The Saddle Form of Cyclotriveratrylene

Herbert Zimmermann,[†] Peter Tolstoy,[‡] Hans-Heinrich Limbach,[‡] Raphy Poupko,[§] and Zeev Luz*[,§]

Max-Planck-Institut für Medizinische Forschung, Jahnstrasse 29, 69120 Heidelberg, Germany, Institut für Organische Chemie, Freie Universität, Berlin, Takustrasse 3, 14195 Berlin, Germany, and Weizmann Institute of Science, Rehovot 76100, Israel

Received: July 8, 2004

Cyclotriveratrylene (CTV), or hexamethoxy tribenzocyclononatriene (hexamethoxy-TBCN) and other peripherally hexa-(or tri-)substituted TBCN were so far only known to exist in their crown form. Attempts to detect the corresponding saddle isomers failed, even though when structurally chiral these compounds undergo racemization, a process that is believed to proceed via the saddle form. We show that the saddle form of CTV (and other peripherally hexa-substituted TBCN) can be obtained by rapidly quenching a hot solution or the high-temperature melt to below room temperature. The saddle form of CTV was quantitatively separated from the quenched material by column chromatography, and some of its thermodynamic and kinetic properties in solution and in the solid state were determined by proton and carbon-13 NMR. Detailed measurement were performed in chloroform solutions, for which it was found that at room temperature the equilibrium constant, K = [saddle]/[crown] = exp[$-(\Delta H - T\Delta S)/RT$, is ~0.1 (with $\Delta H = 9.96 \pm 0.5$ kJ mol^{-1}, $\Delta S = 13.8 \pm 1.6$ J mol^{-1} K^{-1}). The isomerization half-life at room temperature is about 1 day with the rate constant for the crown to saddle transformation, (k(crown→saddle) = A exp($-E_a/RT$), characterized by the kinetic parameters, $E_a = 97.4 \pm 4.8$ kJ mol^{-1} and log[A (s^{-1})] = 11.0 ± 0.8). These parameters are consistent with those for the racemization rate of the isotopically chiral CTV-d_9 measured by Collet and Gabard (*J. Org. Chem.* **1980**, *45*, 5400−5401). Attempts to freeze-out the fast pseudorotation of the saddle isomer by cooling a Freon solution to almost 100 K, failed, setting a lower limit of 10^6 to 10^7s^{-1} for the pseudorotation rate at 120 K. Carbon-13 MAS spectra indicate that the saddle isomer of CTV in the solid state is crystalline with two (nonequivalent and distorted) molecules per asymmetric unit.

Introduction

Cyclotriveratrylene (CTV) is the parent compound of many homologous series based on the tribenzocylononatriene (TBCN) core (Figure 1a).[1−4] These compounds gained considerable interest throughout the years because of their special (crown/saddle) conformational isomerism, structural chirality,[13−18] tendency to form molecular complexes in solutions as well as solid inclusion compounds,[3,19,20] and when suitably substituted with long side chains, their mesomorphic properties.[21−23] They are also important because they serve as starting materials in the synthesis of cryptophanes.[24] The growing interest in these compounds is demonstrated by the fact that the term cyclotriveratrylene has been cited in the literature less than ninety times between its coining in 1963[8] and 1996, and more than one hundred times between 1996 and 2003.

The TBCN core can acquire two energy-minimum conformations, a rigid crown and a flexible saddle (Figure 1b). In most derivatives of TBCN the saddle form is less stable than that of the crown, apparently due to repulsive interactions between the inward pointing methylene hydrogen and the opposite benzene ring. In fact, the energy minimum of the saddle corresponds to a twisted, rather than the symmetric (C_s) structure shown in Figure 1b. It has been estimated that the saddle conformation is at least 12−16 kJ/mol higher in energy than the crown isomer.[1] It is, however, stabilized (relative to the corresponding crown) when the cyclononatriene ring is perturbed (for example, by oxidizing a ring methylene group, substituting it with a bulky substituent, or replacing it by a heteroatom), or when the ortho positions in the benzene rings are substituted with bulky groups ($R_3 \neq H$ in Figure 1a). The two isomers then coexist in solution in thermal equilibrium.[23] On the other hand the parent hydrocarbon ($R_1 = R_2 = R_3 = H$), CTV and all other peripherally tri- and hexa-substituted (symmetrically) derivatives (R_1 and/or $R_2 \neq H$, $R_3 = H$, in the following referred to as cyclotriveratrylenes) have so far only been known to exist in the rigid crown form.

Yet, it is known that the crown form of the cyclotriveratrylenes can undergo inversion in which the umbrella-shaped core is inverted into its reflected structure. This was unambiguously demonstrated by observing the (admittedly very slow) racemization of numerous structurally chiral cyclotriveratrylenes[13−17] including the isotopically chiral CTV-d_9 (X = OCH_3, Y = OCD_3 in Figure 1c).[15] Inspection of molecular models and quantum chemical calculation suggests that this inversion process involves the saddle form as an intermediate, rather than a strained planar transition state.[1] It might therefore be expected that at least a small amount of the saddle isomer is present at equilibrium with the crown form in solution. As indicated, so far there is no report claiming the observation of the saddle conformer in solutions of cyclotriveratrylenes. In fact, early attempts to detect it in CTV, using NMR at high temperatures or in quenched samples failed.[11,12] In the present

* Corresponding author. E-mail: zeev.luz@weizmann.ac.il.
[†] Max-Planck-Institut für Medizinische Forschung.
[‡] Freie Universität.
[§] Weizmann Institute of Science.

