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ANALYSIS OF CYCLOHEPTANONE CONFORMATION FROM TEMPERATURE DEPENDENT CIRCULAR DICHROISM MEASUREMENTS OF (+)-(3*R*)-METHYLCYCLOHEPTANONE AND (−)-(4*R*)-METHYLCYCLOHEPTANONE

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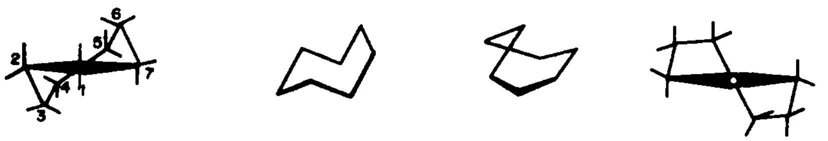
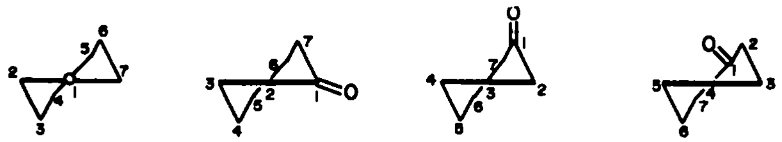
Abstract—Conformational analysis of methylcycloheptanones was achieved by relating CD rotational strengths to conformational free energies. Twist conformers with C_1 on the symmetry axis (TC_1) were found to be more stable than those with C_2 or C_7 on the symmetry axis (TC_2 or TC_7). The free energy differences were found to range from 0.2 to 1.2 kcal/mole. A similar analysis of (+)-(3*R*)-methylcyclohexanone showed the equatorial chair conformer to be most stable, by 0.50–0.75 kcal/mole.

Although numerous conformational studies have been reported for cyclohexanones using various methods, including ORD and CD,[1-5] magnetic CD,[6] NMR,[7-10] thermochemical equilibrations [11-14] and molecular mechanics calculations,[15] there have been relatively few investigations of cycloheptanone conformation.[7,15-19] The conformations of cycloheptanone have not been examined as thoroughly as those of cycloheptane, whose preferred conformation has the twist-chair (TC) geometry,[20] with C_2 symmetry, shown in Fig. 1, Strauss *et al.*[21] have calculated that cycloheptane lies at an energy minimum in a pseudorotation sequence interconverting TC, chair, boat and twist boat conformers. For cycloheptanone, Allinger[16,22] and others[18,23] concluded that the TC conformation also lies at an energy minimum with preferred location of the carbony group at site 1 and 2 or 7. Using the convention[18,20,24] that the C_2 axis of the TC ring is denoted by a subscript indicating the ring carbon through which it passes, Fig. 2 shows the conformational energies calculated for TC cycloheptanones.[16] NMR investigations on dimethylcycloheptanones are consistent with TC_1 and TC_2 or TC_7 being the energetically lower conformers.[17] A detailed conformational analysis of (+)-(3*R*)-methylcycloheptanone (1) and (−)-(4*R*)-methylcycloheptanone(2) considered twenty-eight possible conformation, of which eight TC forms were said to be of equivalent energy.[18] On that basis, the authors[18] could rationalize the observed ORD Cotton effect (CE) signs.[25] Very recently, Kirk[15] reinvestigated the conformations of chiral cycloheptanones and found that he could nicely predict the observed CE magnitudes for 1 and 2 by considering only the more stable TC_1, TC_2 and TC_7 conformations. For those same conformers of 1, $\Delta\epsilon$ values of $+7$ (TC_1), -10 (TC_2) and -9 (TC_7) were calculated based on the Me contribution and the (major) contributions of C_α–H and C_α–C_β bonds. The latter were assessed using an empirically derived equation. Similarly, for 2, $\Delta\epsilon$ values of -7 (TC_1), $+10$ (TC_2) and $+10$ (TC_7) were calculated. When the calculated $\Delta\epsilon$ values are population weighted and summed, the experimentally derived $\Delta\epsilon$ values ($+1.05$ for 1 and -1.2 for 2) were reproduced best assuming a population of 65% TC_1 and 35% ($TC_2 + TC_7$), with an estimated free energy difference of 0.75 kcal/mole. The analysis points to the TC_1 conformer being more stable than the TC_2 or TC_7 conformers rather than less stable (by 0.25 kcal/mole) as calculated by Allinger *et al.*[16] (Fig. 2). It should, however, be recognized that the presence of Me groups is expected



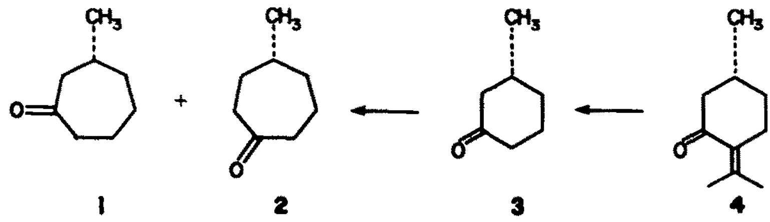
ΔE (kcal)
Twist Chair (TC) 0.00
Chair (C) 1.08
Boat (B) 0.79
Twist Boat (TB) 0.59

Fig. 1. Conformations of cycloheptane.



