4802 J. Org. Chem. 1991, 56, 4802–4804

1-Cyclohexylidene-1,4-bis(methylthio)-4-pentene (6c). In a similar manner, **5** (1.00 g, 3.16 mmol) was treated with dimethyl disulfide (0.30 g, 3.16 mmol) and cyclohexanone (0.31 g, 3.16 mmol) to give 0.12 g (16%) of **6c** as a pale yellow syrup: IR (neat) 1600 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 4.90 (s, 1 H, C=CH_2), 4.43 (s, 1 H, C=CH_2), 2.53–1.77 (m, 14 H), 1.77–1.23 (m, 6 H); MS (75 eV) m/z 242 (M$^+$).

2,5-Undecanedione (7a).[7h] A mixture of **6a** (1.86 g, 7.60 mmol) in dry CH$_3$CN (45 mL), distilled water (15 mL), and HgCl$_2$ (4.13 g, 15.2 mmol) was stirred at 50 °C for 20 h. After being cooled to rt, the suspension was neutralized with saturated aqueous Na$_2$CO$_3$. The supernatant was filtered off through hyflo-supercel and extracted with ether. The organic layer was washed with water, dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (102 °C (1 mmHg)) to yield **7a** (1.11 g, 79%) as crystals (mp 32.1–33.0 °C): IR (neat) 1720 (C=O) cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 2.54 (s, 4 H), 2.37 (t, 2 H, J_{HH} = 6 Hz), 2.10 (s, 3 H, CH_3), 1.87–0.63 (m, 11 H); MS (75 eV) m/z 184 (M$^+$).

1-Phenyl-2,5-hexanedione (7b).[7h] In a similar manner, **6b** (0.42 g, 1.68 mmol) was treated with HgCl$_2$ (0.91 g, 3.36 mmol). The residue was purified by Kugelrohr distillation (125–130 °C (3.0 mmHg)) followed by chromatography on silica gel using CHCl$_3$ to give 0.22 g (69%) of **7b** as a pale yellow syrup: IR (neat) 1710 (C=O) cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 7.10 (s, 5 H, Ph), 3.57 (s, 2 H, PhCH_2), 2.50 (s, 4 H, CH_2), 2.03 (s, 3 H, COCH_3); MS (75 eV) m/z 190 (M$^+$).

1-Cyclohexyl-1,4-pentanedione (7c).[7i] In a similar manner, **6c** (0.09 g, 0.37 mmol) was treated with HgCl$_2$ (0.20 g, 0.74 mmol). The residue was purified by Kugelrohr distillation (125–130 °C (10 mmHg)) followed by chromatography on silica gel using CHCl$_3$ to give 0.057 g (84%) of **7b** as a pale yellow syrup: IR (neat) 1710 (C=O) cm^{-1}; ^{1}H NMR (60 MHz, CDCl$_3$) δ 2.57 (s, 4 H, CH_2), 2.07 (s, 3 H, COCH_3), 1.90–1.0 (m, 10 H, cyclic CH_2); MS (75 eV) m/z 182 (M$^+$).

Acknowledgment. We thank Professor R. Irie and Miss H. Karasawa of the Faculty of Agriculture, Shinshu University, for 250-MHz NMR spectral measurements. We are grateful to Ihara Chemical Co. Ltd. for the gift of triphenylphosphine.

Registry No. **1**, 55759-75-6; (*Z*)-**2**, 133967-68-7; (*E*)-**2**, 133967-69-8; **3**, 133967-70-1; (*E*)-**4**, 58761-29-8; (*Z*)-**4**, 21944-96-7; **5**, 133983-56-9; (*E*)-**6a**, 133967-71-2; (*Z*)-**6a**, 133967-72-3; (*E*)-**6b**, 133967-73-4; (*Z*)-**6b**, 133967-74-5; **6c**, 133967-75-6; **7a**, 7018-92-0; **7b**, 32776-14-0; **7c**, 61771-79-7; hexanal, 66-25-1; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; dimethyl disulfide, 624-92-0.

Supplementary Material Available: ^{1}H NMR spectra for compounds **2–5**, **6a–c**, and **7a–c** (14 pages). Ordering information is given on any current masthead page.

