in 200 mL of benzene was treated with 0.5 mL of concentrated H_2SO_4 at room temperature. Over a 1-h period the temperature of the solution was gradually raised to reflux. Refluxing was maintained until water, collected in a Dean–Stark trap, ceased to separate (ca. 3 h). The cooled solution was washed with $NaHCO_3$ solution. The aqueous wash was extracted once with ether. The combined organic solutions were dried (Na_2SO_4), concentrated under reduced pressure, and then distilled.

4,4,5-Trimethyl-2-cyclohexen-1-one. A mixture of 61 mL (0.75 mol) of isobutyraldehyde and 47 mL (0.48 mol) of 3-penten-2-one was treated with 0.5 mL of concentrated H_2SO_4 and then warmed slowly to reflux. Unlike the condensation with methyl vinyl ketone, no initial exotherm was noted. In fact, NMR spectra revealed that the starting materials were consumed gradually throughout the course of the reaction. Removal of water via reflux through a Dean–Stark trap required 16 h. Considerably more than the theoretical amount of water was collected. Distillation of the mixture at reduced pressure followed by redistillation of the product gave 24 g (36% yield) of material with a slightly broad boiling range but which appeared by NMR to be relatively clean: NMR ($CDCl_3$) δ 1.0 (br m, 5-H), 1.0 (s, 3 H, 4-CH_3), 1.1 (d, J = 7 Hz, 3 H, 5-CH_3), 1.2 (s, 3 H, 4-CH_3), 2.3 (br m, 6-H's), 5.8 (d, J = 10 Hz, 1 H, 3-H), 6.7 (d, J = 10 Hz, 1 H, 2-H).

Registry No. 1 (R = Me; R′ = Me), 78-84-2; 1 (R = Me; R′ = Et), 96-17-3; 1 (R = Et; R′ = Et), 97-96-1; 1 (R = Me; R′ = Ph), 93-53-8; 1 (R,R′ = $-(CH_2)_5-$), 2043-61-0; 2 (R″ = H), 78-94-4; 2 (R″ = Me), 3102-33-8; 3 (R = Me; R′ = Me; R″ = H), 1073-13-8; 3 (R = Me; R′ = Et; R″ = H), 17429-32-2; 3 (R = Et; R′ = Et; R″ = H), 35161-14-9; 3 (R,R′ = $-(CH_2)_5-$; R″ = H), 30834-42-5; 3 (R = Me; R′ = Me; R″ = Me), 17429-29-7; 3 (R = Me; R′ = Ph; R″ = H), 17429-36-6.

Optically Active (C_3)-Cyclotriveratrylene-d_9. Energy Barrier for the "Crown to Crown" Conformational Interconversion of Its Nine-Membered-Ring System

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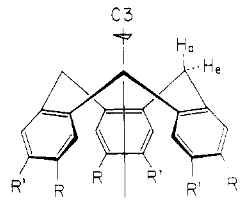
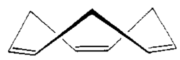
It has been widely accepted[1–5] that cyclotriveratrylene[6] (CTV) 1 exists as a single rigid "crown" conformer having C_{3v} symmetry.[7–10] The invariance of the ^1H NMR spectrum of 1 over a temperature range up to 200 °C[2] and the resolution of several of its derivatives into enantiomers which are optically stable at room temperature[11,12] indicate that the inversion barrier is greater than 23 kcal·mol^{-1}. However, evidence that ring inversion may occur on heating has recently been reported.[12] In this paper, we describe the synthesis of optically active (C_3)-cyclotriveratrylene-d_9, 2, and the determination of its thermal optical stability. We conclude that the activation energy for the conformational "crown to crown" interconversion process (which leads to racemization) is 26.5 kcal·mol^{-1}.

Reaction of optically pure triphenols (+)- and (−)-3, previously described,[12] with excess 99.6% deuterated methyl-d_3 iodide and 25% aqueous sodium hydroxide in HMPA at room temperature[13] afforded the desired (+)- and (−)-2, respectively. Although the methylation appeared complete within a few minutes (as indicated by TLC), all preparative runs were carried out by using longer times (3 to 16 h) so as to ensure that the last traces of phenolic material were consumed. Conventional workup (see Experimental Section) followed by thin-layer or column chromatography on silica gel afforded samples of (+)- and (−)-2 having optical rotations in the range of $[\alpha]^{25}_D$ 3.0 to 3.4 ± 0.2° (in chloroform). In order to ascertain that contamination with a trace of 3 (i.e., 1.3%) or of incompletely methylated phenolic products was not responsible for these rotations, a sample having $[\alpha]^{25}_D$ +3.1 ± 0.2° was chromatographed over basic alumina; 91% was recovered, with $[\alpha]^{25}_D$ +3.0 ± 0.2°. A control experiment showed that CTV 1, contaminated with 1.3% (+)-3, was completely cleaned of this impurity by passage through basic alumina. Additionally, the latter sample of (+)-2 was recrystallized from benzene to give a clathrate[7] [(+)-2, 0.5 C_6H_6, ca. 2 H_2O]; once desolvated this product again exhibited $[\alpha]^{25}_D$ +3.0 ± 0.2°.



