J. Am. Chem. Soc. 1982, 104, 6040–6045

Chair–Boat Conformational Equilibrium in (+)-(1S,5R)-1,8,8-Trimethylbicyclo[3.2.1]octan-3-one

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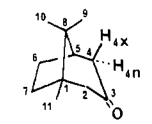
Received March 1, 1982

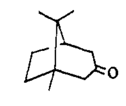
Abstract: The title ketone (**1**), prepared from α-campholenic acid, exhibited temperature-dependent circular dichroism spectra in methylcyclohexane–isopentane for its n → π* transition. At room temperature, the Cotton effect was bisignate [(+) near 280 nm, (–) near 330 nm], but at –180 °C it was essentially completely negative. Analysis of the data suggests that in hydrocarbon solvent at room temperature about 20% of a boat or boatlike conformer is present with about 80% of a slightly flattened chair conformer. Analysis of the ^{1}H NMR H\|H vicinal coupling constants leads to the prediction that the title compound in $CDCl_3$ assumes a chair cyclohexanone conformation with ring flattening near the C=O group, a conclusion supported by molecular mechanics calculations. The latter calculations yield an optimized geometry for 4-*tert*-butylcyclohexanone that is nearly the same as the one from X-ray crystallographic measurements but without as much flattening of the six-membered ring.

Work on the octant rule for optically active ketones[1,2] has been concerned, inter alia, with determining signed values of perturbing groups.[3-5] For example, it has been found repeatedly[4-7] that β-equatorial methyl or other alkyl groups (and even electronegative groups, except fluorine) are normal, consignate perturbers when the octant rule is applied to cyclohexanones. Indeed, numerous examples drawn from studies with substituted cyclohexanones, decalones, perhydrophenanthrenones, and steroids support that generalization.[5,8] In particular, investigations of conformationally restricted or immobile model ketones, which have a β-equatorial (methyl) group as the lone dissymmetric perturber, provide convincing supporting evidence. The latter include 4(e)-methyladamantanone[6] and 2(*endo*)-methyl-7-norbornanone.[7] We add further insight into understanding the octant contributions of β-equatorial methyl groups on cyclohexanone systems with the following conformational analysis of (+)-(1*S*,5*R*)-1,8,8-trimethylbicyclo[3.2.1]octan-3-one (**1**),[9] a ketone that would be achiral if the β-equatorial C_{11} methyl group were replaced by hydrogen (Chart I).

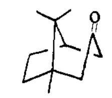
Chart I



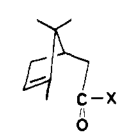
1-C



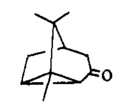
1-S



1-B



2: X = OH
3: X = Cl
4: X = CHN_2
5: X = CH:



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Synthesis and Stereochemistry

The starting material for the preparation of **1** was optically pure (+)-camphorsulfonic acid monohydrate, $[\alpha]^{20}_D$ +19.9° (*c* 2, H_2O), which was converted easily to (+)-α-campholenic acid (**2**) by treatment with molten potassium hydroxide.[10] The diazo ketone (**4**)[9] of **2**, prepared by reaction of acid chloride **3** with diazomethane, was converted to tricyclic ketone **6**, presumably via keto–carbene intermediate **5**[11] formed by reaction with copper powder. Treatment of **6** with lithium in liquid ammonia led to cyclopropyl ring opening and formation of **1**.

Results and Discussion

The circular dichroism (CD) and ultraviolet (UV) data for **1** are given in Figures 1 and 2. Application of the octant rule[1,2] to **1** with the expected chair cyclohexanone conformation leads to the prediction of a moderately intense (–) n → π* Cotton effect (CE) (Figure 3). We do, in fact, observe a (–)-CE for **1** at room temperature (see Figure 1) in methanol and in chloroform solvents, with Δε values ($\Delta\epsilon_{295}$ = –0.16 in methanol and $\Delta\epsilon_{300}$ = –0.13 in chloroform) noticably reduced when compared with the predicted values for (–)-(3*S*(e))-methylcyclohexanone ($\Delta\epsilon_{292}$ = –0.55, –0.6, EPA)[12] and the observed value for (–)-(1*R*,3*S*,4*S*(e))-methyladamantan-2-one[6] ($\Delta\epsilon_{295}$ = –0.67, EPA)[13] —all of the same absolute configuration. However, the CD spectrum of **1** in *n*-heptane solvent (Figure 1) is strikingly different. Not only is the CD curve mainly *positive* for the n → π* transition at room temperature but there is considerable fine structure on the long-wavelength side (vibrational spacing = 1075 cm^{-1}). Bisignate CD curves with an apparent "antioctant" or dissignate behavior have *not* heretofore been observed with the principal reference model compounds in hydrocarbon solvent: (–)-(1*R*,3*S*,4*S*(e))-methyladamantan-2-one[6] ($\Delta\epsilon_{305}$ = –0.54, methylcyclopentane–isopentane)[13] and (–)-(1*S*,4*R*,2*S*(*endo*))-methyl-7-norbornanone ($\Delta\epsilon_{305}$ = –0.6, isopentane).[7] Bisignate curves do occasionally show up in CD spectra of ketones[14-17] and have been ascribed both to conformational equilibria and to asymmetric solvation. We initially surmised that the observed room temperature CD of **1** in *n*-heptane was due to a mixture of conformers involving the chair cyclohexanone moiety (**1–C**) and (the less stable) boat (**1-B**). The octant rule predicts a (–)-CE for **1-C** and a (+)-CE for **1-B**, but only a very weak (+)-CE for a third conformer, **1-S** (sofa[18]), see Figure 3. In an

