Organic and Biological Chemistry

Separation of Conformers. II. Axial and Equatorial Isomers of Chlorocyclohexane and Trideuteriomethoxycyclohexane

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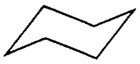
Abstract: The rate of chair–chair interconversion of cyclohexane derivatives is sufficiently slow at -150° that the conformational isomers may be separated by ordinary recrystallization techniques. Using this method, partial separation of axial and equatorial forms of chlorocyclohexane has been effected. The nmr spectra of pure equatorial chloro- and trideuteriomethoxycyclohexane have been obtained by dissolution of the conformationally pure crystalline materials at -150°. Equatorial cyclohexyl chloride has a half-life of 22 years at -160°, 23 min at -120°, 0.25 sec at -60°, and 10^{-5} sec at 25°.

The importance of conformational preference in determining the physical, chemical, and spectroscopic properties of organic molecules is well established.[1,2] A wealth of data has led to a reasonably sound understanding of the conformational idiosyncrasies of the cyclohexane ring system.[2] Nmr spectroscopy has been uniquely valuable in such studies.[3]

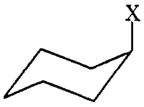
Since the early postulation of the existence of the chair (I), the boat (II), and the twist (III) conformations of cyclohexane,[4] the possibility of separating axial and equatorial isomers of comparable stabilities or boat forms of monosubstituted cyclohexanes has intrigued chemists. Claims of the isolation of conformational isomers of monosubstituted cyclohexanes (stable at room temperature) have been made,[5] but the validity of these reports can be effectively challenged on thermodynamic and kinetic grounds.[2,6] Certain monosubstituted cyclohexanes have been observed to be conformationally pure in the crystalline state. For example, liquid chlorocyclohexane exhibits two carbon–chlorine infrared stretching frequencies for axial chlorine (684.5 cm^{-1}) and equatorial chlorine (731 cm^{-1}).[7] Upon crystallization, the band at 684.5 cm^{-1} disappears completely indicating the conformationally pure equatorial isomer. Similar behavior has been noted for 1,2-dichloroethane,[8] 1,2-dibromoethane,[8] and 1,1,2,2-tetrabromoethane.[9] Although crystallization as a conformationally pure species constitutes a separation of conformers in a sense, obtaining the pure conformer in the solid state does not make it available for certain important studies which must be carried out in solution.


I


II


III

Although a significant effort has been expended to study the rates of conformational equilibration[10] and conformational preferences[2,11] in rapidly equilibrating monosubstituted cyclohexanes, little effort has been made to isolate axial (IV) and equatorial (V) isomers of comparable stabilities in *solution.*[12] Now that the barriers ($\Delta G^{\ddagger}$) to chair–chair interconversion in cyclohexane derivatives are known,[10] the temperatures at which axial and equatorial isomers have substantial half-lives can be calculated. At appropriately low temperatures, either isomer will exist as a separate, *isolable* compound.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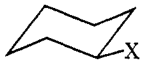
V

This report concerns the partial or complete isolation of the axial and equatorial isomers of chlorocyclohexane and trideuteriomethoxycyclohexane in solution.

Results

Using available activation parameters for chair–chair equilibration in chlorocyclohexane (eq 1),[13] calculations indicate that the half-life of axial chlorocyclohexane is approximately 350 hr at -150° (Table I).

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(11) E. L. Eliel and R. J. L. Martin, *J. Am. Chem. Soc.*, **90**, 682, 689 (1968), and references therein.

(12) F. R. Jensen and C. H. Bushweller, *ibid.*, 88, 4279 (1966).

(13) Unpublished results.

