Entropy Contribution to the Axial–Equatorial Energy Difference of Isopropylcyclohexane

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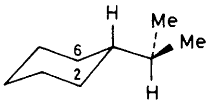
Use of a cryogenic high temperature equilibrium trapping technique in conjunction with dynamic ^{13}C n.m.r. spectroscopy shows that the entropic term for the free energy difference of isopropylcyclohexane is 2.2 cal K^{-1} mol^{-1} based on our determination of a statistical average of the *anti* and *gauche* rotamers of the equatorial isomer with a free energy of activation for the conversion of these two isomers found to be 4.1 ± 0.1 kcal mol^{-1} (1 kcal = 4.184 kJ).

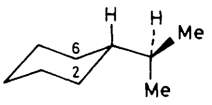
The energy differences between the equatorial and axial forms of substituted cyclohexanes (*A* values) have long been of interest to organic chemists.[1] In particular the mono alkyl (methyl, ethyl, and isopropyl) cyclohexanes have attracted attention as model systems for more complicated natural products and other molecules of synthetic interest. However, there has been a controversy surrounding the entropic contribution to the $-\Delta G^\circ$ values of even these simply substituted cyclohexanes.[2,3] This communication reports low temperature dynamic n.m.r. evidence that the entropic term is, in fact, important for isopropylcyclohexane.

The accepted $-\Delta G^\circ$ values are 1.7, 1.8, and 2.2 kcal mol^{-1} for methyl, ethyl, and isopropylcyclohexane respectively.[4] The increase along this series was believed to be a result of increasing size in these groups. However, an early force-field calculation suggested that the enthalpic isomeric differences actually *decrease* along this series and that therefore the entropic term must be responsible for the increase in the observed free energy differences.[2] Estimates of the entropic contributions were made by calculating the energies of the possible rotamers about the exocyclic single bond and using the resulting fractional populations to arrive at an entropy of mixing. A recent n.m.r. study by Booth and Everett on ^{13}C labelled and 1,4-disubstituted cyclohexanes essentially agreed with the early force-field results, reporting 1.75 kcal mol^{-1}† and 1.52 kcal mol^{-1} ΔH° values for methyl and isopropylcyclohexane respectively.[3] These authors used rotamer population arguments similar to those presented in the original force-field calculations to explain the apparent entropic contribution to the *A* value of isopropylcyclohexane. We have repeated the force-field calculations with a more recently parameterized force field[5] and find that the axial–equatorial enthalpy differences do not decrease, but vary slightly along the methyl, ethyl, and isopropyl series (1.78, 1.81, and 1.71 kcal mol^{-1} respectively). These values disagree in part with the n.m.r. results of Booth, which may have been influenced by the assumption of additivity of $-\Delta G^\circ$ values for 1,4-disubstituted cyclohexanes and the still necessarily small temperature range available for these experiments. Nevertheless, the enthalpy differences calculated do not show the increase apparent in the $-\Delta G^\circ$ values and this suggests that there is an entropic contribution to the isomeric free energy difference especially for isopropylcyclohexane. Thus the rotameric contribution to both the axial and equatorial isomers may significantly influence the free energies of these systems.

Isopropylcyclohexane was predicted to have large entropic contributions to its *A* value because the equatorial form was calculated to have nearly equal energy *anti* (I) and *gauche* (II) rotamers, while the axial form had only one low-energy rotamer (III). There has been, however, no direct experimental evidence concerning the rotameric population of isopropropylcyclohexane. Isopropylcyclohexane is a 1,1,2,2-tetrasubstituted ethanes exist only in the *gauche* conformation,[6] the only exception being 2,3-dimethylbutane which shows a 1 : 2 *anti* : *gauche* ratio.[7,8] The rotameric populations for isopropylcyclohexane are, then, of interest not only for their importance to the axial–equatorial free energy difference but also as a reference point for 1,1,2,2-tetrasubstituted ethanes in general.



