Complete ¹³C NMR Spectra of the Axial Forms of Methyl-, Ethyl- and Isopropylcyclohexane

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Low-temperature ¹³C NMR spectral data have been obtained for equatorial and axial methyl-, ethyl- and isopropylcyclohexane using a high-temperature cryogenic trapping technique. ¹³C chemical shift differences between major and minor conformations of each compound are discussed in terms of chemical shift theories. A convenient synthesis of deuteriated dichlorofluoro- and diffuorochloromethane, which are excellent low-temperature NMR solvents, is also presented.

KEY WORDS Low temperature ¹³C NMR; methylcyclohexane; ethylcyclohexane; isopropylcyclohexane; axial and equatorial conformers.

INTRODUCTION

The study of conformational equilibria in substituted cyclohexanes and the resulting free energy differences (A values) between the equatorial and axial forms of these compounds have been important to organic chemists.¹ Monosubstituted alkylcyclohexanes, in particular, have attracted much attention since they are useful as model systems for more complex natural products and other molecules of synthetic interest. Unfortunately, the large ΔG° values associated with these simple cyclohexanes have made their minor conformations difficult, and in some cases impossible, to observe directly.²

Direct observation of the axial isomer of methylcyclohexane was first accomplished as the result of a variable-temperature infrared study,³ where the temperature-dependent bands at 607 and 547 cm⁻¹ were assigned to the axial and equatorial forms. Subsequent instances of direct spectroscopic detection of axial methylcyclohexane have involved NMR methods which require low temperatures in order to increase the average lifetime of the molecule in the minor conformation. Although this makes the minor form observable on the NMR time scale, it also results in small minor form populations. Nevertheless, low-temperature ¹³C NMR has yielded the C-3,5, C-2,6 and C-Me resonances,⁴⁻⁶ while low-temperature ¹H NMR of a high-temperature equilibrium sample⁷ yielded the ¹H-Me resonance of the axial form.

Only one direct measurement of the axial ¹³C resonances of isopropylcyclohexane has previously been attempted.⁶ While ¹³C labelling of the methine carbon allowed observation of the weak axial isopropyl C-methine resonance, no other minor form resonances could be detected. To our knowledge, the

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0749-1581/87/010053-04\$05.00 © 1987 by John Wiley & Sons, Ltd. axial isomer of ethylcyclohexane has never been directly observed, and thus none of its axial form ¹³C resonances are known.

In the interest of determining the spectral properties of simple monoalkylated cyclohexanes, we have refined a previously described^{7,8} high-temperature cryogenic trapping method and employed it in the study of a series of monosubstituted alkylcyclohexanes. Consequently, we are able to present the complete low-temperature ¹³C NMR spectra of axial and equatorial methyl-, ethyl- and isopropylcyclohexane. The shift differences between the axial and equatorial isomers of these alkylcyclohexanes, and the changes in these differences that occur when the alkyl substituent is varied, are pertinent to current discussions of the origins of conformationally induced ¹³C chemical shifts.⁹⁻¹³

RESULTS AND DISCUSSION

Using the cryogenic trapping method described elsewhere,8 we have obtained the low-temperature ¹³C spectra of a high-temperature equilibrium mixture of the axial and equatorial conformers of methyl-, ethyland isopropylcyclohexane. The ¹³C NMR spectrum at -150 °C of each monosubstituted cyclohexane deposited from 600 °C is shown in Fig. 1. A mixture of deuteriated dichlorofluoro-, difluorochloro- (see Experimental) and dichlorodifluoromethane proved to be an excellent low-temperature NMR and deuterium lock solvent for these compounds. Two sets of resonances were observed for each alkylcyclohexane, one of which corresponds to the equatorial conformer of each (Fig. 1B, D and F). The second set of signals rapidly disappeared, with a concurrent increase in the intensities of the equatorial conformers' signals, after the sample was warmed to -120 °C. The spectra

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Figure 1. Left: ¹³C NMR spectra of trapped conformational mixtures of axial and equatorial (A) methyl-, (C) ethyl- and (E) isopropylcyclohexane at -150° C in CDCl₂F-CDClF₂-CCl₂F₂. The axial form resonances are assigned. Right: ¹³C NMR spectra of the same samples warmed to -120° C and recooled to -150° C, leaving only equatorial resonances. The equatorial resonances are assigned for (B) methyl-, (D) ethyl- and (F) isopropylcyclohexane.

obtained after complete decay are essentially identical with those obtained from ordinarily prepared samples of methyl-, ethyl- and isopropylcyclohexane in $CDCl_2F-CDClF_2-CCl_2F_2$. Consequently, we have assigned the additional signals to the metastable axial conformers of each monosubstituted cyclohexane. Table 1 gives the ¹³C chemical shifts and shift differences of the axial and equatorial resonances of methyl-, ethyl- and isopropylcyclohexane. Assignments of the equatorial conformers have been reported previously,^{4,6,14} and those of the axial conformers were made by analogy with reported axial methyl⁴⁻⁶ and isopropyl⁶ shifts, comparison of relative intensities and averaged high-temperature chemical shifts.