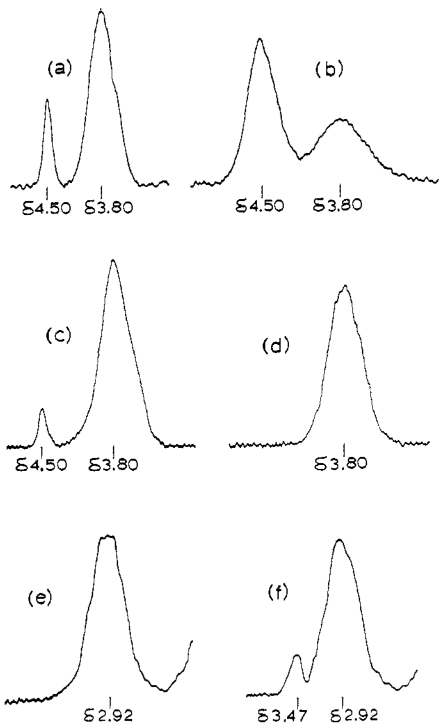
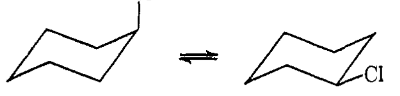


Figure 1. The nmr spectra (60 MHz) of the methine (HCX) hydrogens of chlorocyclohexane and trideuteriomethoxycyclohexane under various conditions: (a) equilibrated axial and equatorial chlorocyclohexane at −115°, (b) axial isomer-enriched chlorocyclohexane at −150°, (c) 95% pure equatorial chlorocyclohexane at −150°, (d) 100% pure equatorial chlorocyclohexane at −150°, (e) 100% pure equatorial trideuteriomethoxycyclohexane at −150°, (f) equilibrated axial and equatorial trideuteriomethoxycyclohexane at −120°. The nmr spectra are not necessarily on exactly the same scale.

Thus, two approaches were taken in an attempt to isolate either axial or equatorial chlorocyclohexane in *solution* at −150°. The first method involved a preferential crystallization and the second technique took advantage of the conformational purity of crystalline chlorocyclohexane.



(1)

Table I. Half-Life of Equatorial Cyclohexyl Chloride at Various Temperatures[a]

Temp, °C	25	−60	−120	−160
$t_{1/2}$	1.3×10^{-5} sec	0.025 sec	23 min	22 years

[a] Reference 13. Back-reaction is not included in the calculation. These half-life values were obtained by extrapolation of kinetic data for the interconversion obtained at about −128° by observing the rate (nmr spectroscopy as the analytical tool) at which the equatorial isomer converts to the equilibrium mixture, and at about −60° using the usual nmr techniques for measuring the rates of fast conformational interconversion.

The preferential crystallization was performed in the following manner. A 0.35-g sample of chlorocyclohexane was placed in an nmr tube at low temperature (−80°) and trideuteriovinyl chloride (CD_2CDCl) added until the chlorocyclohexane had completely dissolved (total volume = 0.6 ml). An nmr spectrum (60 mHz) of the resultant solution at −115° (Figure 1a) revealed the typical broad axial methine proton (*H*CCl) resonance (δ 3.80 ppm) and the more narrow equatorial methine proton signal (δ 4.50 ppm). The observation of the two *H*CCl resonances at −115° indicates that chair–chair isomerization (eq 1) is now slow at least on the nmr time scale. The sample was then cooled to −150° and the nmr spectrum examined. After 1 hr, the axial methine proton (equatorial chlorocyclohexane) resonance (δ 3.80 ppm) had decreased substantially in intensity compared to the equatorial methine proton (axial chlorocyclohexane) signal (δ 4.50 ppm). The axial:equatorial chlorine ratio was 58:42 (Figure 1b) at this point indicating the *preferential crystallization of equatorial chlorocyclohexane.* A complete spectrum of chlorocyclohexane enriched in the axial isomer is illustrated in Figure 2a.