Reexamination of the Conformational Preference of the Benzyl Group in Cyclohexane. Enthalpic and Entropic Contributions to $\Delta G°(CH_2Ph)$†

Eusebio Juaristi,* Victoria Labastida, and Sandra Antúnez

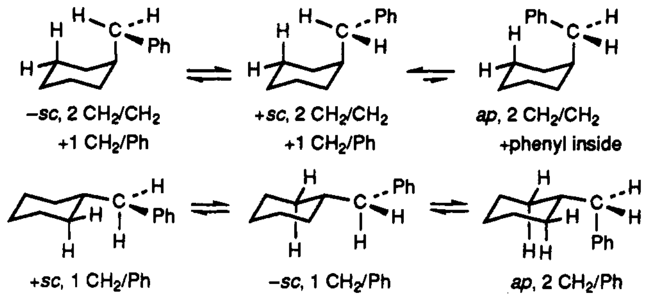
Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apdo. Postal 14-740, 07000 México, D.F. México

Received April 5, 1991

Introduction

The energy differences between the equatorial and axial conformations of monosubstituted cyclohexanes (*A* values) are of great interest to organic chemists since they serve as models for more complicated molecules.[1] Alkyl groups prefer equatorial over axial positions in order to avoid the repulsive steric interactions with the axial hydrogens of the 3- and 5-positions, and it is usually observed that bulkier the alkyl group the larger the preference for the equatorial form.[2]

Scheme I

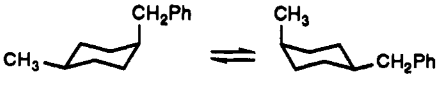


In this regard, the accepted *A* values for methyl, ethyl, and isopropyl are 1.74, 1.8, and 2.15, respectively,[2] in line with their increasing size. However, early force-field calculations indicated that the *enthalpic* contributions to the equatorial preference actually *decrease* along this series.[3] By contrast, more recent force-field results suggest that the axial–equatorial enthalpy differences do not decrease, but vary slightly along the methyl, ethyl, and isopropyl series.[4] Nevertheless, experimental NMR data agreed with the early theoretical results, affording, in kcal/mol, $-\Delta H°(\mathrm{Me}) = 1.75$, $-\Delta H°(\mathrm{Et}) = 1.6$, and $\Delta H°(i\text{-Pr}) = 1.52$.[5]

The conformational study of benzylcyclohexane was deemed important in this context because the analysis of the gauche interactions present in the axial and equatorial conformers (Scheme I) suggests that the overall enthalpy difference must be *less* than the two gauche butane interactions present in axial methylcyclohexane. On the other hand, three populated rotamers in equatorial benzylcyclohexane versus two in the axial form[6] imply that the entropy of mixing should make a substantial contribution to the free energy difference.

Results and Discussion

cis- and *trans*-1-benzyl-4-methylcyclohexanes (*cis*- and *trans*-**1**) were prepared and separated according to the procedure of Anderson.[7] The ambient-temperature 270-MHz NMR spectrum of *cis*-**1** (solvent CD$_2$Cl$_2$) presents a doublet (J = 7.9 Hz) at δ 2.57 due to the benzyl methylene hydrogens. At 202 K the signal appears as two doublets at δ 2.65 and 2.46, in a 56.4:43.6 ratio. Because the methylene signal in conformationally fixed *trans*-**1** has δ 2.47, a reasonable conclusion is that the downfield signal corresponds to the axial benzyl. Therefore, at low temperature the conformational equilibrium of *cis*-**1** (eq 1) appears to be displaced to the left, with $\Delta G°_{202K} = +0.10$ kcal/mol.



(1)

---

† Dedicated to Professor Fernando Walls, Instituto de Química, UNAM, on the occasion of his 60th birthday.

[1] Barton, D. H. R. *Experientia* **1950**, *6*, 316. Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562. Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience: New York, 1965. Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, in press.

[2] Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985.

[3] Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J.; Van-Catledge, F. A. *J. Am. Chem. Soc.* **1968**, *90*, 1199.

[4] Squillacote, M. E. *J. Chem. Soc., Chem. Commun.* **1986**, 1406.

[5] Booth, H.; Everett, J. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 255.

[6] The phenyl-inside rotamer of axial phenylcyclohexane is nearly 3 kcal/mol higher in energy and can be disregarded.

