers[a]

Molecule	Relative energies (kJ/mol)[a], dihedral angles[b], and dipole moments			
	a (crown)	**b** (C2 side saddle)	**c** (pseudo-Cs saddle)	**d** (twist Cs center saddle)
1 **(CTV)**	0	+16.7 kJ/mol		
	3.1 D	4.0 D		
2 **(CTV ketone)**	0	+13.2 kJ/mol	+20.7 kJ/mol	+21.9 kJ/mol
	79.1°, 80.8°	31.0°, 31.8°	25.7°, 87.3°	82.5°, 61.7°
	2.8 D	5.5 D	5.3 D	4.2 D
3 **(CTV oxime)**	0	+28.0 kJ/mol	---	+18.9 kJ/mol
	86.9°, 86.7°	38.6°, 33.4°	---	79.1°, 63.0°[c]
	1.3 D	4.1 D	---	3.3 D

[a]Semi-empirical AM-1 equilibrium geometries. [b]Absolute values, as defined in Table 3.[c]Oxime hydroxyl *syn* in relation to back (distal) aryl.

Summary and Conclusions

In contrast to $CDCl_3$, the crown conformation of the CTV oxime is favored at equilibrium in all of the more polar solvents by about an order of magnitude. All of the thermodynamic parameters determined here for the CTV oxime dissolved in acetonitrile-d_3 and DMSO-d_6 are quite similar, while those determined in acetone-d_6 are different. In particular, the saddle-crown equilibrium in acetonitrile-d_3 or DMSO-d_6 is shifted more toward the crown than in acetone-d_6. Also, the other thermodynamic parameters are somewhat greater for the conversion of crown to saddle in acetonitrile-d_3 and DMSO-d_6, when compared with those determined for the CTV oxime dissolved in acetone-d_6.

These trends suggest that the crown conformer is stabilized through solvation by acetonitrile-d_3 and DMSO-d_6 to a greater extent than in acetone-d_6. The geometry of the crown affords greater accessibility to the oxime hydroxyl group for hydrogen bonding with solvent. Perhaps solvation by DMSO-d_6 and acetonitrile-d_3 increases the relative energy differences between the crown and saddle through stronger hydrogen bonding relative to CTV oxime dissolved in acetone-d_6.

As in the case of $CDCl_3$, for the CTV oxime dissolved in 1,4-dioxane-d_8 there was no change in the saddle-crown equilibrium constant with changing temperature. Thus, within experimental error $\Delta H \approx 0$ here also. However, unlike the equilibrium in $CDCl_3$, in 1,4-dioxane-d_8 the crown conformation is always slightly favored. Also, because the position of thermodynamic equilibrium in 1,4-dioxane-d_8 lies in the same direction as in the acetonitrile-d_3, DMSO-d_6, and acetone-d_6, it seems reasonable that the crown conformer may be stabilized relative to the saddle primarily by hydrogen bonding in the non-polar solvent 1,4-dioxane-d_8.

Earlier, Zimmermann, in studying the thermodynamic interconversion of the crown and saddle CTV conformers by NMR, observed a considerably lower value for K_{eq} determined in dimethylformamide-d_7 (K_{eq}(300K) ≈ 0.008) than in $CDCl_3$ (K_{eq}(300K) ≈ 0.1).[24] He postulated that that the thermodynamic equilibrium is shifted in favor of the crown conformation in DMF due to polarity considerations. It was theorized that the saddle conformation may be considered to be the nonpolar form due to averaging of its electric dipole over the pseudorotation cycle, whereas the rigid crown conformation has a permanent electric dipole. In that study, the considerably higher ΔH (22.3 kJ mol^{-1}) value reported for the interconversion of CTV dissolved in DMF as compared to ΔH (9.96 kJ mol^{-1}) determined in $CDCl_3$ was attributed to a nonpolar saddle conformation being disfavored in polar solvents.

For this theory to be reasonable, the pseudorotation cycle would have to be extremely fast - so fast that the solvent molecules around the pseudorotating saddle isomers cannot adjust to the changing dipole moments. Then the solvent cage would reflect an on-average very low dipole moment for the saddle conformers, which would explain the observations of Zimmermann *et al.* However, we propose that such a rapid rate of conformational interconversion does not seem possible for the individual saddle conformers, particularly for the oxime where such a rapid exchange of the solvate molecules would also involve the breaking and forming of relatively strong hydrogen bonds formed between the oxime hydroxyl group and the solvent molecules.