10.1021/jp040482r CCC: $27.50
Published on Web 11/06/2004

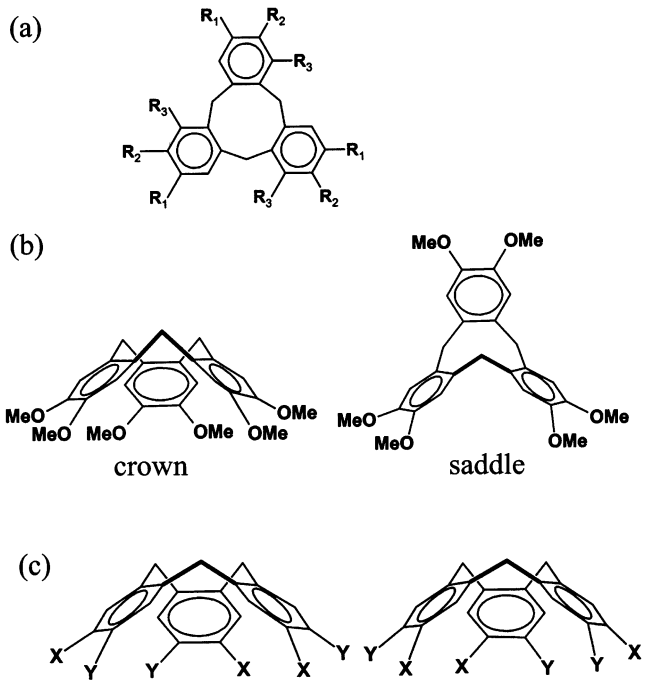

Figure 1. (a) Structural formulas of substituted tribenzocyclononatriene (TBCN). (b) Crown and saddle forms of cyclotriveratrylene (CTV). (c) Enantiomers of a structurally chiral cyclotriveratrylene.

paper we describe a simple procedure to produce and isolate the neat saddle form of CTV (and other cyclotriveratrylenes) in sufficiently large quantities for characterization experiments. We describe some thermodynamic and kinetic properties of the CTV isomers and relate them to those of the racemization process of CTV-d_9.[15]

The idea behind our procedure is essentially the same as that of Miller and Gesner[11] and Cookson et al.[12] and is also similar to (but experimentally much less demanding than) that of Anet[25] to cold-trap thermodynamically unstable conformers of cyclohexane derivatives. Recalling that the equilibrium concentration of such species increases with temperature, the procedure involves heating a solution or a melt to as high a temperature as possible without decomposing the compound. After thermal equilibration is achieved, the sample is rapidly quenched to low temperature. If, as is the case for the cylotriveratrylenes, the room-temperature isomerization rate is sufficiently slow, the various isomers, in particular the less stable ones, can be chromatographically separated and stored at low temperatures.

Preparation of the Saddle Isomer of CTV and ^{1}H NMR Spectra

The CTV (crown form) used in our experiments was synthesized and purified as described earlier.[21] The final crystallization was done from benzene and the sample dried by lengthy pumping at 185 °C. A differential scanning calorimetry (DSC) thermogram of this solid is shown in trace a of Figure 2.

The thermogram exhibits a single endothermic peak at 232 °C corresponding to its melting transition. In nondried samples solvent molecules are often trapped by the CTV lattice to form solvates.[19] In these cases an additional endothermic peak appears below the melting transition, which evidently corresponds to expulsion of the guest molecule. This peak does not appear on subsequent heating cycles. A proton NMR spectrum of the product in a chloroform solution is shown in trace a of Figure 3. It is fully consistent with that expected for the (rigid) crown

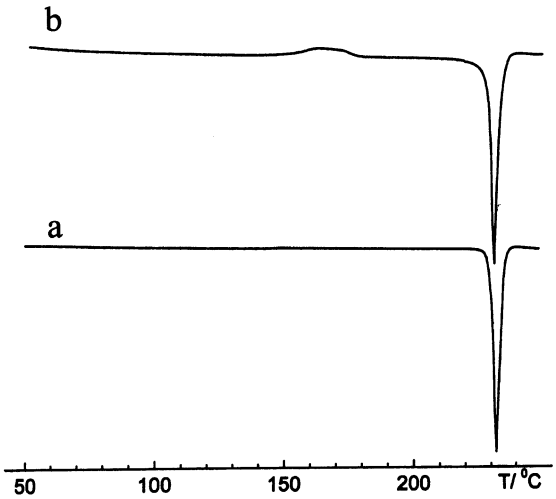

Figure 2. Differential scanning calorimetry (DSC) thermograms of the crown (a) and saddle (b) forms of CTV. Both thermograms were recorded on first heating of freshly prepared samples. Heating rate: 5 K/min.

form of CTV: two singlets at 3.82(6) and 6.83 ppm (relative intensities 3:1) due, respectively, to the methoxy and aromatic protons and an AX quartet (total relative intensity, 1) centered at 4.17 ppm (J = 13.71 Hz) due to the inner (4.78 ppm) and outer (3.57 ppm) hydrogens of the ring methylenes.[1,18]

In our first attempt to trap the saddle isomer of CTV a few milligrams of the solid crown was placed between two glass slides, which were inserted into a (microscope) hot stage. The sample was heated to slightly above the melting point (to about 235 °C) for ca. 1 min followed by rapid quenching in liquid nitrogen. It was then allowed to warm to room temperature and was dissolved in chloroform, and the ^{1}H NMR spectrum recorded; see Figure 3b. The spectrum now shows, in addition to the crown peaks, also a minor subspectrum, which we ascribe to the saddle isomer. It consists of three singlets at 6.62, 3.88, and (an unresolved shoulder) at 3.82(8) ppm, which on the basis of previous NMR studies of nona-substituted TBCN (R_1, R_2, $R_3 \neq$ H),[23] are identified with, respectively, the aromatic, ring-methylene, and methoxy protons of the saddle isomer. The simplicity of this spectrum reflects the averaging effect of the pseudorotation process, which renders the different types of hydrogens equivalent (see below). It effectively corresponds to a TBCN core with D_{3h} symmetry. From the relative intensities of the crown and saddle peaks in the NMR spectrum of the quenched sample a ratio saddle/crown of 0.17 was calculated. This may be considered as a lower limit of the equilibrium constant, K = [saddle]/ [crown] in the melt at 235 °C (lower limit, because some saddle → crown transformation might have occurred during the quenching procedure). Similar results were obtained by using somewhat larger quantities of melt, for example, by quenching a melt placed in an NMR measuring tubes.