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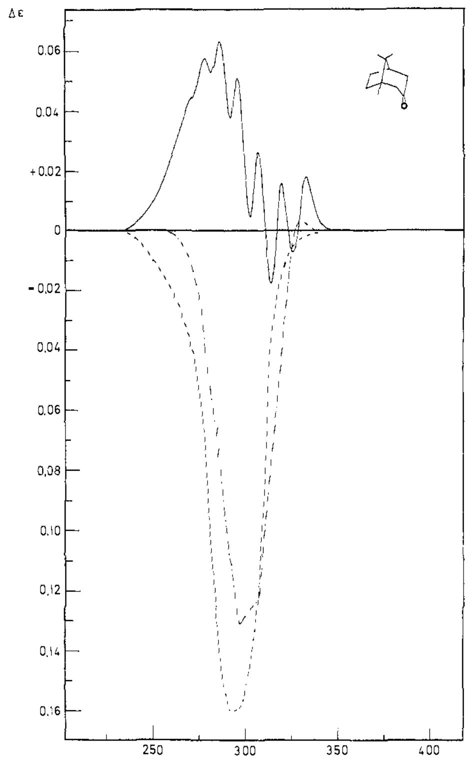

Figure 1. Room temperature circular dichroism spectra of (+)-(1S,5R)-1,8,8-trimethylbicyclo[3.2.1]octan-3-one (**1**) n-heptane (—), chloroform (-•-) and methanol (---). Concentrations are: 0.013 M (n-heptane), 0.0074 M (chloroform), and 0.0016 M (methanol).[38]

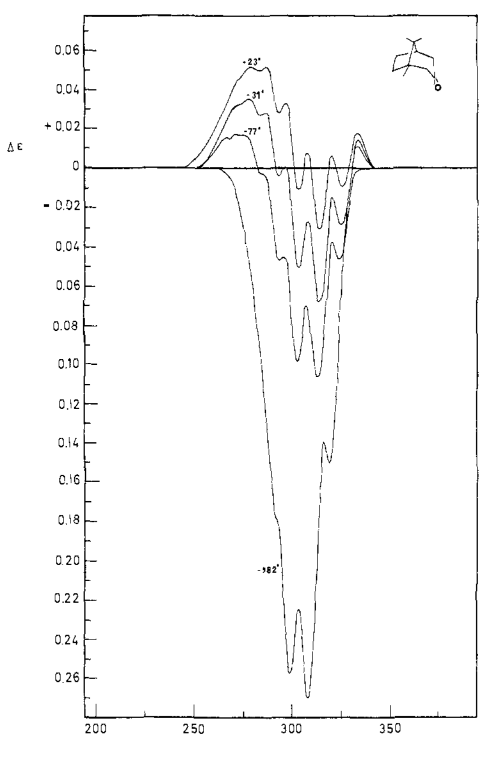

Figure 2. Variable-temperature circular dichroism spectra of 0.0050 M (+)-(1S,5R)-1,8,8-trimethylbicyclo[3.2.1]octan-3-one (**1**) in methylcyclohexane–isopentane (4:1, v/v). Temperatures in °C are indicated on the curves.

attempt to explore the equilibrium, we measured the CD spectra at low temperatures.

The variable-temperature CD spectra of **1** (Figure 2) in methylcyclohexane–isopentane (v/v) were most revealing. The curves became increasingly negative with temperature lowering and completely negative at −182 °C. Assuming a two-conformer equilibrium[38] and applying the analysis of Moscowitz, Wellman, and Djerassi,[15,17] we find a free-energy difference of 0.74 kcal/mol and a reduced rotational strength of −0.488 for the chair conformer and +2.28 for the boat. The conformational free-energy difference (0.74 kcal/mol) is considerable less than the calculated conformational energy difference (5.33[19] and 5.89[20] kcal/mol) between chair cyclohexanone and its C_S boat conformer. Of course, calculated values typically assume no influence of solvent, and in this case there is clearly a pronounced solvent effect; cf. Figure 1. Then, too, the six-membered ring of bicyclo[3.2.1]octan-3-one differs from that of cyclohexanone in that the enthano bridge of the former tends to compress the ordinary 3,5-diaxial positions of cyclohexanone with a resultant puckering near C 8 and flattening near C_2–C_3–C_4 of the bicyclic system.[21] This structural phenomenon, described as an anti-reflex effect,[21,22] has been investigated extensively by Fournier[21] and Fournier et al.[20,22]