[7] Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1974**, 10.

0022-3263/91/1956-4802$02.50/0

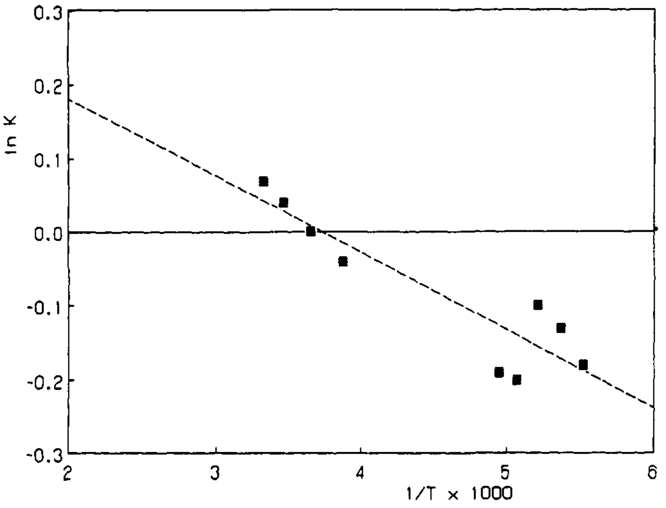


Figure 1. ln K as a function of $1/T$ for *cis*-4-methylbenzylcyclohexane (*cis*-1).

In view of the fact that Anderson has made an opposite assignment of the low-temperature ^{1}H NMR spectrum of *cis*-1,[7,8] we recorded the corresponding ^{13}C NMR spectra. Two carbon signals are particularly informative: that for the methyl group, which shows δ 20.40, and the one of the methylene carbon at δ 41.06, both at ambient temperature. Below coalescence (T = 202 K), these signals split into two signals each that can be easily assigned with consideration of the γ-gauche shielding effect.[9] In this way, the signals at δ 17.53 (44.6%) and 37.20 (54.1%) correspond to the axial methyl and methylene, respectively, whereas those at δ 23.39 (55.4%) and 44.39 (45.9%) correspond to the same groups in equatorial positions. It is therefore confirmed that the low-temperature equlibrium (eq 1) favors the conformer with equatorial methyl and axial benzyl groups, $\Delta G^\circ_{202K} = +0.08$ kcal/mol, in spite of the larger size of the latter.

Most interestingly, application of Eliel's equation[10] ($K = (\delta_{eq} - \delta_{mobile})/(\delta_{mobile} - \delta_{ax})$) to the ^{13}C NMR data[11] affords $\Delta G^\circ_{298K} = -0.04$ kcal/mol. That is, at ambient temperature the equilibrium in eq 1 is displaced to the right, so that now the bigger benzyl substituent predominates over the methyl group in the equatorial position. This temperature-dependent behavior clearly reflects a substantial entropy effect. Indeed, from the conformational free energy differences at ambient temperature (298 K) and at 202 K, $\Delta S^\circ = +1.17$ cal/K·mol and $\Delta H^\circ = +0.31$ kcal/mol are obtained. Therefore, at low temperature, i.e., 170–200 K, the ΔG° for eq 1 is dominated by the enthalpy term and the preference for the equatorial orientation follows the order $CH_3 > CH_2Ph$. On the other hand, at ambient and higher temperatures, the ΔG° values are dominated by the entropy term $T\Delta S^\circ$, ensuring that the preference for an equatorial orientation follows the "expected" order $PhCH_2 > CH_3$.

These thermodynamic data were confirmed by means of plots of ln K versus $1/T$ (Figure 1 is a representative example), which were linear and allowed for the derivation of ΔH° and ΔS°.[12] The low-temperature (T = 181, 186, 191.5, 197, and 202 K) data were obtained by integration of the corresponding signals for each isomer below coalescence, while the high-temperature data (T = 258, 273, 288, and 300 K) were obtained by use of Eliel's equation.[10,11] Therefore, a total temperature range of 119° was employed, which allows a reliable estimation of ΔH° and ΔS°. The resulting average values of six experiments are $\Delta H^\circ = +0.23 \pm 0.1$ kcal/mol and $\Delta S^\circ = +0.90 \pm 0.3$ cal/K·mol (eq 1). On the other hand, consideration of $\Delta H^\circ(Me) = -1.75$ kcal/mol and $\Delta S^\circ(Me) = -0.03$,[5] gives $\Delta H^\circ(CH_2Ph) = -1.52 \pm 0.1$ kcal/mol and $\Delta S^\circ(CH_2Ph) = +0.81 \pm 0.3$ cal/K·mol.