1 R = R′ = OCH_3
2 R = OCH_3 R′ = OCD_3
3 R = OCH_3 R′ = OH


4

Optical rotations of (+)- and (−)-2 in the visible region are among the highest values previously reported for chirality due to isotopic substitution.[14,15] Compound (+)-2 shows a comparatively[15] strong circular dichroism consisting of an exciton couplet (276 nm, $\Delta\epsilon$ −0.23; 297 nm, $\Delta\epsilon$ +0.26) which remained unchanged at each step of the purification process described above. A detailed discussion

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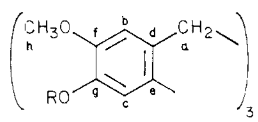
Table I. ^{1}H NMR Spectral Data[19] [δ (Me_4Si) in $CDCl_3$]

	aromatics	H_a^{a}	H_e^{a}	OCH_3	OR
1	6.82	4.75	3.54	3.82	
(+/–)-2	6.82	4.76	3.54	3.83	
(+/–)-3	6.87, 6.77	4.70	3.47	3.83	OH ca. 5.4

^{a} AB (nearly AX) quartet for H_a, H_e with ^2J = 14 Hz.

Table II. ^{13}C NMR Spectral Data[19] [δ (Me_4Si) in $CDCl_3$]^a



	a	b, c	d, e	f, g	h
1	36.3	113.2	131.7	147.7	55.9
(+/–)-2	36.4	113.2	131.7	147.7	56.0
(+/–)-3	35.2	112.7, 115.9	130.0, 131.8	144.2, 145.3	55.5

^{a} For 3, in $CDCl_3$/Me_2SO-d_6 (5:1).

of the CD and absolute configuration of 2 will be forthcoming.

The mass spectrum of (–)-2 exhibits a molecular ion peak at m/e 459 (corresponding to $C_{27}H_{21}D_9O_6$). Other peaks indicate loss of 15, 31 (OCH_3), 34 (OCD_3), 141, and 154 mass units. This fragmentation mode is quite similar to that of 1 discussed earlier by Erdtman et al.[1] The deuterium content in 2 was estimated by comparing the relative intensities of peaks M and M – 1 in the mass spectra of 1 and 2 recorded under the same experimental conditions; we conclude that >97% of the molecules in 2 contain nine deuterium atoms. No evidence was found for the presence of residual 3 (m/e 408) or of monophenol (m/e 442) in the sample examined ($[\alpha]^{30}_D$ –3.4°).

Tables I and II summarize NMR data for compounds 1, 2, and 3. The ^{1}H and ^{13}C NMR spectra of 1 and of (+)- or (–)-2 display practically identical chemical shifts. The actual incorporation of three OCD_3 groups in 2 is evidenced by the integration ratio of the OCH_3 peak in the ^{1}H spectrum; however, we were unable to detect the $O^{13}CD_3$ multiplet in the proton-decoupled ^{13}C spectrum of 2.

It appears that (+)- or (–)-2 is relatively easily racemized on moderate heating. The racemization of (+)-2 was followed polarimetrically at 365 nm in chloroform solution. From the first-order rate constants of the ring interconversion process, i.e., (+) → (–), the following activation parameters were derived: E_a = 26.5 ± 0.5 kcal·mol^{-1}, A = (7 ± 5) × 10^{12}; $\Delta G^{\ddagger}_{25}$ = 26.5 ± 0.1 kcal·mol^{-1}, with $\Delta H^{\ddagger}$ = 25.9 ± 0.5 kcal·mol^{-1} and $\Delta S^{\ddagger}$ = –1.9 ± 2 eu. The calculated lifetimes ($t_{1/2}$) for racemization, i.e., (+) → (±), are of the order of 960 days, 36 days, and 3 min at 0, 20, and 100 °C, respectively. The estimated rate constant at 200 °C ($k \simeq 4$ s^{-1}) is small with respect to the NMR frequency difference of the exchanging sites $H_a \rightleftharpoons H_e$ ($\Delta\nu$ = 75 Hz at 60 MHz); this is consistent with the earlier observations which show the invariance of the ^{1}H NMR spectra of CTV[2] and its analogues[8e] upon heating.