Fournier,[21] using Westheimer-type molecular mechanics energy minimization procedures, has calculated a value for the C_1–C_8–C_5 bond angle of bicyclo[3.2.1]octan-3-one smaller (99.68°) than the corresponding bond angle (111.17°) of cyclohexanone. The same calculations revealed that the C_2–C_3–C_4 bond angle is opened (117.07°) relative to the corresponding angle (115.59°) of cyclohexanone. Of particular relevance, the torsion angle[23] C_2–C_3–C_4–C_5 of bicyclo[3.2.1]octan-3-one is severely compressed: 40.26° vs. 52.83° for the corresponding angle in cyclohexanone. Thus, considerable ring flattening may be predicted for **1** in the vicinity of its C=O group. This translates into α-equatorial H becoming more axial-like (β = O–C_3–C_4–H_{eq} = 18.18° for bicyclo[3.2.1]octan-3-one vs. 5.79° for cyclohexanone and the axial H becoming quasi-axial (β' = O–C_3–C_4–H_{ax} = 99.19° for bicyclo[3.2.1]octan-3-one vs. 112.00° for cyclohexanone). Fournier's calculations also reveal that the boat cyclohexanone conformer of bicyclo[3.2.1]octan-3-one is only 3.6 kcal/mol higher energy than the chair.[20]

Thus, there was strong indications that the conformation of **1** might involve a chair cyclohexanone moiety with some degree of ring flattening near the C=O group. We proceeded to explore this probability by using Allinger's MM2 molecular mechanics method,[24] with which we calculated the energy-minimized geometry of **1**. In order to establish a connection between Fournier's calculations and those from MM2, we recalculated the energy-minimized geometries of the parent ketone, bicyclo[3.2.1]octan-3-one, and cyclohexanone by using MM2. The relevant data are given in Table I. Our MM2 calculations produce essentially the same internal angles (C_1–C_8–C_5 and C_2–C_3–C_4) and endocyclic torsion angle [$\phi(3,4)$ = C_2–C_3–C_4–C_5] as do Fournier's. Only in the β torsion angles (Figure 4) do the results differ significantly. MM2 predicts a somewhat more axial-like α-equatorial H (20.4° vs. 18.18°) and a more quasi-axial α-axial H (96.4° vs. 99.19°) for bicyclo[3.2.1]octan-3-one. Similar coincidences and differences are found in cyclohexanone, for which Fournier predicts the α-equatorial H to be more eclipsed with the C=O (5.79° vs. 8.91°) than does MM2. Introduction of methyl groups on the bicyclo[3.2.1]octan-3-one skeleton to give **1** produces only small changes in the internal angles (Table I) but somewhat larger differences in the more sensitive torsion angles. Thus, the endocyclic torsion angle $\phi(3,4)$ is relatively more compressed (33.6° vs. 39.4°) in **1** than in its parent ketone, and the β torsion angles clearly show that the former α-equatorial and α-axial hydrogens both become more quasi-axial. On the basis of these calculations, we conclude that **1** is a bit farther along the way to the sofa

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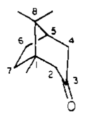
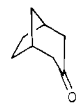
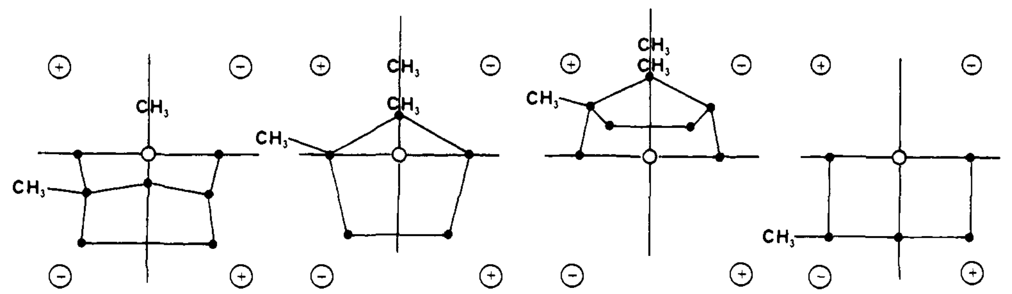
Table I. Comparison of Selected Internal and Torsion Angles Calculated for 1,8,8-Trimethylbicyclo[3.2.1]octan-3-one (1), Bicyclo[3.2.1]octan-3-one, Cyclohexanone, and 4-*tert*-Butylcyclohexanone from MM2[a] Molecular Mechanics Calculations

	internal angle, deg		torsion angle,[b] deg		
			$\phi(3,4)$	β	β'
	C_1-C_8-C_5	C_2-C_3-C_4	C_2-C_3-C_4-C_5	O-C_3-C_4-H_{eq}	O-C_2-C_3-H_{ax}
 1	98.95	117.34	33.62	26.54	88.65
	100.41 99.68[c]	116.12 117.07[c]	39.39 40.26[c]	20.43 18.18[c]	96.40 99.19[c]
 [d]	110.9 111.17[c] 109.5 ± 2.5[e]	115.4 115.59[c] 117 ± 3[e]	51.48 52.83[c]	8.91 5.79[c]	108.2 112.00[c]
 [d]	106.34[f] 108.5 109.0[g]	117[f] 114.7 115.5[g]	 51.78 47.35[h]	 8.67 12.89[h]	 108.27 110.75[h]

[a] See ref 24. Limited certainty in the values begins with the fourth significant figure. [b] See Figure 4 for a description of these angles. [c] Values from the molecular mechanics calculations of Fournier, ref 20 and 21. [d] The angles of the cyclohexanones correspond to the same angles of the cyclohexanone moieties of bicyclo[3.2.1]octan-3-one and 1. [e] Electron diffraction data, which incorporate the assumption that all internal angles are 109° 28′ except C_2-C_3-C_4; see ref 28. [f] Microwave data, assuming *inter alia*: all C-H bonds are 1.09 A, C=O is 1.24 A, C_4-C_5 = C_5-C_8 = 1.54 A, C_2-C_3-C_4 is 117°, and H-C-H angles are 109° 30′; see ref 27. [g] From X-ray crystallography; see ref 25. [h] Calculated from the atomic coordinates of ref 25 by using MM2.