TC₁ 0.25
TC₂ 0.00
TC₃ 1.80
TC₄ 1.62

Fig. 2. Conformation energies for Twist Chair (TC) conformers of cycloheptanone (Ref. 16).



Scheme 1.

to cause the ring to twist somewhat from its idealized conformation. Consequently, any comparison of the parent cycloheptanone and Me derivative will be only approximate. We have investigated the conformation of 1 and 2 using temperature dependence CD measurements and report our finding and analyses below.

SYNTHESIS AND RESULTS

In 1959 Djerassi and Krakower reported[19] that the diazomethane ring enlargement of (+)-(3*R*)-methylcyclohexanone (3), derived from retroaldolization of pulegone (4) gave (−)-3-methyl- and (−)-4-methylcycloheptanone (Scheme 1). A few years after this report, data published on the ring expansion of optically active 2-methylcyclohexanone[26] caused Djerassi and others to reexamine their original work on the ring expansion of 3. On reexamination[25] it was found that the products of the ring expansion of 3 were actually (+)-3-methyl- and (−)-4-methylcycloheptanones, 1 and 2, respectively. Thus, the earlier reported negative rotation (and negative Cotton effect)[19] were due to contamination of ketone 1 with the strongly levorotatory ketone 2. Since the absolute configuration of (+)-4 has been determined in other studies,[27–29] the absolute configurations of 1–3 follows as shown in Scheme 1.

We synthesized 1 and 2 for our studies by the diazomethane ring enlargement of 3. The two cycloheptanones could be isolated and purified by preparative gas chromatography and/or distillation through a teflon annular spinning band column.

The ORD spectra of 1 and 2 agreed in detail with the published spectra.[25] Their variable temperature CD spectra in the $n-\pi^*$ region were recorded in EPA (diethyl ether/isopentane/ethanol – 5 vol/5 vol/2 vol) and P5:M1 (isopentane/methylcyclohexane – 5 vol/1 vol) and are presented in Figs. 3–6. The relevant chiroptical data, corrected for solvent contraction and corrected to 100% enantiomer excess, are given in Table 1. For both compounds fine structure did not appear at room temperature in EPA but it began to appear at −26°. In P5:M1 fine structure was evident at room temperature. The variable temperature CD curves showed increased rotational strengths as the temperature was lowered. Also, no new CD bands appear in the $n-\pi^*$ region. Rotational strengths, R_0^T, were calculated using a Gaussian approximation and the equation $R_0^T = 0.696\ (\sqrt{\pi})\ 3300\ \Delta\epsilon_{max} \cdot \Delta_\lambda \cdot \lambda_{max}$, where $\Delta\lambda$ is the half band width at $1/e$ height and λ_{max} is the wavelength of $\Delta\epsilon_{max}$. Alternatively, the curves were cut and weighed and then related to the room temperature R_0^T value derived by the Gaussian approximation.

DISCUSSION

An analysis of Dreiding model conformations of 1 and 2 leads to the same conclusions as that of Jones *et al.*,[18] namely, that eight TC conformations, all with pseudoequatorial Me groups, are lower energy than other TC,

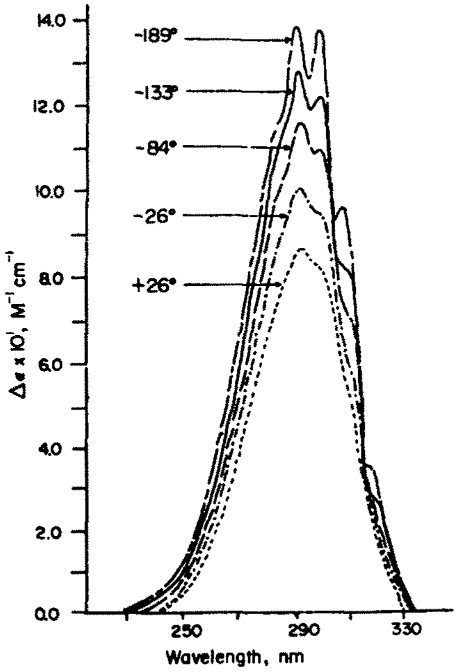


Fig. 3. Variable temperature circular dichroism (CD) spectra of (+)-(3*R*)-methylcycloheptanone in EPA. Temperatures in °C are noted beside the curves, and the +26° concentration is 3.5×10^{-2} M.