For the parent ring system *cis,cis,cis*-1,4,7-cyclononatriene (4), the preferred conformation is also a crown, with activation parameters for ring inversion in the range of 10–15 kcal·mol^{-1}, from dynamic NMR measurements.[16] Two mechanisms have been postulated to explain the "crown to crown" interconversion of 4 and of CTV and its analogues.[17] In the former, inversion of a crown occurs through a readily pseudorotating "saddle" form obtained by flipping one of the benzene rings (or one cis double bond for 4),[8g,16c] whereas the latter consists of a one-step concerted process with a planar transition state.[16b] We are, at present, working on the synthesis of other optically active CTV-type compounds for various reasons,[18] including the obtention of additional information on their conformational behavior.

Experimental Section

In order to prevent racemization, all reactions and subsequent workup involving chiral CTV derivatives must be carried out at or below room temperature. Polarimetric measurements, including kinetic experiments, were carried out with a Perkin-Elmer 241 automatic polarimeter, using spectrometric-grade chloroform (Merck Uvasol) as solvent. Melting points, with simultaneous check of purity, were recorded on a Perkin-Elmer DSC2 microcalorimeter. Circular dichroism spectra (in dioxane) were recorded independently on a Jouan-Dichrograph III and on a Jasco J-500A spectropolarimeter; we are grateful to J. Bolard and to G. Gottarelli, respectively, for these measurements.

10,15-Dihydro-3,8,13-trimethoxy-2,7,12-tris(methoxy-*d*$_3$)-5*H*-tribenzo[*a,d,g*]cyclononene, (+)-2. The triphenol (+)-3, $[\alpha]^{30}_D$ +253° (in $CHCl_3$; ee >90%), has been described.[12] According to the procedure described by Shaw et al.,[13] a slurry of (+)-3 (100 mg) and HMPA (4 mL) was stirred at 20 °C under N_2 with 0.19 mL of a 25% aqueous NaOH solution (50% excess), until complete dissolution occurred (ca. 30 min). To the pale orange-yellow solution was added 99.6% deuterated ICD_3 (0.25 mL; 5-fold excess), which resulted in an immediate change of the color to pale yellow. At the end of 2 h, crystallization of 2 occurred. After 3 h, the mixture was poured into ice and extracted with CH_2Cl_2. The organic layer was washed with 1 N NaOH and then with water until neutral. Finally, it was again washed with 0.5 N HCl and then with water, dried over Na_2SO_4, and evaporated to dryness under vacuum, without heating. The crude product, which was contaminated with HMPA, was chromatographed on a column loaded with 10 g of silica gel 60 (230–400 mesh, Merck), using ethyl acetate/hexane (6:4) as an eluant; 75 mg (67%) of 2, homogeneous by TLC, were obtained, exhibiting $[\alpha]^{25}_D$ +3.1° (29.15 mg in 1.40 mL of $CHCl_3$; reading +0.065°). This product (70 mg) was chromatographed over 10 g of basic alumina (aluminiumoxid 90, activity II–III, 70–230 mesh, Merck), using pure CH_2Cl_2 as an eluant; the recovered sample (64 mg) had $[\alpha]^{25}_D$ +3.0° (24.50 mg in 1.30 mL of $CHCl_3$; reading +0.057°). Finally, 60 mg of the above sample was recrystallized from benzene, without heating, to yield 55 mg of a clathrate (from ^{1}H NMR, see text). The latter (46 mg) was desolvated under 10^{-2} torr for 12 h to give 40 mg of (+)-2, $[\alpha]^{25}_D$ +3.0°, $[\alpha]^{25}_{578}$ +3.2° $[\alpha]^{25}_{546}$ +3.7°, $[\alpha]^{25}_{436}$ +7.7°, $[\alpha]^{25}_{365}$ +16.6° (26.35 mg in 1.30 mL of $CHCl_3$; estimated error range ±5%). The product showed a sharp melting point (with subsequent decomposition) at 229 °C.

Control Experiment. Cyclotriveratrylene 1 (75 mg) was contaminated with ca. 1 mg of (+)-3 so as to obtain a specific rotation $[\alpha]^{25}_D$ +3.0° (in $CHCl_3$). This mixture was chromatographed over basic alumina as described above. The product recovered (66 mg) was found optically inactive from 589 to 365 nm (25.50 mg in 1.30 mL of $CHCl_3$; observed rotations 0.000 ± 0.001°).

Kinetic Experiments. The following first-order rate constants (k) corresponding to the process (+) → (–) were measured (T in K, ±0.1): 313.1, k = 1.98 × 10^{-6} s^{-1}; 317.8, k = 3.96 × 10^{-6} s^{-1}; 329.3, k = 1.64 × 10^{-5} s^{-1}. Linear regressions of $k = A \exp(-E_a/RT)$ and of $k = RT/Nh \exp(-\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R)$ were computed from standard programs (HP 85 calculator).

Registry No. 1, 1180-60-5; (+)-2, 75399-69-8; (–)-2, 75399-70-1; (+)-3, 68198-62-9; (–)-3, 68182-93-4.

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(18) These compounds are of interest for their circular and linear dichroism properties and for the synthesis of new chiral cryptates.

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