	1-C	1-S	1-B	3^e-CH_3-cyclohexanone
Predicted CE:	−	weak +	+	−

Figure 3. Octant diagrams for the various conformers of **1** and 3(e)-methylcyclohexanone of the same absolute configuration. The signs of the back octant contributors are given, circled, for each octant.

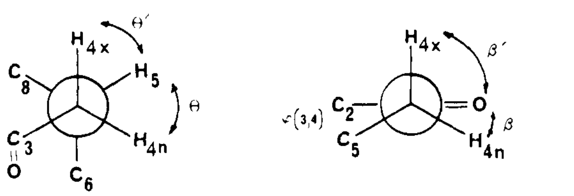


Figure 4. Newman projections for **1**. The left half shows torsion angles θ and θ' looking down the C_4-C_5 bond from C_4 to C_5. The right half shows the carbonyl torsion angles (β and β') and $\phi(3,4)$ looking down the C_3-C_4 bond from C_4 to C_3.

conformer (**1-S**) than is bicyclo[3.2.1]octan-3-one, possibly due to interactions of the C_{11} CH_3 with H_{2x} and H_{2n}. Both clearly exhibit ring flattening, relative to cyclohexanone, in the vicinity of the C=O group (anti-reflex effect[21,22]).

In order to calibrate the calculation method, we compared the MM2-derived optimized molecular geometry for 4-*tert*-butylcyclohexanone with that determined by X-ray crystallography.[25,26] Those data are presented in Table II, a table in which structural parameters for cyclohexanone may also be found. (It is worth noting here that the structures of cyclohexanone dertermined by microwave[27] and electron diffraction[28] methods are built upon *assumed* but reasonable values for many bond lengths and angles.) MM2 reproduces the experimental bond lengths and bond angles satisfactorily; however, it fails to reproduce the smaller (47.4° vs. 51.8°) torsion angle $\phi(1,2)$ and consequently does not yield the larger (12.9° vs. 8.67°) β torsion angle for the α-equatorial H. It is not entirely unexpected that MM2 should fail to reproduce these parameters exactly, especially since crystal-packing requirements may lead to adjustments in an otherwise optimal (gas phase or solution) molecular geometry.[29] this explanation has, in fact, been invoked to explain the surprising flattening of ring

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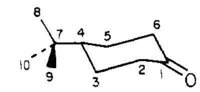
(29) For example, the MM2 optimized geometry of 4-tert-butylcyclohexanone has a lower total energy (12.58 kcal/mol) than that (47.69 kcal/mol) generated by MM2 using the atomic coordinates determined by X-ray crystallography. A referee offered the suggestion that the difference in angles probably corresponds to very little in terms of energy because the MM2 torsional potentials are fairly "soft". Also, molecular mechanics, X-ray crystallography, electron diffraction, and microwave spectroscopy all involve averaging over vibrational motions. Since the methods of averaging differ for each of these, the bond lengths, angles, and torsional angles might be expected to have different values, values characteristics of the method.

Table II. Comparison of Experimental[a] and Molecular Mechanics (MM2[b]) Calculated Molecular Parameters for 4-*tert*-Butylcyclohexanone and for Cyclohexanone



	X-ray	MM2[b,c]	MM2[b,c]
	Bond Length, A		
O-1	1.214	1.210	1.210
1-2	1.488	1.516	1.518
2-3	1.533	1.536	1.534
3-4	1.516	1.545	1.536
4-7	1.558	1.561	
7-8	1.544	1.543	
7-9	1.529	1.548	
	Bond Angles, Deg		
O-1-2	122.2	122.6	122.3
2-1-6	115.5	114.7	115.4
1-2-3	112.1	110.7	110.7
2-3-4	112.4	112.3	111.1
3-4-5	109.0	108.5	110.9
3-4-7	113.7	114.2	
4-7-8	111.5	112.7	
4-7-9	109.5	110.6	
8-7-9	108.7	108.1	
9-7-10	108.7	106.6	
	Internal Dihedral Angles, Deg		
$\phi(1,2)$	47.35	51.75	51.48
$\phi(2,3)$	52.09	54.40	53.30
$\phi(3,4)$	56.61	56.99	57.52
	52.03[d]	54.31[d]	54.10[d]
	θ Torsion Angles, Deg		
H_{2e}-C_2-C_3-H_{3a}	53.50	54.60	54.55
H_{2e}-C_2-C_3-H_{3e}	61.99	61.13	62.73
H_{2a}-C_2-C_3-H_{3e}	58.19	57.62	56.00
	β Torsion Angles, Deg		
O-C_1-C_3-H_{2e}	12.89	8.67	8.91
O-C_1-C_2-H_{2a}	110.75	108.27	108.22

[a] From the X-ray crystallographic structure of 4-*tert*-butylcyclohexanone, ref 25. [b] Reference 24. Reliability in the numbers is reduced past the third significant figure. [c] Bond lengths, bond angles, dihedral angles, and torsion angles are the same for the corresponding positions across the molecular symmetry plane. [d] Mean internal torsion angle, an indicator of ring flattening relative to cyclohexane (mean internal torsion angle = 55.9°); see ref 25.