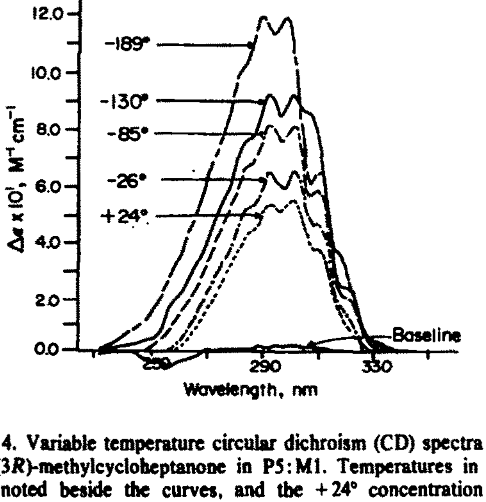


Fig. 4. Variable temperature circular dichroism (CD) spectra of (+)-(3*R*)-methylcycloheptanone in P5:M1. Temperatures in °C are noted beside the curves, and the +24° concentration is 4.9×10^{-3} M.

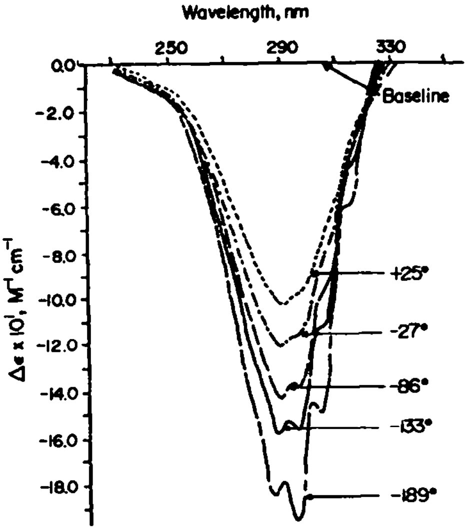


Fig. 5. Variable temperature circular dichroism (CD) spectra of (−)-(4*R*)-methylcycloheptanone in EPA. Temperatures in °C are noted beside the curves, and the +25° concentration is 1.8 × 10^{-2} M.

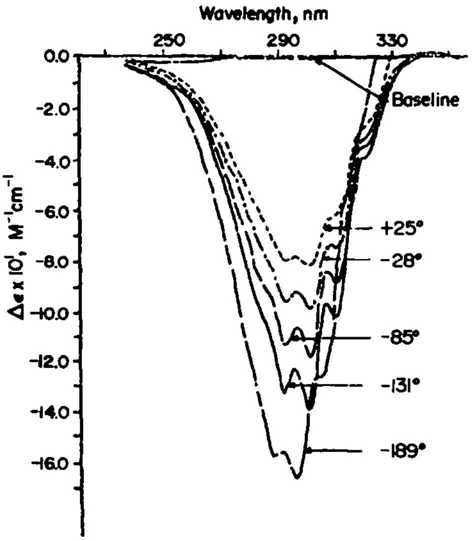


Fig. 6. Variable temperature circular dichroism (CD) spectra of (−)-(4*R*)-methylcycloheptanone in P5:M1. Temperatures in °C are noted beside the curves, and the +25° concentration is 9.7 × 10^{-3} M.

Table 1. Rotational strengths, R_0^T, of (+)-(3*R*) and (−)-(4*R*)-methylcycloheptanones (1) and (2)

Compound	Solvent	Temperature (°K)	$\Delta\epsilon^{\dagger}$	$R_0^T \times 10^{-40}$ cgs †
1	EPA*	299	+0.86	+2.81
		247	1.01	2.95
		189	1.16	3.30
		140	1.28	3.54
		84	1.39	3.67
1	P5:M1**	297	+0.52	+1.52
		247	0.63	1.85
		188	0.80	2.30
		143	0.91	2.71
		84	1.2	3.20
2	EPA*	298	-1.01	-3.39
		246	1.21	3.65
		187	1.43	3.97
		140	1.59	4.23
		84	1.96	4.72
2	P5:M1**	298	-0.80	-2.60
		245	-0.97	2.91
		188	-1.16	3.30
		142	-1.36	3.61
		84	-1.63	3.83

† Data are corrected for solvent contraction.

*Ethanol / isopentane / ethyl ether - (2:5:5) vol.