However, to produce large quantities (tens of milligrams) of the saddle isomer, a somewhat different procedure was adopted in which, instead of quenching the melt, a hot solution is splashed over cold ice. This procedure has the advantage that larger amounts of CTV can be processed, the quenching is more efficient, and the final product is free from decomposition impurities. In a typical experiment, about 1 g of CTV (prepared as described above) was dissolved in 25 mL of dimethyl sulfoxide (DMSO). The flask containing the solution was inserted in an oil bath that was preheated to 200 °C and the solution allowed to reflux for ca. 5 min (the boiling point (BP)

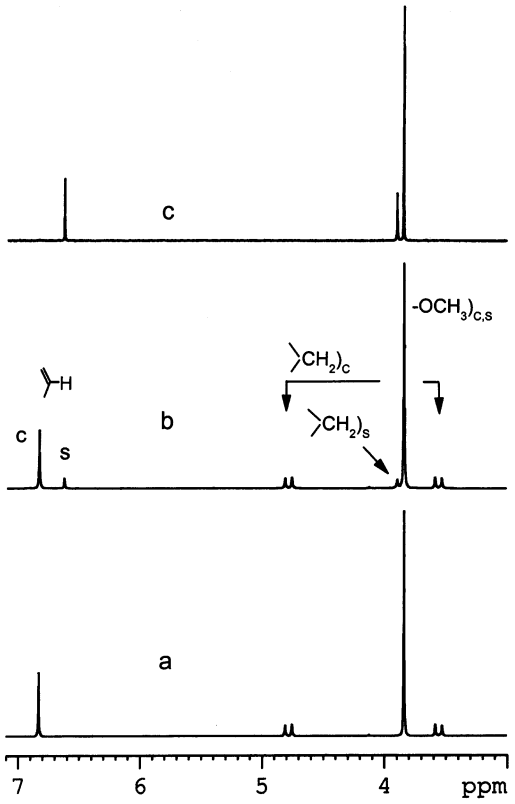

Figure 3. High-resolution ^{1}H NMR spectra (400 MHz) of CTV in chloroform solutions. The peak assignment is indicated in the middle trace, with the letters c and s indicating crown and saddle isomers, respectively. (a) Neat crown isomer. (b) CTV sample quenched from the melt. (c) Neat saddle isomer.

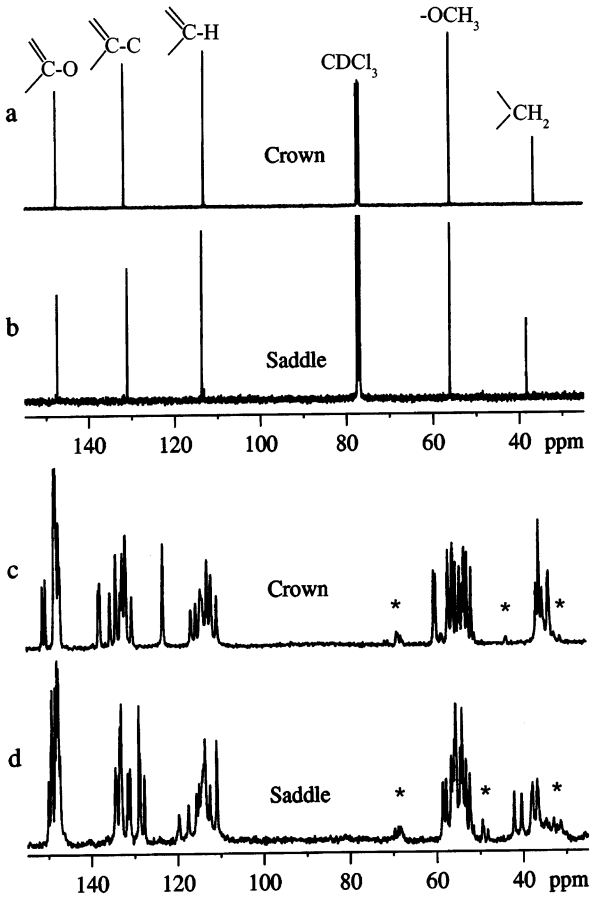

Figure 4. Room-temperature carbon-13 NMR spectra of the CTV isomers in solution and in the solid state. Peak assignment is given in the top trace, with the C−X corresponding to the aromatic carbons linked to the methoxy groups (X = O), the hydrogens (X = H), and the ring methylenes (X = C). (a) and (b) high-resolution spectra (100.6 MHz) in chloroform solution of the crown and saddle isomers, respectively. (c) and (d) MAS spectra (75 MHz, spinning rate, 6 kHz, several thousands scans) of the crown and saddle isomers, respectively. The center band is shown. Asterisks indicate spinning sidebands.

of DMSO is 189 °C). The hot solution was then splashed into a beaker containing about 1.5 kg of crushed-ice/water/NaCl (at −20 °C). The mixture was allowed to thaw, filtered by suction through a G4 glass, and washed with water, and the recovered solid was dried by pumping for several hours at room temperature (yield: 900 mg). Thin-layer chromatography (TLC: silica, ether/CH_2Cl_2, 1/9) of the product gave two unequal, but well resolved, spots due to the two CTV isomers. No additional impurities were found. The neat saddle isomer was then obtained by chromatographic separation. The columns used (130 cm length, 1.5 cm diameter) were prepared by packing (under a slight pressure) a slurry of a 1:2 mixture of silica 60 (Merck) and Matrex-silica (Amicon Corp., particle size 35−70 My) in chloroform as the mobile phase. A 700 mg sample of the quenched CTV sample was passed through the column, and the fractions enriched with the saddle isomer (which elutes first) were collected. The solvent was evaporated (under pumping at room temperature) and the separation procedure repeated. After the first separation run the product contained 80% of the saddle form and more than 99% after the second run (yield: 105 mg). A ^{1}H NMR spectrum of the final product is shown in Figure 3c.