(I)



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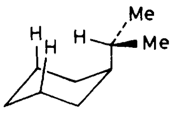

(III)

Results have now been obtained which relate to the rotameric populations of axial and equatorial isopropylcyclohexane. Low temperature dynamic n.m.r. spectroscopy in conjunction with a conformational trapping technique allows isolation and spectroscopic examination of a high-temperature equilibrium mixture containing substantial amounts of a high-energy conformer. This technique is described in detail elsewhere,[9] but briefly, in these experiments isopropylcyclohexane vapour was heated to 600 °C by passing it through a tubular oven. The high-temperature axial–equatorial equilibrium thus established was trapped by allowing the heated vapour to impinge on the sides of an n.m.r. tube cooled to −196 °C. The solvent (a mixture of $CDCl_2F$, $CDClF_2$, and CCl_2F_2) was slowly distilled into the tube while the sample was kept at liquid nitrogen temperature. The ^{13}C n.m.r. spectrum at −150 °C of a sample prepared in this manner is shown in Figure 1. The ^{13}C chemical shifts are reported elsewhere,[10] but the assigned carbon resonances are indicated in Figure 1. As seen in Figure 1 the intensities of the axial form resonances have the expected relative magnitudes but surprisingly the 2, 6, and β-carbon atoms of the equatorial conformer show low intensities and large linewidths. This broadening is indicative of a dynamic rotameric equilibrium occurring in this isomer. Dynamic n.m.r. spectra of a tetrasubstituted ethane of this type have been seen only once before with 2,3-dimethylbutane.[7,8]

Figure 2 shows the temperature dependent ^{13}C n.m.r. spectrum of equatorial isopropylcyclohexane.‡ Both *anti* and

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† 1 kcal = 4.184 kJ.

‡ Our dynamic n.m.r. spectra were obtained on a Bruker WM-250 with a sample of 30 mg of isopropylcyclohexane dissolved in 2 ml of a 50 : 50 mixture of ethene and $[^2H_1]$ethane. The free energy of activation was calculated as an average of six free energies of activation obtained from −150 °C to −181 °C assuming no change in $\Delta S^\ddagger$ over this temperature range. The largest contribution to the error was from a 2 °C uncertainty in the sample temperature which was measured by a calibrated thermocouple placed in the cooling stream just below the sample.

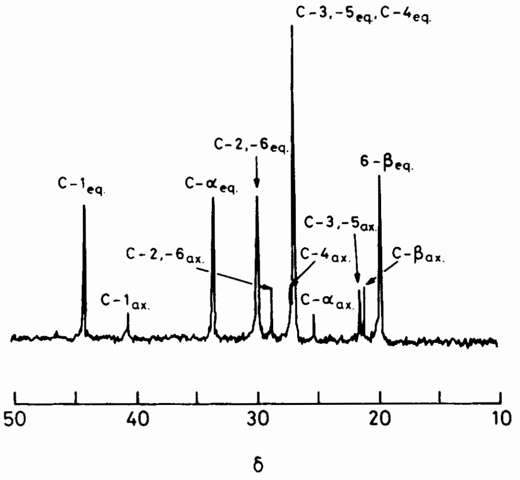

Figure 1. ^{13}C N.m.r. spectrum of a trapped high-temperature equilibrium sample of isopropylcyclohexane at −150 °C in $CDCl_2F$–$CDClF_2$–CCl_2F_2. Chemical shift assignments for the axial (ax.) and equatorial (eq.) carbon atoms are indicated.

gauche rotamers are present as is evidenced by the broadening and splitting of the resonances of the 2, 6, and β carbon atoms. At −181 °C both C-2 and C-6 of the *anti* rotamer (I) together with C-6 of rotamer (II) which is *gauche* to a methyl and a hydrogen, all appear at δ 32.2. The C-2 of the *gauche* rotamer (II) shows a resonance at δ 24.4. Similarly the β methyl carbon atoms split into two peaks at δ 21.4 and 15.8.

Our force-field calculations on the equatorial isopropylcyclohexane system gave exactly the same strain energies for the *anti* and *gauche* rotamers. We also used force-field calculations to examine the two possible interconversion routes for the *gauche* rotamers. These are a route directly from one mirror image *gauche* rotamer to the other and an indirect pathway *via* the *anti* rotamer. Our force-field calculations show that the direct route has a barrier more than 2 kcal mol^{-1} higher than the barrier *via* the *anti* form. This is in agreement with the results for 2,3-dimethylbutane[7] and suggests that at the temperature of our experiments less than 1% of the interconversion occurs *via* the direct route.