A in 3-oxo-5α-androstan-17β-ol *p*-toluenesulfonate, which has been shown to have O–C_3–C_2–H_{eq} and O–C_3–C_2H_{ax} β torsion angles of 19.8° and 99.8°, respectively, and the relevant $\phi(2,3)$ torsion angle of 37.2° by X-ray crystallography.[30] Therefore, we note that the ring flattening determined for 4-*tert*-butylcyclohexanone in the crystal may be a consequence of crystal forces. Accordingly, it should prove interesting to determine its structure in the gas phase by electron diffraction or other methods. We hasten to add that it may be appropriate to exercise caution in assuming that 4-*tert*-butylcyclohexanone in solution will exhibit a "flattened" cyclohexanone ring.[31,32]

In order to provide additional *experimental* evidence for the confromation of **1**, we measured its ^{1}H NMR spectrum at 360 MHz (Table III) and analyzed the vicinal coupling constants between H_{4n} and H_5 and between H_{4x} and H_5 (Table IV). Using a modified Karplus equation, $^3J = 9.3\cos^2\theta + \cos\theta$,[33] we were able to determine the H_{4n}–C_4–C_5–H_5 and H_{4x}–C_4–C_5–H_5 torsion angles (θ and θ', respectively, see Figure 4) from the relevant vicinal H|H NMR coupling constants, ^3J. We have found the cited equation, one due to Teisseire et al.,[33] to be superior to many other Karplus-type equations in that it has consistently given good agreement with the constraining relationship $\theta + \theta' = 120°$. The torsion angles (θ and θ') of **1** determined in this way may be compared with those determined from Dreiding models for conformational structures **1**–C, **1**–B, and **1**–S as well as with the MM2 geometry-optimized structures of **1** and cyclohexanone (Table IV). Interestingly, the β and β' torsion angles (Figure 4) calculated for ketone **1** by MM2 are essentially the same as those determined following analysis of the $H_{4n}|H_5$ and $H_{4x}|H_5$ vicinal coupling constants. The NMR data thus point to **1** in $CDCl_3$ at room temperature as possessing a chair cyclohexanone conformation, somewhat flattened in the vicinity of the C=O group—essentially that predicted by MM2 molecular mechanics calculations.

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Table III. Proton and Carbon-13 NMR Data for Ketone 1

360-MHz ^{1}H NMR in $CDCl_3$				25-MHz ^{13}C NMR		
H[a] no.	δ	multiplicity	coupling constants	C[a] no.	δ	OFR multiplicity
$CH_3(11)$	0.92	s		1	44.46	s
$CH_3(9)$	0.99	s		2	53.94	t
$CH_3(10)$	1.10	s		3	212.60	s
H_{7n}	1.36	ddd	$J_{7n,7x}$ = 13.5 Hz, $J_{7n,6n}$ = 9–10 Hz, $J_{7n,6x}$ = 4.7 Hz	4	47.04	t
H_{6n}	1.57	ddd	$J_{6n,6x}$ = 13.5 Hz, $J_{6n,7n}$ = 9.9 Hz, $J_{6n,7x}$ = 4.7 Hz	5	45.75	d
H_{7x}	1.70	m	complex multiplet	6	27.44	t
H_{6x}	1.97	m	complex multiplet	7	36.15	t
H_5	1.97	br s		8	43.12	s
H_{2n}	2.05	dd	$J_{2n,2x}$ = 17.3 Hz, $J_{2n,4n}$ = 2.1 Hz	9	20.77	q
H_{4n}	2.20	ddd	$J_{4n,4x}$ = 16.9 Hz, $J_{4n,5}$ = 2.1 Hz, $J_{4n,2n}$ = 2 Hz	10	23.58	q
H_{2x}	2.42	dd	$J_{2x,2n}$ = 17.2 Hz, $J_{2x,7x}$ = 3 Hz	11	18.84	q
H_{4x}	2.63	ddd	$J_{4x,4n}$ = 17.0 Hz, $J_{4x,5}$ = 3.3 Hz, $J_{4x,6x}$ = 3.0 Hz			

[a] For numbering system, see Chart I.

Table IV. Torsion Angles (θ, θ', β, β') (Deg) and Energies (kcal/mol) Determined for 1 from Vicinal H|H NMR Coupling Constants and from MM2 Molecular Mechanics Calculations

torsion angle[a]	from NMR[b,c]	from MM2[d]	idealized conformations,[e] θ and θ' from Dreiding models 1-C	1-S	1-B	cyclohexanone by MM2[d]
θ	65	60	70	80	100	63
θ'	57	57	50	40	20	55
β	30	27	34	43	74	9
β'	87	89	82	73	40	108
rel energies from MM2	0.20	0.00	0.40	1.45	4.33	

[a] Refer to Chart I and Figure 4. [b] (θ, θ') torsion angles were calculated from 360-MHz NMR vicinal H|H coupling constants (Table III) by using the formula $^3J = 9.3\cos^2\theta + \cos\theta$; ref 33. [c] ($\beta$, β') torsion angles were determined by using MM2 and the given θ angles as input data. [d] Program of Allinger and Yuh, ref 24. [e] See Chart I for conformations.