The saddle isomer can be kept in a refrigerator (as solid or in solution) for months and years. At room temperature, in solution, a saddle/crown equilibrium is established within several days (see below). In the solid state only the crown form is thermodynamically stable, whereas the saddle is metastable. Yet, at room temperature it can survive for long periods. In one experiment a solid saddle sample left at 22 ± 2 °C retained its conformation for 6 months. However, another sample kept under similar conditions was found to have completely transformed to the crown when checked after approximately 4 months. Perhaps traces of impurities catalyze the saddle−crown transformation in the solid state. A DSC thermogram of a neat saddle sample is shown in Figure 2b. It shows a broad exothermic peak at around 160 °C, followed by a melting transition at 232 °C, identical to that of the neat crown. The exothermic peak evidently corresponds to the saddle → crown transformation. This was confirmed by recording the NMR spectra of aliquots taken during the heating cycle. Below 140 °C the spectrum was that of the saddle, and above 180 °C it was entirely that of the crown. Clearly, the driving force for the transformation in the solid is the packing in the solid state. Once a crown molecule occupies a crystal site near other crown molecules it will retain its conformation. On the other hand, if a saddle molecule sublimes from the surface or from a bulk defect, it has a higher probability to recrystallize in the more stable crown form and thus initiate a complete transformation.

Carbon-13 NMR Spectra in Solution and in the Solid State. We have also recorded the carbon-13 NMR spectra of the two isomers in solution, as well as in the solid state. Examples of spectra in chloroform solution (with peak assignment[19,23] are shown in traces a and b of Figure 4. The spectrum of the crown isomer consists of just five peaks, three due to the three types of aromatic carbons and one each due to the ring

methylene and methoxy carbons. The spectrum of the saddle isomer is almost identical to that of the crown. As for the proton NMR, the simplicity of the saddle spectrum is due to the averaging effect of the pseudorotation process.

In contrast to the simple solution spectra, the MAS spectra of the solid isomers (traces c and d of Figure 4) are quite complex. This complexity arises from two effects: molecular distortion which render carbons which are equivalent in solution, nonequivalent in the packed state, and the presence of nonequivalent molecules in the crystalline lattice. Carbon-13 MAS spectra of the crown isomer were published earlier by Burlinson and Ripmeester.[19] Due to possible formation of solvates the spectra depend somewhat on the type of solvent and crystallization method used. Our crown sample was prepared by crystallization from benzene, followed by drying at 185 °C under reduced pressure. The resulting spectrum is similar to that of Burlinson and Ripmeester for samples prepared by a similar procedure and interpreted by them in terms of a crystal structure containing two (distorted) molecules per asymmetric unit. This interpretation stems from the high multiplicity observed for the spectral bands of the different carbons in the molecules. It is best seen in the band due to the methoxy carbons, which exhibits a twelve-line multiplet (eight single peaks and two of double intensity). This can only be explained in terms of two symmetry unrelated and distorted molecules in the crystal. Similar multiplicity of lines is also observed for the aromatic carbons whereas the ring methylene exhibits, as expected, just six lines (four single peaks and one of double intensity). Note the large dispersion of the aromatic C−H carbon band with a well separated peak at 123 ppm. The distortion of the molecule from C_{3v} symmetry apparently results from internal repulsions between the benzene rings and from the difficulty of packing the crown shaped moieties in a crystalline structure. The above result differs from that of Zhang and Atwood[26] who found that CTV crystallized from dry toluene consists of guest-free crystals with a single molecule per asymmetric unit.

Our solid saddle sample was prepared, as described above, by crystallization from chloroform. One would expect its MAS spectrum to be more dispersed than that of the crown due to the conformational nonequivalence of its benzene rings.[23] In fact (see traces c and d in Figure 4), both spectra appear very similar and, except for the methylene carbons, the dispersion of the various bands is even slightly smaller in the saddle than in the crown. Thus, the effect of packing on the carbon-13 chemical shift in solids appears to be at least as important, and perhaps even more important, than that of conformational nonequivalence. At least in the present case, the spectra are therefore not sufficiently characteristic to serve as fingerprints for conformational analysis in the solid state. However, from the structure of the spectrum, in particular the multiplet of the methoxy band (eight single peaks and two of double intensity), we may conclude that the saddle isomer too forms a well ordered crystalline solid with two (distorted) molecules per asymmetric unit.

The Saddle-Crown Equilibrium and Its Interconversion Kinetics

From the results described above it appears that the equilibrium abundance of the saddle isomer in solution is not as minute as generally believed to be. We therefore set up experiments to quantitatively determine the saddle-crown equilibrium constants (K) and interconversion rates (k_1 and k_2) in solution,

$$\text{crown} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{saddle} \qquad K = k_1/k_2 = [\text{saddle}]/[\text{crown}]$$