Simulated spectra[11] of our temperature dependent n.m.r. results reveal a ratio of the *anti* to the two mirror image *gauche* isomers of 1 : 2 ± 0.2 which is similar to that found for 2,3-dimethylbutane.[7] This ratio is in agreement with our force field calculations which predict a statistically determined ratio of rotamers. Thus isopropylcyclohexane is at a borderline of the 1,1,2,2-tetra-alkylethane system in that there is a balance between a destabilizing geminal interaction which favours the *gauche* form[6] and destabilizing steric effects between *gauche* alkyl groups which favour the *anti* rotamer.

We have also been able to obtain the free energy of activation for the *gauche–anti* interconversion. Using a three site exchange program based on the development by Binsch,[11] we simulated the dynamic n.m.r. results (Figure 2) assuming that the indirect interconversion pathway greatly predominates. Our results give rate constants which correspond to a barrier for the *gauche–anti* conversion of 4.1 ± 0.1 kcal mol^{-1}.

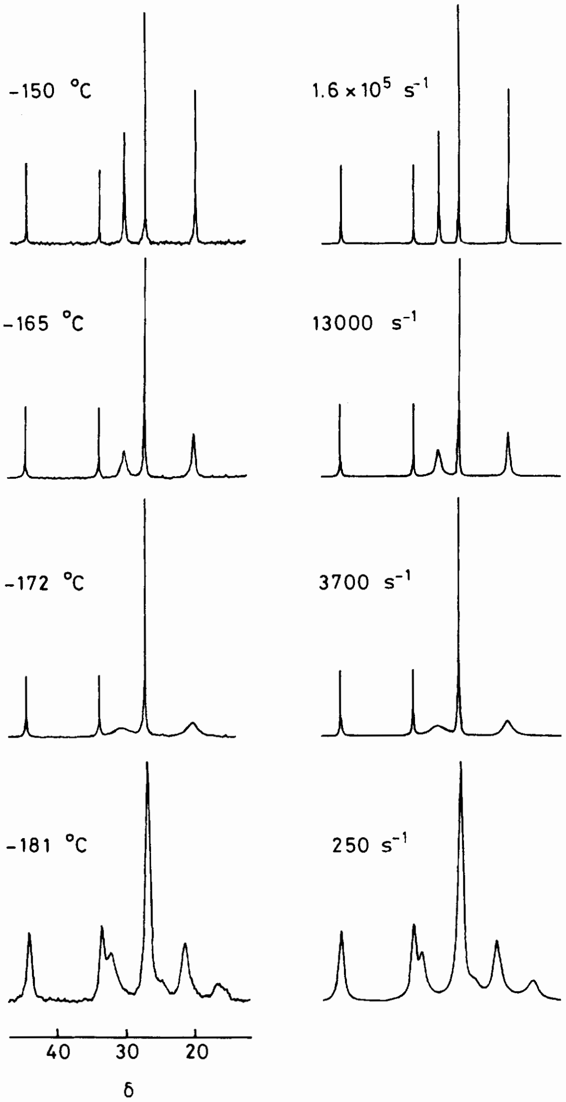

Figure 2. Dynamic ^{13}C n.m.r. spectra of isopropylcyclohexane. The simulated spectra appear at the right with the calculated rate constant indicated.

The axial isomer shows no dynamic n.m.r. effects and thus, as expected, this conformer has only one rotamer. The nearly equal energies of the *anti* and two *gauche* forms of the equatorial isomer imply that the entropy of mixing contribution to the entropic difference between the axial and equatorial isopropylcyclohexane is 2.2 cal K^{-1} mol^{-1} (R ln 3) and thus makes a substantial contribution to the isomeric free energy difference of isopropylcyclohexane at room temperature.§ Since other examples of the importance of entropy in axial–equatorial energy differences are known,[12] temperature effects on these energy differences must be recognized. This is

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§ This value for $\Delta S°$ corresponds well to that found by Booth and Everett.[3] However, the $\Delta H°$ values found in that study no longer agree with modern force-field calculations which are correctly parameterized for hydrogen, unlike the early calculations.[2] Some of the sources for this difference may be the inherent inaccuracies of the force-field program. In addition, errors may ensue from assuming additivity of $-\Delta G°$ values for 1,4-disubstituted cyclohexanes as seen with 1-ethyl-4-isopropylcyclohexane.[3]

of particular importance for systems of synthetic interest where low temperature reactions are carried out.

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