Conclusions

The expected ring flattening of **1** in the vicinity of its C=O group is indicated by analysis of H|H vicinal coupling constants (from 360-MHz NMR) and by molecular mechanics (MM2[24]) calculations. A preferred slightly flattened chair cyclohexanone conformation (akin to **1**-C) is also qualitatively in keeping with the observed CD CE ($\Delta\epsilon = -0.13$, $CHCl_3$) for the $n \rightarrow \pi^*$ transition—see Figures 1 and 3 and Chart I. The smaller ($\Delta\epsilon = -0.16$) than expected ($\Delta\epsilon \simeq -0.6$) CE magnitude for **1** in methanol (and even $CHCl_3$) may be due to the ring deformation cited above (see Figure 3), but it may also reflect the intrusion of higher energy boatlike (**1**-B) or sofa (**1**-S) conformers. The unexpected (+)-CE for **1** in *n*-heptane clearly implicates a boatlike conformer. Analysis of the variable-temperature CD curves of **1** run in methylcyclohexane–isopentane (4:1) leads to the prediction of a (−)-CE for the somewhat flattened and preferred chair conformer (**1**-C) with $[R] = -0.48$, and a (+)-CE with $[R] = +2.3$ for a higher energy conformer—like **1**-B, or possibly **1**-S. The analysis[15,17] also predicts a conformational free energy difference between the two conformers of 0.74 kcal/mol. The calculated value $[R] = -0.48$ of the rotational strength of **1**-C is considerably smaller than that of the structurally related (−)-(1*R*,3*S*, 4*S*(e))-methyladamantan-2-one $[R] = -1.8$ (M4:I1).[13] However, it is to be expected that $[R]$ for **1** should become increasing positive as the cyclohexanone moiety is deformed from a full chair in the direction of the sofa conformation, viz., ring flattening near the C=O group. The calculated conformational free energy difference (0.74 kcal/mol) between **1**-C and a higher energy conformer (like **1**-S or **1**-B) seems small when compared with the relative energies calculated by MM2 (see Table IV); it may reflect the importance of solvent. Interestingly, the $\Delta G°$ from CD analysis is lower than that calculated (molecular mechanics) for either the parent ketone, bicyclo[3.2.1]octan-3-one (3.6 kcal/mol[21]) or cyclohexanone itself (5.33 kcal/mol[19]).

Experimental Section

Circular dichroism spectra were recorded on a JASCO J-40A instrument equipped with a photoelastic modulator and J-DPY data processor. Ultraviolet spectra were recorded on a Cary 219 spectrophotometer, and sodium D-line rotations were determined on a Perkin-Elmer Model 141 polarimeter. Nuclear magnetic resonance spectra were determined on a JEOL FX-100 instrument at 100 MHz (^1H) and 25 MHz (^{13}C) in $CDCl_3$ solvent, and infrared spectra were recorded on a Perkin-Elmer Model 599 spectrophotometer. Analytical gas chromatography was performed on a Varian Model 2400 instrument using a 6 ft × $^1/_8$ in. column packed with 5% FFAP on Chromosorb W, AW-DMCS. Preparative gas chromatography was performed on a Varian-Aerograph Model 1700 instrument using a 6 ft × $^3/_8$ in. column packed with 10% FFAP on Chromosorb W, AW-DMCS. Spectal data were obtained with Spectral Grade solvents (Matheson). (+)-Camphorsulfonic acid was obtained from Aldrich.

(+)-(2*R*)-(2,2,3-Trimethylcyclopent-3-enyl)acetic Acid [(+)-α-Campholenic Acid] (2).[10] After 25 g (0.45 mol) of KOH pellets in a porcelain dish was melted by flame heat, 12 g (0.05 mmol) of (+)-10-camphorsulfonic acid (100% enantiomeric excess) was added in 2-g portions with constant stirring and heating in a fume hood. An additional 25 g (0.45 mol) of KOH pellets was added, and 12 g (0.05 mol) more of (+)-10-camphorsulfonic acid was added in 2-g portions. After all the acid was added, heating was continued for 40 min. Before it was fully cooled, lumps from the dark brown reaction mixture were added to 100 mL of H_2O. The casserole was washed with CH_2Cl_2 (50 mL) into the aqueous solution, which was then acidified to pH 3 with dilute hydrochloric acid. Extraction with ether (3 × 60 mL) followed by drying ($MgSO_4$) and solvent removal on a rotary evaporator afforded 12 g of crude product. Distillation afforded 11.1 g (66%) of acid **2**: b.p. 106–108 °C (0.75 mm) [lit.[34] b.p. 157 °C (15 mm)]; $[\alpha]^{25}{}_D$ +10.64° (neat) [lit.[35] $[\alpha]^{25}{}_D$ +10.9°]; IR (neat) ν 3500–2200, 1710 cm^{-1}; ^1H NMR δ 0.79 (s, 3 H, CH_3), 1.00 (s, 3 H CH_3), 1.58 (s, 3 H, CH_3), 1.7–2.6 (m, 5 H), 5.15 (br s, 1 H, =CH); ^{13}C NMR δ 12.48 (q), 19.73 (q), 25.46 (q), 35.18 (t), 35.53 (t), 46.12 (d), 46.76 (s), 121.53 (d), 147.74 (d), 180.61 (s); MS, *m/z* (relative intensity) 168 [M^+] (1%), 153 (2%), 108 (6%), 88 (100%).