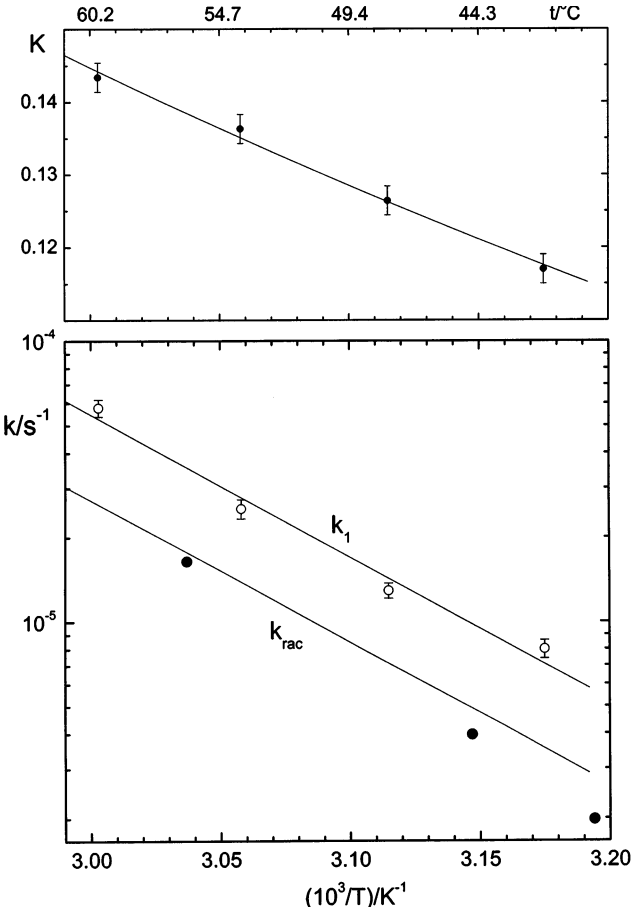

Figure 5. Top: equilibrium constant, K = [saddle]/[crown], as measured from the NMR spectra in chloroform solutions as a function of the inverse absolute temperature. Note that due to the small range of K values a linear, rather than a semilogarithmic, plot is displayed. Bottom: Arrhenius plots of the crown → saddle conversion rate, k_1 (open symbols), as measured from NMR spectra of the type shown in Figure 6 and of the racemization rates, k_{rac}, of chiral CTV-d_9 as measured by Collet and Gabard.[15] The solid symbols are experimental results, and the line near these points corresponds to $k_1/2$.

For the sake of comparison with the racemization process of CTV-d_9 (X = OCH_3, Y = OCD_3, in Figure 1c), which was measured in chloroform solution,[15] we have also measured these parameters in more detail in this solvent. The equilibrium constant was measured at several temperatures in the interval 40−60 °C. A CTV (crown) solution in chloroform (less than 1 wt %) was placed in an NMR tube and inserted into a thermostated hot bath for several hours. The ^{1}H NMR spectrum was recorded (at room temperature), and the measurements were repeated at regular time intervals until no change in the relative intensities of the crown to saddle peaks was observed (4 h at 60 °C and some 26 h at 42 °C). The equilibrium constant was taken as the ratio of the aromatic C−H peak intensities of the two isomers. The results for K, so obtained, are plotted as a function of the inverse absolute temperature in the upper part of Figure 5. Analysis of the results in terms of the equilibrium equation,

$$K = \exp[-(\Delta H - T\Delta S)/RT] \qquad (1)$$

yielded the following thermodynamic parameters, ΔH = 9.96 ± 0.5 kJ mol^{-1}, ΔS = 13.8 ± 1.6 J mol^{-1} K^{-1}.

Extrapolating the equilibrium data to room temperature gives K(300K) ≈ 0.1, i.e., a saddle fraction of ca. 10% of the total

CTV. It is therefore somewhat surprising that the spectrum of the saddle isomer was not observed before, especially in the experiments that were specifically designed to detect it.[11,12] Perhaps the reason lies in unfortunate choice of solvents, where the equilibrium constant is especially small. For example, measurements in dimethylformamide (DMF) gave a considerably lower K value than in chloroform ($\Delta H = 22.3 \pm 1.2$ kJ/mol, $\Delta S = 34 \pm 3.2$ J mol^{-1} K^{-1}, K(300K) ≈ 0.008). It is likely that polar solvents disfavor the saddle form that (on the average over the pseudorotation cycle) is nonpolar, and favor the crown form that has a permanent electric dipole (cf. the ΔH values for chloroform and DMF). The saddle form can also easily be missed if not enough time is allowed for isomerization. The half-life for the crown−saddle equilibration at room temperature is approximately 1 day, so that unless the solution is heated or enough equilibration time is allowed, the saddle form may easily escape detection.

To measure the crown−saddle interconversion rates, k_1 and k_2, we found it more convenient to start with the neat saddle form. A freshly prepared solution was transferred to an NMR tube and placed in the spectrometer's probe head, which was preheated to the desired temperature. After a short thermal equilibration period (a few minutes) spectra were recorded at regular time intervals until about 90% of the reaction elapsed. The approach to equilibrium is governed by the equation,[23]

$$[\Delta(t) - \Delta(\infty)]/[\Delta(0) - \Delta(\infty)] = \exp(-kt) \qquad (2)$$

where $k = k_1 + k_2 = k_1(1 + 1/K)$, and $\Delta(x) = [\text{crown}](x) - [\text{saddle}](x)$ is the difference in the concentration of the crown and saddle isomers at time x ($x = 0$ at the beginning of the experiment and $x = \infty$ at equilibrium). The Δ values were derived from the aromatic C−H signals and the results analyzed according to eq 2. Examples of ^{1}H NMR spectra (recorded at 315 K) and corresponding plots, for all temperatures measured, are shown in Figures 6 and 7, respectively. An Arrhenius plot for k_1 is shown in the bottom part of Figure 5.

Analysis of these results in terms of Eyring's absolute rate theory,

$$k_1 = A \exp(-E_a/RT) = (\kappa k_B T/h) \exp[-(\Delta H^* - T\Delta S^*)/RT] \qquad (3)$$

(where the symbols have their usual meaning)[27] and taking a transmission coefficient, $\kappa = 1$, yielded the following kinetic parameters for k_1,

$$E_a = 97.4 \pm 4.8 \text{ kJ mol}^{-1} \qquad \log[A\ (\text{s}^{-1})] = 11.0 \pm 0.8$$
$$\Delta H^* = 94.9 \pm 4.8 \text{ kJ mol}^{-1}$$
$$\Delta S^* = -43.5 \pm 15.0 \text{ J mol}^{-1} \text{ K}^{-1}$$

The results of Figures 5 can be summarized in terms of the energy potential diagram of Figure 8. A similar diagram was presented by Garcia and Collet[17] in their discussion of the racemization process of cyclotriveratrylenes with C_3 symmetry. The diagram shows the relative enthalpy of the saddle and crown (in chloroform) and the huge barrier to their interconversion. The right and left global minima correspond to the right and left chiral crown enantiomers of CTV (CTV-d_9). The center undulating part of the diagram corresponds to the various degenerate saddle conformers. They are discussed in a separate section below.