**Isopentane / Methylcyclohexane - (5:1) vol.

chair or boat conformers. On the basis of the Allinger's[15] calculations (Fig. 2) the TC_1, TC_2 and TC_7 conformers can be assumed to be lowest energy. The significantly higher energy conformers (TC_3, TC_4, TC_5 and TC_6) may be considered to be relatively unimportant. This approach is consistent with the analysis of Kirk.[15] The conformational and octant diagrams[30] of TC_1, TC_2 and TC_7 are given in Figs. 7 and 8 for 1 and 2. A cursory examination reveals that the CH_3 octant contribution should be nearly equal in magnitude but opposite in sign

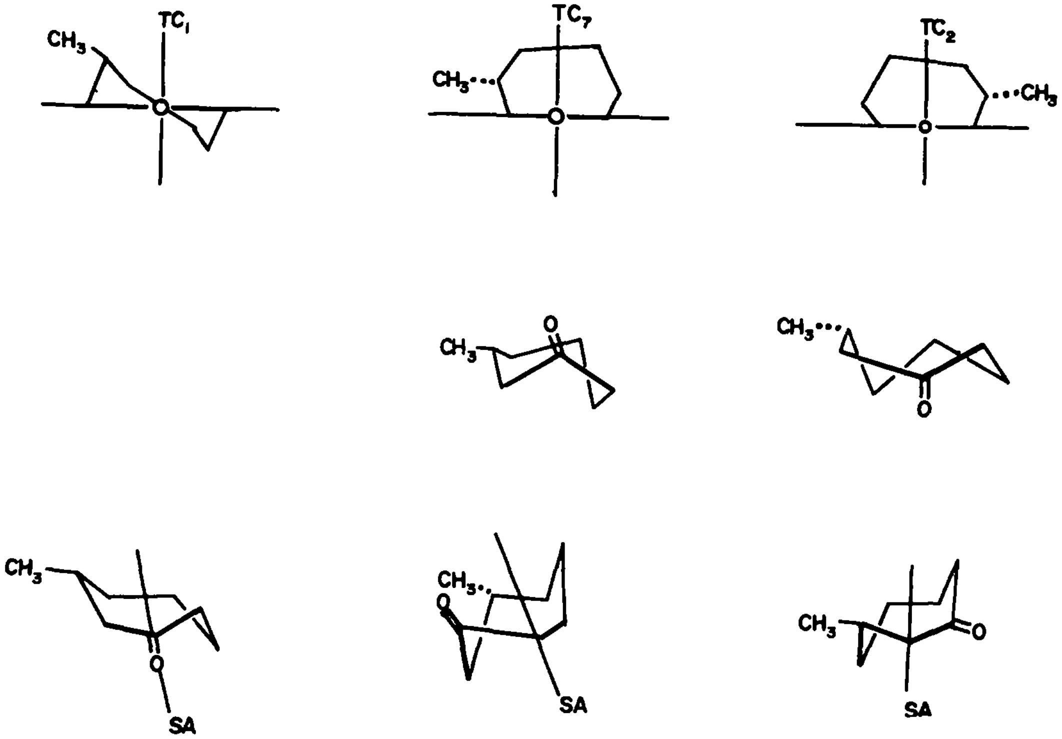


Fig. 7. Octant diagrams for the favored conformations of (+)-(3*R*)-methylcycloheptanone. The "symmetry axis" (SA) is indicated for each conformer.