The chemical shifts for axial methylcyclohexane are, in general, consistent with the predictions of Dalling and Grant^{9b} based on regression analysis of the chemical shifts of a series of methyl-substituted cyclohexanes, and also with the previously experimentally observed C-3,5, C-2,6 and C-methyl resonances.⁴⁻⁶ The only previously observed isopropylcyclohexane resonance, the C-methine,⁶ is also consistent with the shift we have obtained. The discovery of the previously unobserved methylcyclohexane C-1 and C-4, isopropylcyclohexane C-1, C-2,6, C-3,5, C- β and all ethylcyclohexane minor form resonances is significant, since an accurate knowledge of all shifts of these axial conformations is relevant in the structural analysis of natural products. Further, inspection of the chemical shift differences between equatorial and axial conformers of these three alkylcyclohexanes (Table 1) provides an excellent opportunity to acquire information concerning conformationally induced ¹³C chemical shifts.

It is noted from Table 1 that the chemical shift difference of C-1 decreases along the series methyl-, ethyl- and isopropylcyclohexane. This trend can be rationalized in light of an MMII calculation¹⁵ which we conducted for each alkylcyclohexane. Our calculations showed that a major change on going from the equatorial to the axial isomer is a bending of the alkyl substituent away from the cyclohexane ring. The magnitude of this deformation was dependent on the substituent, with methyl being bent back by 12.5°, ethyl by 11.8° and isopropyl by 10.1°. Apparently, back strain with the ethyl substituent, and the even greater back strain with the isopropyl substituent

			Axial form ¹³ C shift	Axial-equatorial shift difference		
Alkyl cyclohexane	Carbon	Equatorial form ¹³ C shift		Experimental	Calculated ^c	Literature ^d
Methyl-	C-1	33.18	27.58	-5.60	-4.56	
	C-2,6	35.45	31.86	-3.59	-3.62	-3.62
	C-3,5	26.68	20.66	-6.02	-6.42	-6.06
	C-4	26.32	27.18	+0.86	+0.16	
	C -α	23.36	17.29	-6.07	-4.80	-6.07
Ethyi-	C-1	39.75	34.73	-5.02		
	C-2,6	33.27	29.75	-3.52		
	C-3,5	26.55	20.90	-5.65		
	C-4	26.78	27.10	+0.32		
	C -α	30.81	23.33	-7.48		
	C-β	11.90	12.63	+0.73		
lsopropyl-	C-1	44.11	40.71	-3.40		
	C-2,6	29.81	28.84	-0.97		
		(32.15) ⁶		(-3.31) ⁶		
	C-3,5	26.87	21.62	-5.25		
	C-4	26.87	27.30	+0.43		
	C -α	33.42	25.37	-8.05		-8.25
	C -β	16.72	21.25	+1.53		
	-	(21.43) ^{<i>b</i>}		(-0.18) ⁶		

Table 1. ¹³C chemical shifts of axial and equatorial methyl-, ethyl- and isopropylcyclohexane^a

^a Chemical shifts are in ppm and were measured in $CDCl_2F-CDClF_2-CCl_2F_2$ at -150 °C relative to the CCl_2F_2 resonance at 100.24 ppm.

^b Shifts in parentheses are the shifts of the axial rotamer of equatorial isopropylcyclohexane only.¹⁶ ^c The calculated shift differences are those calculated by Dalling and Grant^{9b} for methylcyclohexane.

^d The literature values of the shift differences for methylcyclohexane are those reported by Basus.⁵ The C-2 shift difference for isopropylcyclohexane is that reported by Booth and Everett.⁶

which is generated by a β -methyl-equatorial 2,6hydrogen interaction, forces these substituents back toward the plane of the ring and decreases the bending angle. The decrease of the C-1 shift difference along the series suggests that the shift of this carbon is very sensitive to this angle. Angle dependence for this chemical shift has been suggested previously,^{12b} and indeed with a very large axial substituent such as phenyl we have observed a 10 ppm isomeric shift of C-1.⁸