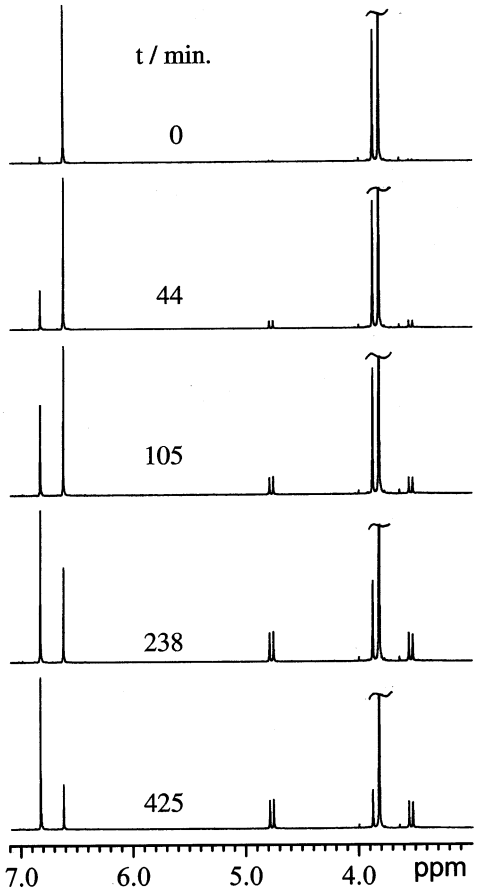

Figure 6. ^{1}H high-resolution NMR spectra of a freshly prepared solution of the saddle isomer in chloroform as a function of time after thermal equilibration at 315 K. To clearly display the weak lines in the spectra, the strong methoxy signals were truncated.

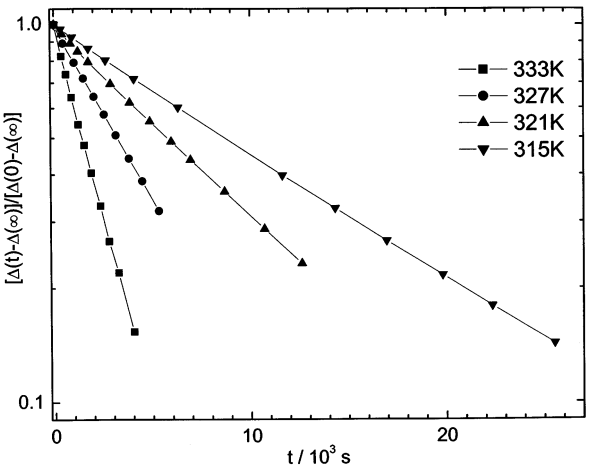

Figure 7. Plots of the approach-to-equilibrium-parameter, $[\Delta(t) - \Delta(\infty)]/[\Delta(0) - \Delta(\infty)]$, as a function of the equilibration time, t (eq 2). The different plots correspond to different temperatures, as indicated. The peak intensities were derived from spectra of the type shown in Figure 6.

Assuming that the racemization of structurally chiral cyclotriveratrylenes proceeds via the saddle form, this diagram also applies to this process and establishes a simple relation between the rate constants of the two reactions. Specifically, we shall refer to the racemization of the optically active CTV-d_9 (Figure 1c with X = OCH_3, Y = OCD_3). This reaction was studied by Collet and Gabard,[15] and their results for the racemization rate,

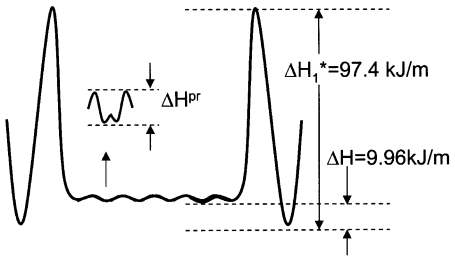

Figure 8. Potential energy profile for the saddle and crown isomers of CTV as derived from the analysis of the data in Figure 5. The two absolute minima correspond to the two crown enantiomers of chiral CTV-d_9. The six local minima correspond to the average saddle conformers. The insert is a vertical expansion for one of these minima; the maximum at its center corresponds to the unstable C_s structure, and the two flanking minima correspond to the stable twisted conformers. The various ΔH's are defined in the text.

k_{rac}, are included in Figure 5. The kinetic parameters derived by them are

$$E_a = 110.9 \pm 2.1 \text{ kJ mol}^{-1} \qquad \log[A\ (\text{s}^{-1})] = 12.8 \pm 0.4$$
$$\Delta H^* = 108.4 \pm 2.1 \text{ kJ mol}^{-1}$$
$$\Delta S^* = -8.0 \pm 8.4 \text{ J mol}^{-1}\text{ K}^{-1}$$

Comparing the measured values of k_{rac} and k_1, we note that they very nearly obey the relation $k_{rac} = 1/2k_1$, as would be expected from the potential diagram in Figure 8**.** We recall that the lifetime in the saddle form is $\tau = 1/k_2$, which is on the order of hours. During this period it undergoes billions of pseudorotation cycles, so that when it reconverts to the crown form it has a probability of one-half to end up in the opposite chirality of its starting configuration, i.e., $k_{rac} = {}^1/_2k_1$, as observed experimentally. We consider this agreement as a proof that the racemization of structurally chiral tribenzocyclononatriene derivatives indeed proceeds via the saddle form.

Structure of the Saddle Isomer and the Pseudorotation Process

As already mentioned, the minimum-energy conformation of the saddle form is not the symmetric (C_s) structure (shown in Figure 1b). In reality, it acquires a twisted conformation to reduce the repulsive interaction between the inner methylene hydrogen and the para-positioned benzene ring. A force field calculation (using the Insight and Discover modules of Accelrys Inc., San Diego, CA) shows that the minimum-energy structure of the twisted form actually has C_2 symmetry (or very nearly so) with the C_2 axis bisecting one of the side benzene rings and passing through the opposite methylene carbon. There are two such structures corresponding to a right and a left twist, as shown in the top of Figure 9. The insert in Figure 8 shows an enlarged section around one of the pseudorotating saddle conformers. The center maximum corresponds to the (unstable) symmetric C_s structure and the two flanking minima to the corresponding right and left twisted conformers. The barrier separating between these two minima is extremely low and, hence the switching between them may be viewed as a large amplitude librational motion. In the following we therefore consider just the six average conformations (with average C_s symmetry) obtained by successively flipping each benzene ring alternately "up" and "down" (instead of the twelve twisted conformations). This "reduced" pseudorotation cycle is shown in the bottom part of Figure 9. The six entries correspond (from top clockwise) to the red, green, and blue benzene rings having the following relative orientations; udd, udu, ddu, duu, dud, uud,