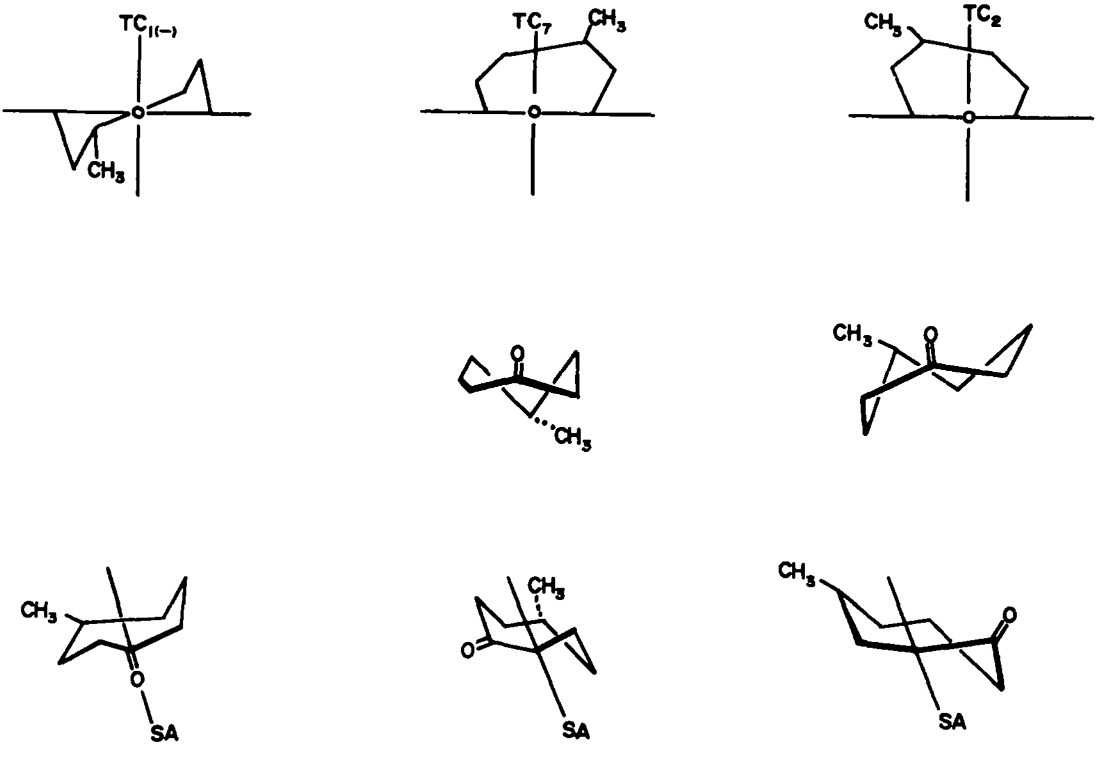


Fig. 8. Octant diagrams for the favored conformations of (−)-(4*R*)-methylcycloheptanone. The "symmetry axis" (SA) is indicated for each conformer.

for TC_2 and TC_7 in either 1 or 2. Consequently, since the *ring* conformations of TC_2 and TC_7 give identical octant projection diagrams for purposes of our conformational equilibrium studies, TC_2 and TC_7 can be treated as though they were a single entity (TC_2+TC_7). Actually, we expect equal concentrations of TC_2 and TC_7 to be present in solution with TC_1, but since the CE signs and magnitudes of TC_2 and TC_7 are predicted to be equal,[15] we find it convenient to treat the system as though it consisted of two components, TC_1 and (TC_2+TC_7), in the method of analysis described by Moscowitz *et al.*[31] This sensitive method has been used in the analysis of variable temperature CD data to determine conformer population[2,31,32] and has recently enabled the determination of free energy differences between chiral 3ª- and 3ᵉ-deuteriocyclohexanones.[33]

For the $n-\pi^*$ absorption band (of 1 and 2), the observed rotational strengths, $R_0{}^T$, are determined from the CD curves at 4 or 5 temperatures ranging from 77 to 299°K. In a two-conformer equilibrium, e.g. TC_1 and (TC_2+TC_7), R_a and R_b denote the rotational strengths associated with the lower energy conformer a and the higher energy conformer b, respectively. Consequently, $R_0{}^T = N_aR_a + N_bR_b$ where N_a and N_b are the mole fractions of a and b, respectively. It is not known *a priori* whether a corresponds to TC_1 or (TC_2+TC_7). Assumption of a Boltzmann distribution for a and b leads to the expression:[31] $R_0{}^T = (R_a - R_b)[1+\exp-(-\Delta G°/NkT)]^{-1} + R_b$, where N is Avogadro's number, k is the Boltzmann constant, T is temperature (°K) and ΔG° is the free energy change associated with the equilibrium, $a \rightleftarrows b$. A plot of $R_0{}^T$ vs $[1+\exp(-\Delta G°/NkT)]^{-1}$ should give a straight line for the proper temperature-dependent values of ΔG°. For ΔG° constant over the temperature range, substitution of various trial values of ΔG° will lead to a family of lines, only one of which (that for the proper ΔG°) is a straight line. The slope of that line is ($R_a - R_b$), and the intercept is R_b.

We have applied this method of conformational analysis to 1 and 2 using the data of Figs. 3–6 reduced in Table 1. The best fit straight lines (Figs. 9 and 10) provide values for ΔG°, R_a and R_b, and the conformational popu-

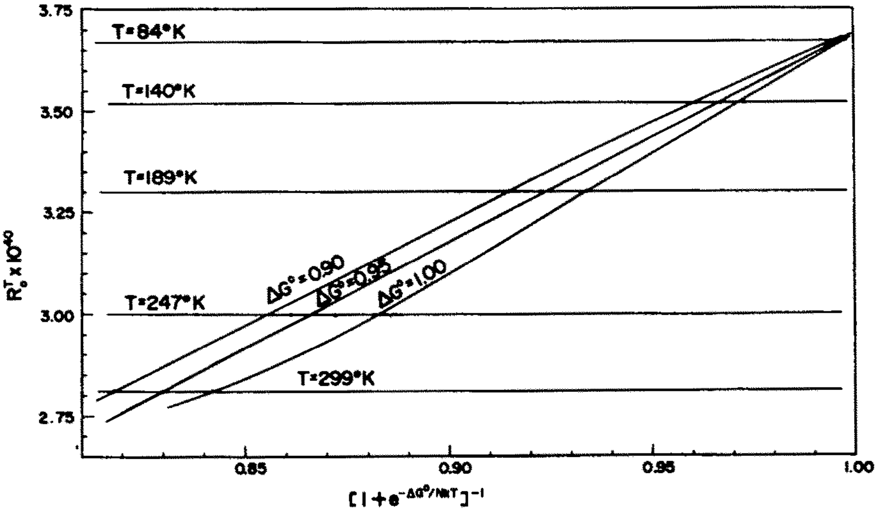


Fig. 9(a). Plot of $R_o{}^T$ vs $1/[1+\exp(-\Delta G°/NkT)]$ for various trial values of ΔG° (kcal/mole) for (+)(3*R*)-methylcycloheptanone in EPA.