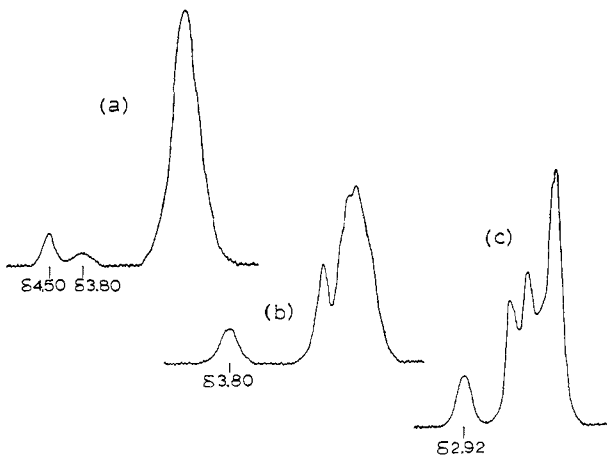


Figure 2. The complete nmr spectra (60 MHz) of (a) axial isomer-enriched chlorocyclohexane at −150°, (b) 100% pure equatorial chlorocyclohexane at −150°, and (c) 100% pure equatorial trideuteriomethoxycyclohexane at −150°. The nmr spectra are not necessarily on exactly the same scale.

The mother liquor was then removed by gentle suction, the crystals washed with additional CD_2CDCl and dissolved in 0.5 ml of CD_2CDCl at −150°. The nmr spectrum of the *H*CCl resonance of the resultant solution showed 95% pure equatorial chlorocyclohexane (Figure 1c). Several attempts at purification of equatorial chlorocyclohexane by preferential crystallization from CD_2CDCl always left about 5% axial isomer as contaminant.

The solution of 95% pure equatorial chlorocyclohexane was warmed to about −125°, and the equatorial HCCl proton resonance (δ 4.50 ppm) increased gradually in intensity. After about 20 min, the two *H*CCl resonances were very similar to that shown in Figure 1a. At −115°, the ratio of equatorial:axial chlorocyclohexane *in equilibrium* is 87:13.

Isolation of 100% conformationally pure equatorial chlorocyclohexane in *solution* was achieved by a simple technique. A 0.09-g sample of neat chlorocyclohexane in an nmr tube was cooled very slowly (*ca.* 5°/0.5 hr) through its melting point (−43.9°), and after crystallization was complete, the sample was cooled to −150°. Then, a 0.5-ml portion of CD_2CDCl was introduced *via* distillation very slowly effecting *complete dissolution* of the crystalline material. An nmr spectrum of the resultant solution revealed only *one* *H*CCl resonance, the axial *H*CCl proton signal at δ 3.80 ppm (Figure 1d). None of the equatorial *H*CCl (axial chlorocyclohexane) signal (δ 4.50 ppm) could be detected even at substantially increased signal amplification. These results constitute the isolation of 100% conformationally pure equatorial chlorocyclohexane as a *stable compound in solution*. A complete nmr spectrum of the pure equatorial chlorocyclohexane is shown in Figure 2b. Significant differences in the methylene proton resonances of the axial isomer-enriched chlorocyclohexane (Figure 2a) and pure equatorial chlorocyclohexane (Figure 2b) may indicate not only differences in the spin–spin splitting patterns but also different diamagnetic anisotropies of axial and equatorial carbon–chlorine bonds.

The nmr spectrum of the pure equatorial chlorocyclohexane was scanned repeatedly over a period of about 2 hr at −150° and no changes were observed. This observation is consistent with the prediction that the half-life of either axial or equatorial chlorocyclohexane is many, many hours at −150°.

Pure equatorial trideuteriomethoxycyclohexane was isolated in a similar manner. A sample of the neat liquid in an nmr tube was cooled slowly to −150°, and the crystalline material dissolved completely in CD_2CDCl. Examination of the methine proton resonance revealed the presence of only *one* signal at δ 2.92 ppm (Figure 1e) due to the axial *H*CO proton (equatorial trideuteriomethoxycyclohexane) and no indication, even at very high amplification, of the equatorial *H*CO (axial trideuteriomethoxycyclohexane) resonance (δ 3.47 ppm). A complete spectrum of 100% conformationally pure equatorial trideuteriomethoxycyclohexane is illustrated in Figure 2c. When the solution of pure equatorial trideuteriomethoxycyclohexane was warmed to about −120°, the equatorial *H*CO proton signal appeared and grew gradually in intensity. An nmr spectrum of the *H*CO proton resonances under equilibrated conditions at −120° is given in Figure 1f. At −96°, the ratio of equatorial:axial trideuteriomethoxycyclohexane is 83:17.