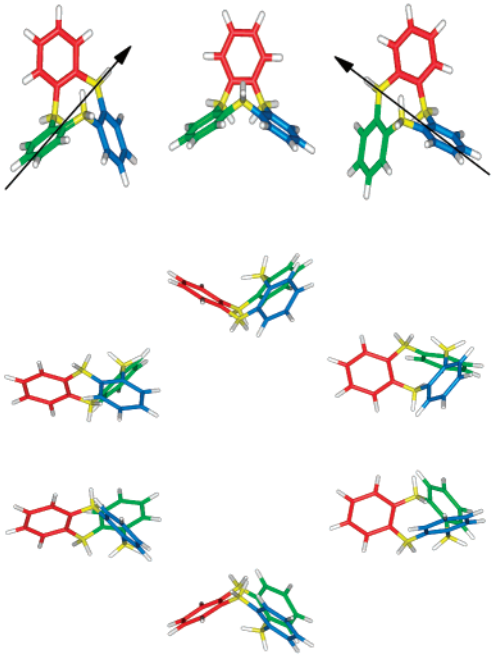

Figure 9. Top: structures of the unstable (C_s symmetry) saddle form (center) and the corresponding right and left twisted stable conformations (C_2 symmetry) (right and left sides). The C_2 axes in both forms are indicated. Bottom: (reduced) pseudorotation cycle of the saddle isomer. Each entry corresponds to an average of a right and left twisted conformer (hence having C_s symmetry). The six entries correspond to the red, green, and blue benzene rings pointing to (from top clockwise) udd, udu, ddu, duu, dud, and uud, where u and d stand for "up" and "down", respectively.

where u and d stand for "up" and "down", respectively. In reality, each entry corresponds to a rapidly interconverting pair of right and left twisted conformers.

To check whether the pseudorotation can be frozen out (or rather slowed to the dynamic NMR regime), we recorded the ^{1}H and carbon-13 spectra of the saddle isomer dissolved in Freon at very low temperatures. This method, first devised by Denisov, Golubev, and co-workers[28,29] consists of synthesizing Freon gas mixtures (CDF_2Cl/CDF_3) from $CDCl_3$ at high pressure and using them, after liquefaction, as low temperature solvents. The samples are prepared using standard vacuum manifolds to which the NMR tubes (equipped with Teflon needle valves, Wilmad, Buena) are attached. With this technique, the slow exchange regime has been reached for various hydrogen bond exchange reactions that are extremely fast at room temperature.[30] For the present measurements we used a Freon solvent consisting of a 1/3 mixture CDF_2Cl/CDF_3. No changes in the structure of the ^{1}H or carbon-13 spectra were observed down to almost 100 K. Some line broadening set in (in both the solute and solvent lines) on cooling to below 120 K, but the broadening was traced back to an increase in the solvent viscosity rather than to slowing down of the pseudorotation. It is therefore safe to assume that the residual exchange broadening, $(1/T_2)_{ex}$, at 120 K does not exceed 1 s^{-1}. From this a lower limit for the pseudorotation rate at 120 K can be calculated using the fast exchange line width equation,[31]

$$(1/T_2)_{ex} = M_2\tau = {}^1/_3(2\pi\nu_L)^2\tau\Sigma_i(\delta_i - \langle\delta\rangle)^2 \qquad (4)$$

where M_2 is the second moment of a particular type of carbon-13, ν_L is the Larmor frequency (125 MHz in the present case), and the δ_i are the chemical shifts of the carbons in the three rings of the saddle conformer. From ref 23 these range up to

about 5 ppm, yielding a lower limit of $1/\tau \sim 10^6$ to 10^7 s^{-1}. The rate is, of course, much faster at room temperature. From this result and eq 3, we estimate an upper limit for the potential barrier for this process (indicated as ΔH^{pr} in Figure 8) of 13−15 kJ/mol. The actual value is most likely much smaller.

Finally, we remark on the relatively high positive equilibrium entropy, ΔS, derived from the analysis of the equilibrium results (eq 1). It is about +14 and +34 J mol^{-1} K^{-1} in chloroform and DMF, respectively, and appears to be dominated by the high flexibility of the saddle form with its twelve local minima in the pseudorotation cycle (compared to the stiff crown form). This effect alone contributes to ΔS the amount $R \ln(12) = 20.7$ J mol^{-1} K^{-1}. Clearly, additional solvent dependent effects, with either positive or negative signs, also contribute.

Summary and Conclusions

The synthesis of CTV always leads, after purification, to the thermodynamic stable crown isomer. We have shown that, contrary to the generally accepted view, in solutions of CTV non-negligible amounts of the saddle isomer may be formed by isomerization. The activation energy for the crown−saddle interconversion is, however, rather high so that the equilibration time at room temperature is of the order of days. Consequently, the formation of the less stable saddle can easily escape detection unless sufficient equilibration time is allowed. Also, the equilibrium constant is solvent dependent, with the saddle form disfavored in more polar solvents. By quenching the melt or hot solutions of CTV, we were able to trap the high-temperature isomeric equilibrium and thus produce macroscopic quantities of its saddle form. The thermodynamically less stable saddle isomer could then be separated chromatographically at room temperature and its equilibrium and kinetic parameters studied. Preliminary measurements showed that other cyclotriveratrylenes, for example, in which the side groups consist of acetoyloxy or long alkanoyloxy as well as alkyloxy chains exhibit similar behavior. The saddle forms of these compounds constitute new homologous series that merit further investigation.

Acknowledgment. We thank Dr. Miriam Eisenstein for calculating the minimum-energy conformations of the saddle form and for computer-drawing of Figure 9.