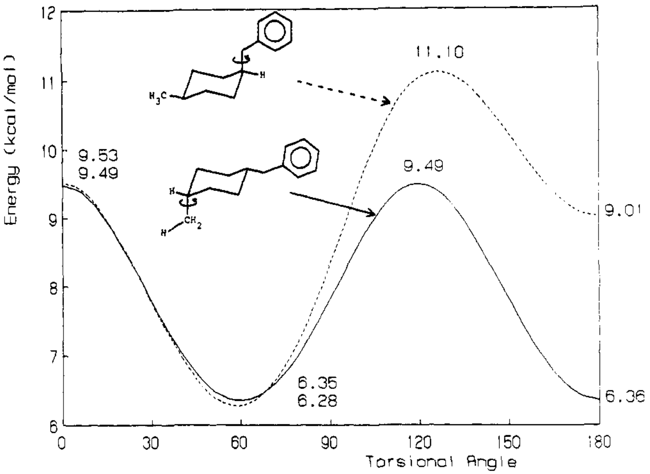


Figure 2. Rotation around axial methyl (—) and axial benzyl (---), according to force-field MM2 calculations (fully optimized geometries).

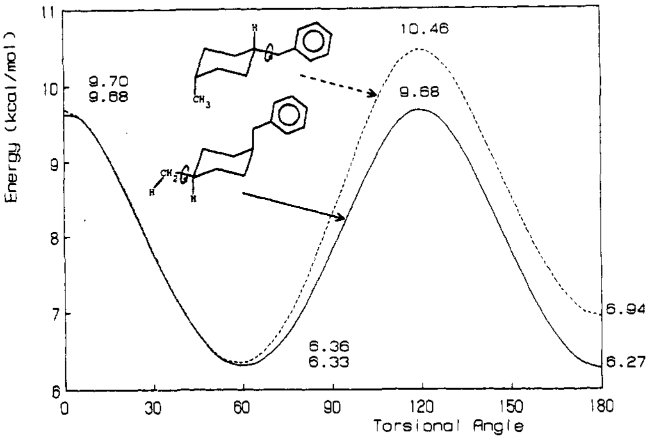


Figure 3. Rotation around equatorial methyl (—) and equatorial benzyl (---), according to force-field MM2 calculations (fully optimized geometries).

The experimental results reported in the previous text are well reproduced by molecular mechanics.[13] Figures 2 and 3 present the energy profiles for rotation around C(1)–CH$_2$ and C(4)–CH$_3$ in both conformations of *cis*-1. While similar enthalpy is calculated for the low-energy rotamers in axial methyl and benzyl, one of the populated rotamers in equatorial benzyl (*ap* in Scheme I) is 0.67 kcal/mol higher in enthalpy than all three rotamers in equatorial methyl.[14] Finally, determination of the entropy

---

(8) This assignment results in an opposite sign for the free energy difference in eq 1, $\Delta G^\circ_{176K} = -0.105$ kcal/mol. See ref 7.

(9) Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* 1967, *89*, 5315. Wilson, N. K.; Stothers, J. B. *Top. Stereochem.* 1973, *8*, 1.

(10) Eliel, E. L. *Chem. Ind.* (*London*) 1959, 568.

(11) Determination of the temperature dependence of ^{13}C NMR shifts of the two conformers in the 181–202 K temperature range affords corrected values for $\delta(CH_3\text{-ax})$ 17.94; $\delta(CH_3\text{-eq})$ 23.62; $\delta(\mathit{C}H_2Ph\text{-ax})$ 38.16; $\delta(\mathit{C}H_2Ph\text{-eq})$ 45.12 (assuming linear temperature dependence).

(12) Cf. Juaristi, E.; González, E. A.; Pinto, B. M.; Johnston, B. D.; Nagelkerke, R. *J. Am. Chem. Soc.* 1989, *111*, 6745.

(13) The MM2 force field for hydrocarbons was used: Allinger N. L. *J. Am. Chem. Soc.* 1977, *99*, 8127. Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN 47405, Program 395.