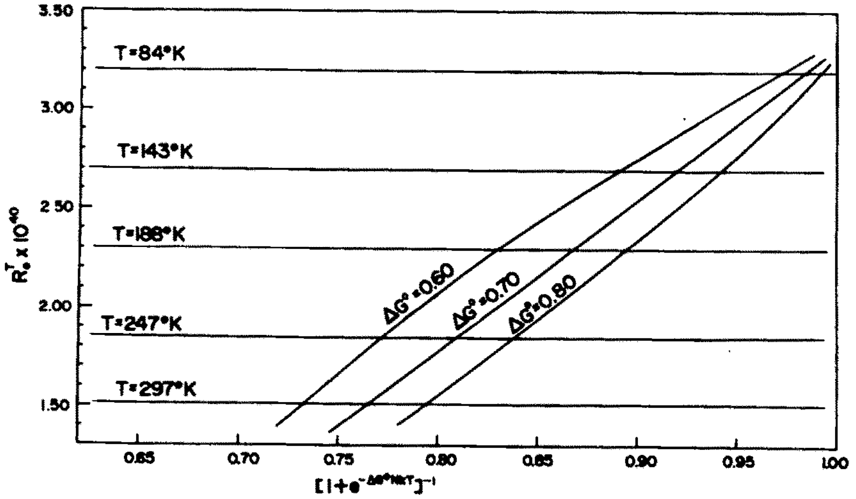


Fig. 9(b). Plot of $R_o{}^T$ vs $1/[1+\exp(-\Delta G°/NkT)]$ for various trial values of ΔG° (kcal/mole) for (+)-(3*R*)-methylcycloheptanone in P5:M1.

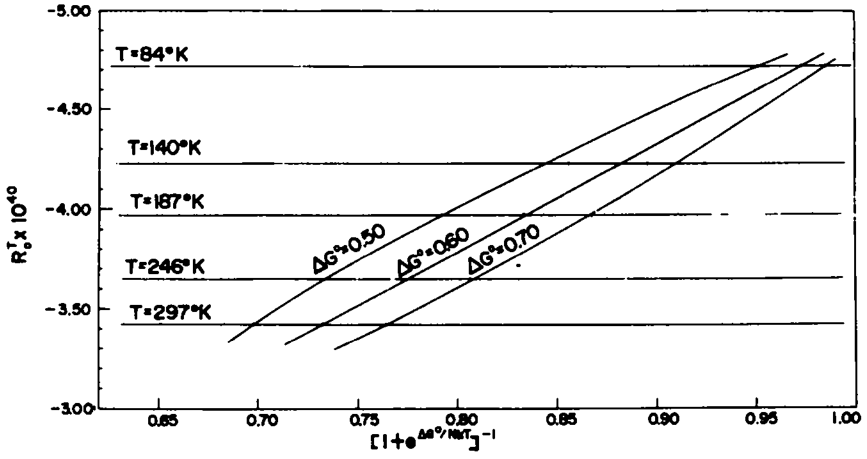


Fig. 10(a). Plot of R_o^T vs $1/[1+\exp(-\Delta G°/NkT)]$ for various trial values of ΔG° (kcal/mole) for (−)-(4*R*)-methylcycloheptanone in EPA.

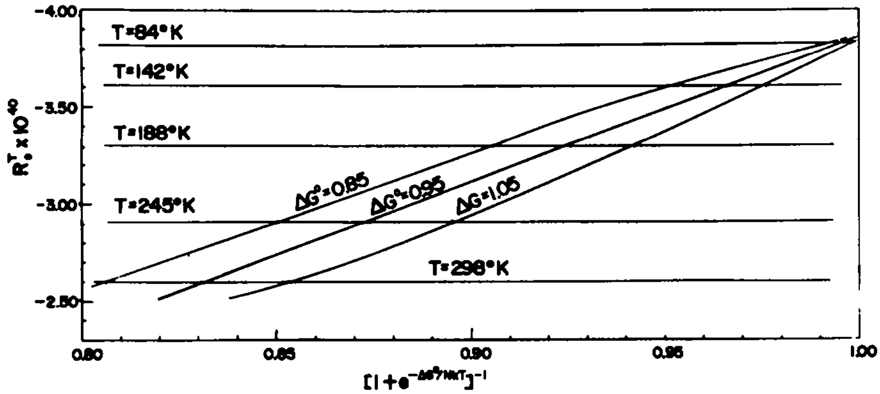


Fig. 10(b). Plot of R_o^T vs $1/[1+\exp(-\Delta G°/NkT)]$ for various trial values of ΔG° (kcal/mole) for (−)-(4*R*)-methylcycloheptanone in P5:M1.