When the solution of equilibrated trideuteriomethoxycyclohexane was warmed further to temperatures above −80°, the two *H*CO resonances coalesced in a manner typical of an increasing exchange rate on the nmr time scale. From such spectral behavior, the barrier ($\Delta G^{\neq}$) for axial isomer to twist-boat conversion is calculated to be 9.4 ± 0.1 kcal/mol at −77°. This observation is in contradiction to speculation that interconversion in methoxycyclohexane may still be rapid on the nmr time scale at −110°.[14] The coalescence phenomenon is difficult to observe in the undeuterated species because of the near coincidence of the equatorial methine (*H*CO) proton and methyl proton resonances.

Attempts to perform the same type of experiment reported here on bromocyclohexane and iodocyclohexane were not entirely successful because of sparing solubilities in CD_2CDCl. Indeed, it was evident that both axial and equatorial isomers of iodocyclohexane were obtained by dissolving the crystalline material in CD_2CDCl at −150°.

Discussion

Although a number of compounds are known to be conformationally pure as solids,[7–9,15] the significance of the experiments in this report is that conformers which have barriers ($\Delta G^{\neq}$) to equilibration less than 11 kcal/mol have been separated, wholly or in part, and examined in *solution*. The availability of conformationally pure isomers or nonequilibrated mixtures in solution provides a means of measuring rate constants for chair–chair interconversion at temperatures very different from those necessary employing conventional nmr site-exchange techniques. Reliable enthalpies and entropies of activation can likely be obtained from these sets of data, and this information should be useful in understanding the nature of the transition state for interconversion.

The availability of pure conformers should enable the study of reactions of such conformers with appropriate reagents. It will not be necessary to make the complicated assumptions necessary for rapidly equilibrating systems or to introduce large, "locking" groups.

The techniques reported here should be general for a host of compounds provided they are conformationally pure in the crystalline state. Attempts are underway to isolate pure axial monosubstituted cyclohexanes and rotational isomers of appropriately substituted ethanes.

Experimental Section

All experiments were performed in standard nmr tubes. The nmr spectra were obtained using a Varian Associates HR-60 spectrometer equipped with a special variable-temperature probe. At −170°, the variation in temperature throughout the entire sample region is less than 0.10°. Temperature was measured using a calibrated copper–constantan thermocouple and is accurate to within 0.1%. Spectral calibrations were performed using the audiomodulation technique.

Trideuteriomethoxycyclohexane. Dry cyclohexanol (50 ml) was treated with 3.9 g (0.06 g-atom) of potassium in chunks, and the reaction mixture was warmed slightly until it was apparent that all the potassium had reacted. The solution was allowed to cool whereupon it solidified. A 15.0-g (0.10 mol) sample of trideuteriomethyl iodide was added in one portion causing the solid mixture to become more mobile. The reaction mixture was stirred at room temperature for 48 hr and filtered (KI), and the crude trideuteriomethoxycyclohexane, bp 130° (756 mm), was isolated by fractionation. The crude product was further purified by preparative glpc on a 20% QF-1 60–80 Chromosorb W column (10 ft × 0.5 in.) at 145° with a helium flow of 120 cc/min. The yield was 2.3 g (30%) of trideuteriomethoxycyclohexane: nmr peaks (60 MHz, CCl_4) at δ 3.06 (1 H multiplet, *H*CO) and at δ 1.00–2.10 (10 H multiplet). The trideuteriomethoxycyclohexane gave the same glpc retention time (3.6 min) as an authentic sample of methoxycyclohexane.

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