References and Notes

(1) Collet, A. *Tetrahedron* **1987**, *43*, 5725−5759.

(2) Garcia, C.; Andraud, C.; Collet, A. *Supramol. Chem.* **1992**, *1*, 31−45.

(3) Collet, A. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Eds.; Pergamon: Oxford, U.K., 1996; Vol. 6, pp 281−303.

(4) CTV was first synthesized via the acid-catalyzed condensation of veratryl alcohol by Mrs. Gertrude Maud Robinson (the first wife of Sir Robert Robinson) in 1915.[5] On the advice of her husband and despite some evidence to the contrary,[6] she identified the compound as the veratryl dimer (tetramethoxy-dihydroanthracene). Thirty seven years later, in 1952, Oliverio and Casinovi[7] reinvestigated Robinson's compound, challenged the dimer hypothesis and proposed, instead, again erroneously, a cyclic hexameric structure. This structure lasted for some 10 years until in 1963 Lindsey published the now generally accepted trimer formula (hexamethoxy-tribenzocyclononene) for the compound.[8] He also proposed the crown structure and coined its colloquial name, cyclotriveratrylene. Lindsey's structure was soon confirmed using new X-ray measurements, molecular weight determination, mass spectrometry, and NMR spectroscopy by a number of independent researchers, some of whom without knowledge of Lindsey's work.[9−12]

(5) Robinson, G. M. *J. Chem. Soc*. **1915**, *107*, 267−276.

(6) Robinson, R. In *Memories of a minor prophet*; Elsevier: Amsterdam, 1976; Vol. 1, pp 51−54.

(7) Oliverio, A.; Casinovi, C. *Ann. Chim. (Rome)* **1952**, *42*, 168−184.

(8) Lindsey, A. S. *Chem. Ind. (London)* **1963**, 823−824. Lindsey, A. S. *J. Chem. Soc*. **1965**, 1685−1692.

(9) Erdtman, H.; Haglid F.; Ryhage, R. *Acta Chem. Scand*. **1964**, *18*, 1249−1254.

(10) Goldup, A.; Morrison, A. B.; Smith, G. W. *J. Chem. Soc.* **1965**, 3864−3865.

(11) Miller, B.; Gesner, B. D. *Tetrahedron Lett.* **1965**, 3351−3354.

(12) Cookson, R. C.; Halton, B.; Stevens, D. R. *J. Chem. Soc. B* **1968**, 767−774.

(13) Lüttringhaus, A.; Peters, K. C. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 593−594.

(14) Collet, A.; Jacques, J. *Tetrahedron Lett.* **1978**, 1265−1268.

(15) Collet, A.; Gabard, J. *J. Org. Chem.* **1980**, *45*, 5400−5401.

(16) Canceill, J.; Collet, A.; Gottarelli, G. *J. Am. Chem. Soc*. **1984**, *106*, 5997−6003.

(17) Garcia, C.; Collet, A. *Bull. Soc. Chim. Fr*. **1995**, *132*, 52−58.

(18) Lesot, P.; Melet, D.; Sarfati, M.; Courtieu, J.; Zimmermann, H.; Luz, Z. *J. Am. Chem. Soc*. **2002**, *124*, 10071−10082.

(19) Burlinson, E.; Ripmeester, J. A. *J. Inclusion Phenom*. **1984**, *1*, 403−409.

(20) Steed, J. W.; Zhang, H.; Atwood, J. L. *Supramol. Chem.* **1996**, *7*, 37−45.

(21) Zimmermann, H.; Poupko, R.; Luz, Z.; Billard, J. *Z. Naturforsch*. **1985**, *40A*, 149−160.

(22) Malthête, J.; Collet, A. *Nouv. J. Chim*. **1985**, *9*, 151−153.

(23) Zimmermann, H.; Bader, V.; Poupko, R.; Wachtel, E. J.; Luz, Z. *J. Am. Chem. Soc*. **2002**, *124*, 15286−15301.

(24) Collet, A.; Dutasta, J.-P.; Lozach, B.; Canceill, J. *Top. Curr. Chem.* **1993**, *165*, 103−129.

(25) (a) Anet, F. A. L.; Squillacote, M. *J. Am. Chem. Soc.* **1975**, *97*, 3243−3244. (b) Squillacote, M.; Sheridan, R. S.; Chapman, O. L.; Anet, F. A. L. *J. Am. Chem. Soc.* **1975**, *97*, 3244−3246.

(26) Zhang, H.; Atwood, J. L. *J. Cryst. Spectrosc. Res.* **1990**, *20*, 465−470.

(27) Martin, M. L.; Martin, G. J.; Delpuech, J.-J. *Practical NMR Spectroscopy*; Heyden: London, 1980; p 339.

(28) Denisov, G. S.; Bureiko, S. F.; Golubev, N. S.; Tokhadze, K. G. In *Molecular Interactions*; Ratajczak, H., Orville-Thomas, W. J., Eds.; John Wiley: New York, 1981; Vol. 2, pp 107−141.

(29) (a) Golubev, N. S.; Denisov, G. S.; Smirnov, S. N.; Shchepkin, D. N.; Limbach, H. H. *Z. Phys. Chem*. **1996**, *196*, 73−84. (b) Shenderovich, I. G.; Burtsev, A. P.; Denisov, G. S.; Golubev, N. S.; Limbach, H. H. *Magn. Reson. Chem*. **2001**, *39*, S91−S99.

(30) (a) Shenderovich, I. G.; Limbach, H. H.; Smirnov, S. N.; Tolstoy, P. M.; Denisov, G. S.; Golubev, N. S. *Phys. Chem. Chem. Phys.* **2002**, *4*, 5488−5497. (b) Shenderovich, I. G.; Tolstoy, P. M.; Golubev, N. S.; Smirnov, S. N.; Denisov, G. S.; Limbach, H. H. *J. Am. Chem. Soc.* **2003**, *125*, 11710−11720.

(31) Piette, L. H.; Anderson, W. A. *J. Chem. Phys*. **1959**, *30*, 890−908.