lation of **a** and **b** can be determined at room temperature (Table 2). For both **1** and **2**, the predominant conformer **a** corresponds to TC_1 and the minor conformer **b** to (TC_2 + TC_7)—an assignment consistent with that of Kirk[15] and with the Octant Rule predictions of CD sign.[1,30,34] Our analysis predictions that TC_1 is more stable than TC_2 or TC_7 by 0.6–1.2 kcal/mole depending upon solvation and Me group location on the cycloheptanone ring. This prediction is opposite to that of Allinger *et al.*[16,42] (Fig. 2) but consistent with the calculations of Kirk.[15] The ΔG° values derived by our analysis are rather small, but consistent with those previously estimated,[15,16] and per-

Table 2. Derived rotational strengths and equilibrium data for (+)-(3*R*)- and (−)-(4*R*)-methylcycloheptanone (1) and (2) and (+)-(3*R*)-methylcyclohexanone (3)

Compound	Solvent	R_o^{298}*	R_a*	R_b*	ΔG° (kcal/mole)	$K^{298}_{(a \rightleftarrows b)}$	% a	% b
1	EPA**	+2.81	+3.65	-1.38	0.95	0.20	83	17
	P5:M1†	+1.52	+3.31	-4.32	0.70	0.31	77	23
2	EPA	-3.39	-4.85	+0.55	0.60	0.37	73	27
	P5:M1	-2.60	-3.95	+3.57	0.95	0.20	83	17
3	EPA	+1.90	+2.79	-0.18	0.50	0.44	70	30
	M‡	+1.74	+2.46	-0.75	0.75	0.29	78	22

* R x 10^{-40} cgs

**Ethanol / isopentane / ethyl ether - (2:5:5) vol.

†Isopentane / methylcyclohexane - (5:1) vol.

‡Methylcyclohexane

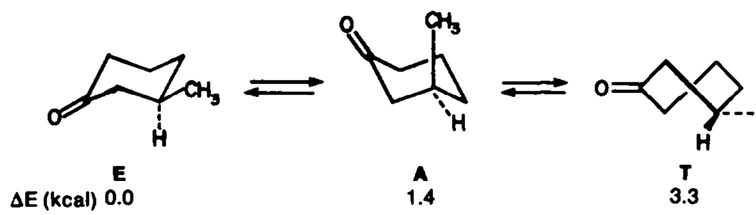


Fig. 11. Conformation energies of (3*R*)-methylcyclohexanone structures (Ref. 12).

haps not easily obtained by other experimental methods. A solvent effect on R_0^T and the equilibrium as found in the CD data of 1 (Tables 1 and 2), or lack of it for 2 has been observed in diverse systems.[2,31,32,42]

By way of comparison, we used the method of analysis on (+)-(3*R*)-methylcyclohexanone (3), the precursor to 1 and 2.[35] Conformational analysis of 3-methylcyclohexanone took on special importance some while ago in connection with the "3-alkylketone effect".[11–14,36] Thermochemical equilibration studies of *cis*-3,5-dimethylcyclohexanone on Pd(C) of Allinger and Freiberg[13] yielded a conformational energy for the 3-axial Me group of 1.4 kcal/mole. The datum differs from that (>1.8 kcal/mole) estimated by Rickborn[14] from isomenthone and methone equilibrations but falls near those data due to Cotterill and Robinson in their base-catalyzed equilibration studies of 2,5-dimethylcyclohexanone ($\Delta H_{(e\to a)} = 1.3$, kcal/mole and $\Delta S_{(e\to a)} = 0.2$ e.u.) and 2-*t*-butyl-5-methylcyclohexanone ($\Delta H_{(e\to a)} = 1.54$ kcal/mole and $\Delta S_{(e\to a)} = -0.5$ e.u.). The conformational energies which Allinger *et al.*[12] have associated with E, A and T (Fig. 11) are 0, 1.4 and 3.3 kcal/mole, respectively, with a room temperature conformational mixture of 94, 5 and 1% respectively. Our analysis of the variable temperature CD data[35] for 3 in the manner described for 1 and 2 led to the results presented in Table 2.[37,42] It is interesting to note that the rotational strengths (R_a) calculated for 3^e-methylcyclohexanone are close to those observed for 4^e-methyladamantanone ($R = +2.33$, ethanol. $R = +1.63$ cyclohexane) of the same absolute configuration.[38] Whether the calculated R_b values can be said to correspond to 3^e-methylcyclohexanone is less clear since the R values for 4^a-methyl-adamantanone[39] are an order of magnitude weaker than those for the equatorial epimer and exhibit CE sign changes: (+) CE in ethanol and (−) CE in isooctane. The octant position of the CH_3 group of 3^a-methylcyclohexanone may not be exactly the same as that for 4^a-methyladamantanone, and a twist form with an inherently intense CE magnitude may intervene to an extent larger than predicted.[12] The ΔG° values (0.50–0.75 kcal/mole) are less than those derived earlier (1.4–1.8 kcal/mole).[11–14] Our conformational value of the 3-axial Me group is rather near to the values of Djerassi *et al.*[40] (0.8 kcal/mole) and Robbins and Walker[40] (0.9 kcal/mole); thus, the "3-alkylketone effect" is closer to the originally postulated value of 0.85 kcal/mole[34] than the more recent values of 0.3–0.4 kcal/mole.[11–14]