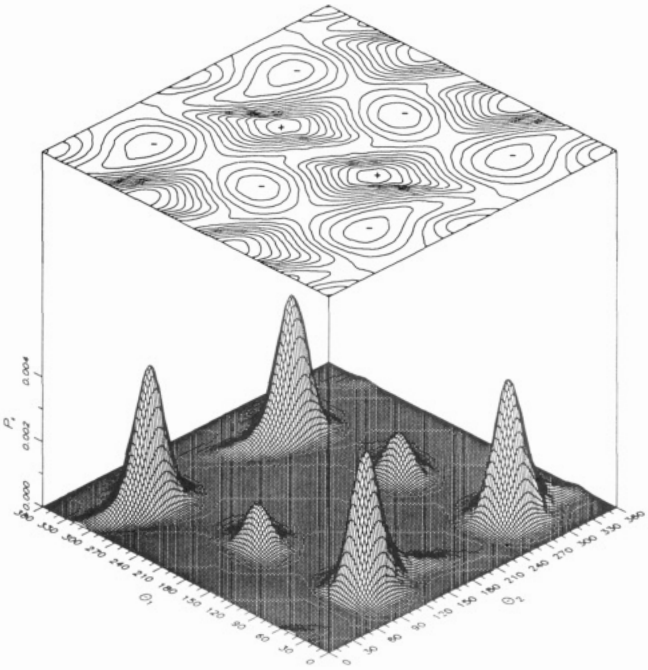


Figure 4. Conformational energy map (+ signs correspond to energy maxima and − signs correspond to energy minima) and Boltzmann populations in equatorial benzylcyclohexane.

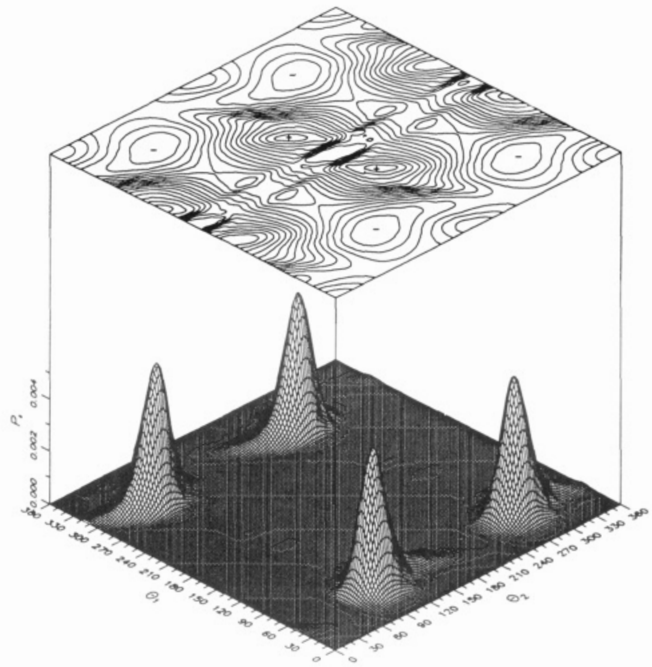


Figure 5. Conformational energy map (+ signs correspond to energy maxima and − signs correspond to energy minima) and Boltzmann populations in axial benzylcyclohexane.

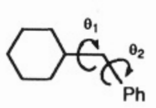
of mixing using the corresponding fractional populations[15] in axial and equatorial benzyl (Figures 4 and 5) provided $\Delta S^\circ = +0.63$ cal/K·mol, in agreement with the experimental estimate.

Experimental Section

General Information. ^{1}H NMR (270-MHz) and ^{13}C NMR (67.5-MHz) spectra were recorded on a JEOL GSX-270 spectrometer. Chemical shifts are given in parts per million downfield from TMS (δ). The probe thermocouple was used for temperature measurement, after calibration. Temperatures are believed to be accurate to within ±2 K.