An increase in bond angle may explain the upfield shift of the 2,6-carbons of the axial conformers.¹⁰ Our calculations also show that the increase in the C-1,2,3 bond angle on going to an axial isomer remains fairly constant along the series methyl-, ethyl- and isopropylcyclohexane, suggesting that the isomeric axial-equatorial shift difference of these carbons should be relatively independent of substituent. The isomeric shifts for the methyl and ethyl substituents are indeed very similar, but the isomeric shift difference of the isopropyl 2,6-carbons seems anomalous. However, this anomaly disappears when one considers that there are three rotamers, an anti and two mirror-image gauche isomers, of essentially equal energy for equatorial isopropylcyclohexane.¹⁶ The interconversion of these rotamers can be slowed and the different ¹³C spectra of the anti and gauche isomers can be observed at very low temperatures $(-180 \,^{\circ}\text{C})$.¹⁶ The rotamer with *anti*-hydrogens is similar to the only viable axial rotamer. The two gauche equatorial isopropyl rotamers contain two carbons, rather than one carbon, gauche to the 2,6-carbons and thus an upfield shift of the equatorial isopropyl 2,6- and β -carbons is evidenced. This causes the shift difference between the axial and equatorial C-2,6 of isopropylcyclohexane to be substantially smaller than those of methyl- and ethylcyclohexane. When only the C-2,6 and C- β shifts of the equatorial anti rotamer are used (32.15 and 21.43 ppm, respectively),¹⁶ the C-2,6 and C- β isomeric shifts for isopropylcyclohexane become very similar (-3.31 and-0.18 ppm, respectively) to those of methyl- and ethylcyclohexane. Since our force field calculations suggest that the C-1,2,3 bond angle is also insensitive to substitution, this angle does indeed correlate with the isomeric shifts of the methyl-, ethyl- and isopropylcyclohexane series. The opening of the C-1,2,3 bond angle, then does appear to be important in determing the shift of the 2,6-carbon.

The shift difference of C-3,5 seems to be independent of the size of the alkyl substituent, since the C-3,5 shift difference is more or less the same for methyl-, ethyl- and isopropylcyclohexane. Thus the γ -gauche effect apparent in the upfield shifts of the axial isomers must be similar. Each of the axial alkylcyclohexanes has a similar geometry, with a hydrogen directly oriented toward the axial 3,5hydrogens. It may be that the major cause of the upfield C-3,5 shift is the absence of the deshielding effect of a 1,3-diaxial- β -hydrogen, as suggested by Beierbeck and Saunders.¹³ Other shielding mechanisms may also contribute.

While the α -carbons of the axial alkylcyclohexanes all experience the expected upfield shift due to the γ -gauche effect, the isomeric shift difference of the α -carbons increases on going from methyl- to isopropylcyclohexane. This trend may be caused by a change in the C- α , 1, 2, 3 dihedral angle, ¹⁰ but may also be caused by a stereochemical modification of the well known α -effect.¹⁷ It is known that the α -effect may be mitigated by the carbon chain to which the α -carbon is attached, ¹⁷ giving rise to the smaller shift difference of the α -carbon between ethyl- and isopropylcyclohexane than between methyl- and ethylcyclohexane in both the equatorial and axial cyclohexanes. However, the α -effect for the axial form is less for both ethyland isopropylcyclohexane. The β -methyls of these groups interact differently with the ring carbons for each isomer, suggesting that the magnitude of the α -effect may be changed not only by groups on the substituted carbon, but also by the stereochemical interactions of these attached groups.

Attainment of the low-temperature ¹³C NMR spectral data of methyl-, ethyl- and isopropylcyclohexane demonstrates the value of the cryogenic trapping method in conformational analysis. A knowledge of the chemical shifts of the high-energy axial conformers of these monoalkylated cyclohexanes is essential in the investigation of natural product structure analysis. Chemical shift differences between the axial and equatorial isomers have enabled us to draw several important conclusions, which are relevant in assessing the derivation of conformationally induced ¹³C chemical shifts. The involvement of bond angle changes in the isomeric shifts of particular carbons may be an important mechanism in this phenomenon, while γ -gauche effects of alkyl groups may be modified by interactions between β substituents and ring carbon atoms.

EXPERIMENTAL

Methyl-, ethyl- and isopropylcyclohexane were obtained from Aldrich and used without further purification. The CDCl₂F-CDClF₂ mixture was prepared by adding CDCl₃ slowly via a syringe pump, at a flow-rate of 0.07 ml min^{-1} , to HFSbF₅. The deuteriated Freons evolved as a gas and were collected in a dry-ice trap. The ratio of CDCl₂F to CDClF₂ was dependent on the flow-rate and, at the flow-rate used above, this ratio was 2:1. At low flow-rates some CDF₃ was produced. The isotopic purity of the deuteriated Freons produced was nearly identical with that of the starting deuteriated chloroform, so no hydrogen incorporation occurred during the substitution procedure. The two Freons are easily separable by distillation, but in fact the mixture produced is ideal for very low-temperature NMR.¹⁸

Low-temperature (-150 °C) ¹³CNMR spectra were recorded on a Bruker WM 250 FT spectrometer operating at 62.89 MHz. The high-temperature equilibrium samples were prepared by a cryogenic trapping method which has been described elsewhere in detail.¹³

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