CONCLUSIONS

Twist chair conformers of 3- and 4-methylcycloheptanones with C_1 on the symmetry axis (TC_1) are more stable than other favored twist chair conformers TC_2 and TC_7. The room temperature population of TC_1 is estimated to be 73–88% depending on methyl position and solvent, and the ΔG° values range from 0.6 to 1.2 kcal/mole. The "3-alkylketone effect" for 3-methylcyclohexanone is determined to be 0.95–1.2 kcal/mole from a similar analysis of 3-methylcyclohexanone conformation by variable temperature CD.

EXPERIMENTAL

All ORD and CD spectra were measured on a Cary 60 spectropolarimeter equipped with a model 6001 CD attachment and spectroscopic Dewar. Optical rotations were recorded using a Zeiss polarimeter. Solvents used for the ORD and CD measurements were spectrograde: MeOH (Merck), methylcyclohexane (MCB), isopentane (MCB) and EPA (American Instrument Co.). All gas chromatographic sample purity checks were made on a Varian Series 1200 basis gas chromatograph equipped with a flame ionization detector using a 6-ft 1/8 in. 7% Carbowax 20M on Chromosorb W column. All preparative gas chromatography was carried out using a Varian Aerograph Series 1700 gas chromatograph equipped with a thermal conductivity detector equipped with the various columns noted in the following. All mass spectra were measured on an AEI MS-9 mass spectrometer by Ms. Elizabeth Irwin.

(+)-(3R)-*Methylcyclohexanone* (3).[19] The pulegone (Aldrich) used for this experiment was freshly distillled at 105–107° using water aspirator pressure. (+)-Pulegone (417.0 g, 2.74 mol) was heated at reflux with 1740 ml water and 346 ml conc HCl and the acetone which was formed was removed continuously by slow distillation through a fractionating column. The product was then stream distilled, the distillate was extracted with 4 × 200 ml ether. The combined ether extract was washed with 3 × 50 ml water and dried over Na_2SO_4. After removal of the ether by distillation, (+)-(3*R*)-methylcyclohexanone was fractionally distilled to yield 217.6 g (71% theory) b.p. 83–85°/50 Torr (lit.[19] 164–166°/760 Torr); $[\alpha]_D^{25} = +13.2°$ (neat, lit.[19] $[\alpha]_D = +12.75°$). The product was at least 99% pure by glpc (5% SE 30, column tem. 145°), and its mass spectrum had a parent ion at *m*/*e* 112 ($C_7H_{12}O$) and a base peak at *m*/*e* 69.

(+)-(3R)- *and* (−)-(4R)-*Methylcycloheptanones* (1) *and* (2).[25] N-Methyl-N-nitroso-*p*-toluenesulfonamide (Diazald, Aldrich) (535.5 g, 0.25 mol) was added over a period of 1 hr to an ice-cooled soln of 11.2 g (0.1 mol) of the previously prepared (+)-(3*R*)-methylcyclohexanone in 2500 ml ether, 1500 ml MeOH, and 28 g KOH. After stirring at 0° for 3 hr and at room temp. for 17 hr, the mixture was neutralized with 300 ml 10% HCl, and filtered with suction through a slurry of celite and water. The ether was evaporated using a steam bath and the aqueous soln which remained was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and the solvent was removed on a rotatory evaporator. The liquid which remained was distilled through a vigreux column, and the fraction boiling at 65–67°/40 Torr was collected. GLPC (column temp. 145°) on the 7% Carbowax 20M column showed two peaks which were very close together. Two major (methylcycloheptanone) products were separated by preparative glpc (3/8 in. × 9 ft 25% Carbowax 20 M on 60/80 firebrick, column temp. 153°, flow rate 150 ml/min and had: For 1 $[\alpha]_D^{25°} = +55.2°$ (MeOH, lit.[25] +54°); for 2 $[\alpha]_D^{25} = -137°$ (MeOH, lit.[25] −136°). Each compound was at least 99% pure by glpc on the 7% Carbowax 20M column (column temp. 120°), and in each case the mass spectrumm showed a parent ion peak at *m*/*e* 126 ($C_8H_{14}O$) with no significant peaks at *m*/*e* 112, 140 and 154, which correspond to starting material and higher homologs.

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