Interestingly, $\Delta H \approx 0$ for the saddle-crown interconversion of the CTV oxime dissolved in $CDCl_3$, whereas ΔH = 9.96 kJ mol^{-1} for the parent CTV dissolved in $CDCl_3$. The average K_{eq}(298K) is 1.4 for the CTV oxime dissolved in $CDCl_3$ and shows no temperature dependence, while K_{eq} for the parent CTV dissolved in $CDCl_3$ demonstrates a measureable temperature dependence and K_{eq}(300K) ≈ 0.1. The K_{eq}(298K) values reported here for the CTV oxime dissolved in the most polar solvents are approximately an order of magnitude greater or more than the K_{eq}(300K) determined for CTV dissolved in DMF. Also, the ΔH values here for the CTV oxime dissolved in the most polar solvents are somewhat lower than ΔH for CTV dissolved in DMF.

In another study Zimmermann found little solvent dependence of K_{eq}(300K) for nonamethoxy-tribenzocyclononene (NM-TBCN) dissolved in $CDCl_3$, 1,4-dioxane-d_8, and DMF-d_7. These values were found to be 0.07, 0.055, and 0.045 respectively.[30] In the same study, Zimmermann reported ΔH = 17.2 kJ mol^{-1} for NM-TBCN dissolved in 1,4-dioxane-d_8, and ΔH = 17.6 kJ mol^{-1} for NM-TBCN dissolved in DMF-d_7. These values are very similar to those determined for the CTV oxime dissolved in DMSO-d_6 or acetonitrile-d_3, while quite different from ΔH determined for the CTV oxime dissolved in $CDCl_3$ or 1,4-dioxane-d_8. This behavior is surprising when compared to the profound differences found here for the CTV oxime dissolved in the most polar solvents and the less polar $CDCl_3$, in that 1,4-dioxane-d_8 is non-polar whereas DMF-d_7 is a polar solvent. Considering that Zimmermann found a substantially higher ΔH for the interconversion of the parent CTV dissolved in DMF-d_7 as compared to ΔH determined in $CDCl_3$, it is evident that the influence of solvent on the saddle-crown equilibrium of these compounds involves more than polarity considerations alone.

Regarding the possible influence on the saddle-crown equilibrium due to hydrogen bonding of the CTV oxime with the most polar solvents in our study, it should be noted that the situation here could be somewhat more complicated. While the dipole moments of DMSO-d_6 and acetonitrile-d_3 are higher than acetone-d_6, DMSO-d_6 and acetone-d_6 are expected to be the best hydrogen bond acceptors of the three most polar solvents, and acetonitrile-d_3 is not expected to be as good at forming hydrogen bonds. This is not reflected in the trends in the thermodynamic parameters determined here. The surprising results obtained for the CTV oxime dissolved in the non-polar 1,4-dioxane-d_8 provides further evidence that solvent polarity and hydrogen bonding considerations are not sufficient to explain the trends observed.

Additionally, the geometries of acetone-d_6 and DMSO-d_6 are similar and acetonitrile-d_3 is quite different, and the exact solvent re-organizational requirements for the saddle-crown interconversion are unclear. The requisite solvent re-organization involved in this process is an entropic consideration. Given these complexities, it is not entirely unreasonable to speculate that there may also be an additional host-guest interaction contributing to the stabilization of the crown in the case of acetonitrile-d_3. Many physical processes in liquids are still quite poorly understood when compared with those in gases and solids, thus these are only possible explanations for the thermodynamic trends that we determined.

The activation energy for the crown-saddle interconversion of the CTV oxime is relatively high in all solvents studied. All of these energy barriers are of the same relative magnitude, and there seems to be a lack of any substantial solvent effect upon the activation energies for the crown-saddle interconversion. Likewise, the enthalpies of activation, $\Delta H^{\ddagger}$, do not seem to show the type of solvent dependence as the thermodynamic parameter ΔH. Therefore, in contrast to the thermodynamic parameters, the energy barrier to the crown-saddle interconversion is not affected by the solvent. Surprisingly, the kinetic parameters for k_1, E_a = 96.2 ± 8.5 kJ mol^{-1} and $\Delta H^{\ddagger}$ = 93.7 ± 8.5 kJ mol^{-1}, determined in this study for the CTV oxime dissolved in $CDCl_3$ are, within experimental error, the same as those determined by Zimmermann *et al.* for CTV dissolved in $CDCl_3$, i.e. E_a = 97.4 ± 4.8 kJ mol^{-1} and $\Delta H^{\ddagger}$ = 94.9 ± 4.8 kJ mol^{-1}.[24] Apparently, the introduction of an sp^2 center in the apex of the parent CTV, which contains only sp^3 centers, has little effect upon the activation energy for the crown-saddle interconversion.