α-Campholenyl Chloride (3). A magnetically stirred solution of 10 g (59 mmol) of acid **2** in 5 mL of pyridine (stored over KOH) and 100 mL of dry benzene (azeotropically dried) at 25 °C was treated dropwise (20 mine with a solution of 7.6 mL (90 mmol) of oxalyl chloride (Aldrich) in 250 mL of dry benzene.[36] The reaction mixture was filtered after 3.5 h of stirring, and the solvents were removed by a rotary evaporator.

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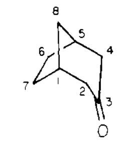
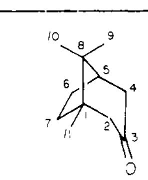
Table V. Selected Bond Lengths, Bond Angles, and Torsion Angles for 1 and Bicyclo[3.2.1]octan-3-one[a]

		 1
	Bond Lengths, Å	
O-3	1.210	1.210
1-2	1.539	1.547
1-7	1.541	1.548
1-8	1.536	1.553
1-11		1.538
2-3	1.519	1.520
3-4	1.519	1.519
4-5	1.539	1.539
5-6	1.541	1.543
5-8	1.536	1.548
6-7	1.542	1.540
8-9		1.543
8-10		1.548
	Bond Angles, Deg	
O-3-2	121.9	121.4
O-3-4	121.9	121.3
1-2-3	111.4	112.9
1-7-6	105.4	105.7
1-8-5	100.4	98.9
2-1-7	111.4	108.0
2-1-8	109.4	110.5
2-1-11		108.9
2-3-4	116.1	117.3
3-4-5	111.4	111.5
4-5-6	111.3	109.2
4-5-8	109.3	111.9
5-6-7	105.4	105.0
5-8-9		113.8
5-8-10		110.1
6-5-8	102.6	103.9
7-1-8	102.6	103.3
7-1-11		111.4
9-8-10		105.8
	Internal Torsion Angles, Deg	
φ(1,2,3,4)	39.38	33.71
φ(2,3,4,5)	39.39	33.62
φ(3,2,1,7)	55.39	58.05
φ(3,4,5,6)	55.37	58.97
φ(3,2,1,8)	57.34	54.26
φ(3,4,5,8)	57.36	55.42
φ(4,5,6,7)	88.38	90.33
φ(4,5,8,1)	72.31	71.80
φ(4,5,8,9)		50.93
φ(4,5,8,10)		169.45
φ(5,6,7,1)	0.03	0.43
φ(5,8,1,2)	72.30	70.93
φ(5,8,1,7)	46.01	45.21
φ(5,8,1,11)		166.50
φ(6,5,8,1)	46.00	45.82
φ(6,5,8,9)		168.55
φ(6,5,8,10)		72.93
φ(6,7,1,2)	88.34	88.83
φ(6,7,1,8)	28.55	28.28
φ(6,7,1,11)		151.54
φ(7,1,8,9)		166.91
φ(7,1,8,10)		71.21
	θ Torsion Angles, Deg	
H_{4x}-4-5-H_5	60.20	57.10
H_{4n}-4-5-H_5	58.17	59.93
H_{6x}-6-7-H_{7x}	0.04	1.14
H_{6x}-6-7-H_{7n}	119.62	119.01
H_{6n}-6-7-H_{7n}	0.03	0.33
	β Torsion Angles, Deg	
O-3-4-H_{4x}	96.40	88.65
O-3-4-H_{4n}	20.43	26.54
O-3-2-H_{2x}	96.40	88.26
O-3-2-H_{2n}	20.45	26.03

[a] Calculated from MM2, ref 24. Computed numbers are not necessarily reliable beyond the third significant figure.

Distillation afforded 9.9 g (90%) of acid chloride **3**: b.p. 42–43 °C (0.3 mm) [lit.[37] b.p. 88–91 °C (10 mm)]; IR (neat) ν 3040, 2960, 1810 cm^{-1}; ^{1}H NMR δ 0.81 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.5–2.8 (m, 5 H), 5.17 (br s, 1 H =CH); ^{13}C NMR δ 12.40 (q), 19.72 (q), 25.45 (q), 35.10 (t), 46.16 (d), 46.86 (s), 48.38 (t), 121.28 (d), 147.48 (s), 173.34 (s); MS, m/z (relative intensity): 127 (10%), 99 (25%), 88 (100%).

(1*S*,2*R*,5*R*,7*R*)-1,8,8-Trimethyltricyclo[3.2.1.0^{2,7}]octan-3-one (6). A 3-fold excess of diazomethane (48.2 mmol) in 160 mL of anhydrous ether at 0 °C was treated dropwise with a solution of 3 g (16.1 mmol) of acid chloride **3** in 50 mL of anhydrous ether and stirred magnetically for 5 h at 0 °C. The ether was removed on a rotary evaporator to give a residue that was dissolved in 100 mL of dry tetrahydrofuran. A catalytic amount (200 mg) of powdered copper metal was added and the mixture heated at reflux with magnetic stirring for 12.5 h. After filtration through Celite, the benzene was removed on a rotary evaporator to afford 2 g (76%) of crude cyclopropyl ketone **6**. Purity (95%) was determined by GC, and the sample could be further purified by preparative G.C. ^{1}H NMR δ 0.78 (m, 1 H), 0.97 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.3–2.5 (m, 6 H); ^{13}C NMR δ 14.04 (q), 19.54 (q), 23.99 (q), 30.19 (t), 30.83 (d), 38.38 (d), 40.01 (t), 40.19 (s), 40.42 (s), 40.83 (d), 208.39 (s). The crude material was used directly in the next step.