***cis*-1-Benzyl-4-methylcyclohexane (*cis*-1).** According to the procedure of Anderson,[7] 4-methylcyclohexanone (2.66 g, 23.7 mmol) was allowed to react in ether with the Grignard reagent prepared from benzyl bromide (2.78 g, 22 mmol) and magnesium turnings (0.57 g, 22 mmol). Crude *cis*- and *trans*-1-benzyl-4-methylcyclohexanol (4.64 g, 96% yield) was distilled at low pressure, bp 104 °C (0.05 mm) [lit.[7] bp, 96 °C (0.03 mm)] and was then heated with *p*-toluenesulfonic acid (1.32 g, 6.9 mmol) in benzene to give 3.19 g (76.2% yield) of a 9:1 mixture of endo- and exocyclic olefins. Hydrogenation over Pd/C (300 mg) during 24 h (ethyl acetate as solvent) afforded 2.26 g (70.6% yield) of a 53:47 mixture of *trans*- and *cis*-1-benzyl-4-methylcyclohexanes, which were separated by preparative VPC (7 ft × $^1/_4$ in. Carbowax 20M at 180 °C) to give first the trans isomer, $n^{25}{}_D$ 1.5087 (lit.[7] $n^{25}{}_D$ 1.5076) and then the cis isomer, $n^{25}{}_D$ 1.5170 (lit.[7] $n^{25}{}_D$ 1.5165): ^{1}H NMR (CDCl$_3$, 270 MHz) δ 0.93 (d, J = 6.6 Hz, 3 H), 1.26–1.72 (m, 9 H), 2.56 (d, J = 7.9 Hz, 2 H), 7.12–7.31 (m, 5 H); ^{13}C NMR (CD$_2$Cl$_2$, 67.5 MHz) δ 20.40, 28.74, 30.62, 31.12, 37.88, 41.06, 125.87, 128.41, 129.45, 142.31.

Molecular Mechanics Calculations. The MM2 force field for hydrocarbons[13] was used to evaluate the intramolecular energetics. Uniform scanning at 5° increments was carried out for θ_1 and θ_2, and the corresponding conformational energy maps were drawn as illustrated in Figures 4 and 5. Minimum-energy conformations for equatorial and axial benzyl were found at (θ_1, θ_2) = (60°, 105°) and (60°, 105°), respectively.



The free-space intramolecular entropy[15] was measured according to eq 2

$$S^\circ = -R\sum_{i=1}^{n} P_i \ln P_i \tag{2}$$

where R is the gas constant, n is the number of conformational states sampled, and P_i is the Boltzmann probability of the ith conformational state. The P_i, in turn, were computed from the relationship

$$P_i = \frac{e^{-E_i/RT}}{\sum_{i=1}^{n} e^{-E_i/RT}} \tag{3}$$

where E_i is the intramolecular conformational energy of the ith state.

For equatorial benzyl, with $n = 5476$, the conformational entropy was found to be 13.29 eu, whereas for axial benzyl, $n = 5476$, $S^\circ = 12.66$ eu. Therefore, $\Delta S^\circ = 0.63$ eu for the equilibrium in eq 1.[16,17]

Acknowledgment. We thank G. Uribe for recording the variable-temperature NMR spectra and CONACYT (México, grant P228CCOX891692) for financial support of this work. We are also indebted to E. Ríos for her expert technical assistance.

Registry No. *cis*-1, 51747-35-4; *trans*-1, 51747-36-5; 4-methylcyclohexanone, 589-92-4.

---

(14) Rotamer *ap* in Scheme I is disfavored by enthalpy ($\Delta H^\circ = 0.67$ kcal/mol) and by the entropy of mixing ($\Delta S^\circ = R \ln 2 = 1.38$ cal/K·mol). Nevertheless, it contributes 14% to the equatorial population at 298 K ($\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -670 - (298)(1.38) = -1.081$ cal/mol; therefore, $K = e^{-\Delta G^\circ/RT} = 0.16$, see also Figure 4).

(15) Flory, P. J. *Statistical Mechanics of Chain Molecules*; Wiley-Interscience: New York, 1969. See also: Lopez de Compadre, R. L.; Pearlstein, R. A.; Hopfinger, A. J.; Seydel, J. K. *J. Med. Chem.* **1987**, *30*, 900.

(16) Calculated $\Delta S^\circ(\mathrm{CH_3}) = 0$, see ref 3.

(17) For another example of control of conformational preference by entropy effects, see: Bailey, W. F.; Connon, H.; Eliel, E. L.; Wiberg, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 2202.