Experimental Section

All solvents and reagents were used without further purification unless otherwise noted. Reactions were performed under an atmosphere of nitrogen. Merck silica gel 60 (230-400 mesh) was used for flash chromatography. Merck Kieselgel 60 F254 DC-Fertigplatten (0.25 mm, Art. 5719) were used for TLC. ^{1}H NMR spectra were obtained utilizing either a Varian INOVA 300 or Varian Gemini 2000 300 MHz spectrometer with tetramethylsilane (TMS) as an internal standard. Decoupled ^{13}C NMR spectra were recorded at 75 MHz on either the Varian INOVA 300 or Varian Gemini 2000 spectrometer. CTV (**1**) was prepared from veratryl alcohol in formic acid according to the general procedure of Garcia and Collet[31] and was recrystallized from dry toluene affording guest-free crystals.[32] CTV Ketone (**2**) was prepared by a modification of the method of Stevens[26] as described previously.[28]

10,15-Dihydro-2,3,7,8,12,13-hexamethoxy-5H-tribenzo[a,d,g]cyclononen-5-oxime, CTV Oxime Crown (3) and CTV Oxime Saddle (4). The crown and saddle CTV oxime conformers were prepared by a modification of our earlier procedure. [28] A solution of CTV monoketone 2 (1.00 g 3.23 mmol) and 2.25 g of hydroxylamine hydrochloride (2.25 g, 36.2 mmol) in pyridine (10 mL) was heated under reflux for 16 h. The pyridine solvent was removed *in vacuo* (50-60 ^{o}C, 10 mmHg) giving a dark orange oil. To the oil was added ice (15 g) and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate layers were washed successively with 10% aqueous HCl (2 x 10 mL), water (10 mL) and brine (15 mL), and then dried over sodium sulfate. Concentration afforded an off-white foam (1.035 g). HPLC analysis indicated 5.0% of CTV-Monoketone and 95.0% combined of the two CTV oximes. The crude mixture was chromatographed on silica gel eluting with ethyl acetate/dichloromethane (20/80). Residual CTV-monoketone was the first component eluted off the column. After all CTV monoketone was eluted, the column was flushed with ethyl acetate (100%) to elute the mixture of conformers. Concentration gave the pure mixture of conformers as a colorless glass which was then separated by chromatography on silica gel (90:1 loading ratio, w/w) eluting with ethyl acetate/diethyl ether (20/80) while cooling the collected fractions in a salt/ice bath. Combined like fractions were rinsed using dichloromethane and concentrated *in vacuo* at room temperature (without application of heat). Saddle conformer **4** is eluted first as a colorless glass (200 mg, 19.2%) which is identical to material described previously. [28] This alternate solvent system elutes the saddle conformer first, enabling isolation of more pure saddle free with respect to crown conformer.

Interconversion Rate Measurements By NMR. All ^{1}H NMR spectra were recorded at 300 MHz. Utilization of a Varian non-linear curve fitting routine furnished the time constant τ. This time constant is equal to the inverse of the rate ($1/k$) for the interconversion of saddle to crown at constant temperature. The temperature was held at 25, 30, 35, 40, or 45 °C for each rate measurement in each of the four NMR solvents. These temperatures were found to be accurate to within ± 0.1 °C. The variable temperature control was checked with a sealed reference containing pure ethylene glycol. All deuterated NMR solvents were used as obtained from the vendor without further purification.

Single crystal X-ray measurements. A single crystal of ketone **2** was mounted on a MiTeGen MicroMesh mount with 25 μm mesh size and diffraction data were collected at 100 K on a

Bruker-AXS APEX CCD diffractometer with graphite-monochromated Mo-Kα radiation (λ=0.71073 Å). The unit cell was determined and data were collected and integrated using Apex2 of Bruker AXS, and were corrected for absorption using Sadabs as built into Apex2. The structure was solved using direct methods and refined with full-matrix, least-squares procedures on F^2 using Shelxtl 6.14. All non-hydrogen atoms were refined anisotropically. Crystal data were deposited with the Cambridge Crystallographic Data Centre and CCDC-721523 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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