(+)-(1*S*,5*R*)-1,8,8-Trimethylbicyclo[3.2.1]octan-3-one (1).[9] A three-nick 500-mL round-bottomed flask, immersed in a dry ice–acetone bath (−78 °C) and equipped with a dry ice condenser (topped with a drying tube) and rubber septa, was filled with 300 mL of condensed liquid ammonia and a stirring bar. After 250 mg (36 mmole of lithium metal, which slowly dissolved (deep blue solution), was introduced, a solution of 850 mg (5.2 mmol) of cyclopropyl ketone **6** in 5 mL of dry ether was added via syringe. After being stirred with a magnetic stirrer for 30 min, 10 g of solid NH_4Cl was added (blue color faded). The dry ice–acetone bath was removed to let the ammonia evaporate over 6 h. The white residue was dissolved in 30 mL of ether and 10 mL of H_2O; the ether layer was isolated and washed with saturated aqueous NH_4Cl. The dried ($MgSO_4$) ether layer was concentrated to afford 600 mg (63%) of crude ketone **1**. The purity (90%) was determined by GC. Further purification (>99%) was achieved by preparative GC to afford pure ketone **1**: m.p. 173–175 °C, (lit.[9] m.p. 175 °C); $[\alpha]^{25}_D$ +39.5° (c 0.2, heptane) [lit.[9] $[\alpha]_D$ +25° (c 5)]1; UV ϵ_{270} = 19 (n-heptane), ϵ_{274} = 23 (methanol), ϵ_{276} = 15 (chloroform); CD R_{289} = +0.19, R_{316} = −0.01 (n-heptane), R_{295} = −0.44 (methanol), R_{300} = −0.32 (chloroform), values $\times 10^{-40}$ cgs at 24 °C; IR ($CHCl_3$) ν 2970, 1710 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table I.

Computational Details. Optimized molecular geometries of cyclohexanone, 4-*tert*-butylcyclohexanone, bicyclo[3.2.1]octan-3-one, and 1,8,8-trimethylbicyclo[3.2.1]octan-3-one (**1**) were calculated by using the molecular mechanics (MM2) method of 24. The first three ketones have a molecular symmetry plane that was reproduced by MM2. Ketone **1** would have a symmetry plane if the C_{11} CH_3 were replaced by H. Its optimized geometry was derived from a symmetrized structure that was allowed to relax. Calculated parameters for cyclohexanone and *tert*-butylcyclohexanone are given in Table II. Corresponding MM2 data for bicyclo[3.2.1]octan-3-one and **1** are given in Table V.

Acknowledgment. We thank the National Science Foundation for support of this work and the Stanford Magnetic Resonance Laboratory (NSF No. GP23633 and NIH No. RR00711) and its director, Dr. A. Rebiero, for assistance in obtaining the 360-MHz spectrum. We are particularly grateful to W. M. D. Wijekoon (this laboratory) for checking the Beer's Law behavior of **1** by running its CD spectra in n-heptane over a 77-fold concentration range: 0.077 M vs. 0.0010 M.

Registry No. 1, 33880-76-1; **2**, 28973-89-9; **3**, 82933-65-1; **6**, 33880-75-0; (+)-10-camphorsulfonic acid, 3144-16-9; bicyclo[3.2.1]octan-3-one, 14252-05-2; cyclohexanone, 108-94-1.

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(38) A referee has reminded us that ketones may form association complexes in hydrocarbon solvents. See: Allinger, J.; Allinger, N. L. *J. Am. Chem. Soc.* **1958**, *2*, 64. In our work, we checked the Beer's Law behavior of ketone **1** by running CD spectra in n-heptane at 0.077 M and 0.0010 M concentrations. We found no difference in the shapes and $\Delta\epsilon$ for the curves. When the curves were subtracted (J-DPY data processor), only a flat line ($\Delta\epsilon$ = 0) remained. Consequently, we believe that we are not observing aggregation in the LCD spectra.

Sulfur–Sulfur Bond Cleavage Processes. Selective Desulfurization of Trisulfides[1]

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Contribution from the Department of Chemistry, McGill University, Montreal, Quebec, Canada, H3A 2K6. *Received July 13, 1981*

Abstract: The selectivity of sulfur removal in the desulfurization of trisulfides by tertiary phosphorus compounds has been investigated in detail. A mechanistic rationalization is proposed to account for central/terminal sulfur extrusion variation as a function of substrate structure and solvent polarity.

The sulfur–sulfur bond is of considerable biological importance; it is present in the structures of a variety of natural products and contributes significantly to the tertiary structures of many proteins such as insulin and ribonuclease.[2] A major consequence of reactions involving the S–S linkage in such systems is the scission of this bond; the cleavage of disulfides by various species and disulfide interchange reactions therefore continue to be extensively studied.[3] Organic trisulfides (RSSSR′) are a closely related class of compounds having two adjacent sulfur–sulfur bonds. Such compounds play a role in biochemical systems, and a considerable number of trisulfides have been isolated from natural sources[4] including a variety of symmetrical and unsymmetrical trisulfides (e.g., **1a,b**) from plants in the onion family (genus *Allium*),[4b–e]

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