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^{13}C Chemical Shift Non-Equivalence in Methylene Carbons of Monosubstituted Cyclohexanes

Hiroshi Ito,* Alfred F. Renaldo, Robert D. Johnson and Mitsuru Ueda
IBM Research Division, Almaden Research Center, 650 Harry Road, San Jose, California 95120-6099, USA

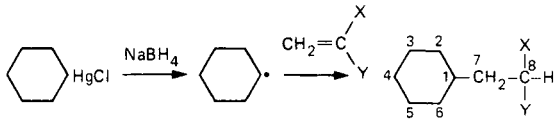
Monosubstituted cyclohexanes were synthesized by addition of a cyclohexyl radical to olefins bearing different substituents at the α-position. Six distinct methylene ^{13}C resonances were observed, indicating that the methylene carbons located at the 2 and 6 positions and at the 3 and 5 positions are not magnetically equivalent. This magnetic non-equivalence (anisochronism) observed in the monosubstituted cyclohexanes is due to the introduction of an asymmetric center β to the prochiral C-1 ring carbon.

KEY WORDS Anisochronism Magnetic non-equivalence Cyclohexyl adducts Mercury method

INTRODUCTION

The effects of molecular asymmetry on NMR chemical shifts and geminal anisochronism at prochiral centers have been discussed in a number of publications. Although NMR chemical shifts are affected also by conformational populations, it has been noted that the geminal non-equivalence could persist even in the absence of a conformational preference.[1,2] Prochiral isopropyl groups in $(CH_3)_2CH(CH_2)_nCHR_1R_2$[3] and $(CH_3)_2CH(X)CH(CH_3)Ph$[4] have been shown by Roberts and co-workers to exhibit chemical shift non-equivalence in ^{13}C and ^{1}H NMR, respectively. Martin *et al.*[5] and Beaulieu *et al.*[6] studied the axial dissymmetry induced chemical shift non-equivalence of isopropyl methyl groups in allene derivatives by ^{1}H and ^{13}C NMR spectroscopy, respectively. Jennings *et al.*[7] have observed unusually pronounced temperature and solvent effects on the geminal anisochronism of the isopropyl methyl groups in the ^{1}H spectra of *N*-[2-methyl-1-(1-naphthyl)propylidene]benzylamine. The diastereotopic methyl carbons of the isopropyl group in isopropylthioacetaldehyde dimethyl acetal sulfoxide exhibit an anisochronism of 1.13 ppm.[8] Adducts of β-isopropyl-β-methylvinyl triflate with *tert*-butylethylene show two distinct ^{1}H and ^{13}C chemical shifts for the diastereotopic isopropyl methyl groups.[9] Carman *et al.*[10] have observed differences in ^{13}C chemical shifts for methyl carbons in terminal isopropyl groups of branched alkanes as a model set for describing monomer sequences in ethylene–propylene copolymers and for reassessment of the empirical Grant–Paul additive coefficient.[11] Tonelli *et al.*[12] have demonstrated that the non-equivalent ^{13}C chemical shifts in the isopropyl methyl carbons in branched alkanes can be interpreted in terms of the conformationally sensitive γ-*gauche* effect. The chemical shift non-equivalence is found in many other prochiral groups, as reviewed by Jennings.[13] It is well known that chemical shifts of long-chain molecules (polymers) are very much affected by configurations of remote units in the chain, giving rise to resonance splittings due to configurational sequences such as diads, triads, tetrads and pentads. Effects of configuration of carbon atoms five bonds (pentad sequences) or even further away on chemical shifts are commonly observed at high magnetic fields.

The effects of substitutents on the ^{13}C chemical shifts of cyclohexanes have been extensively studied.[14,15] Monosubstituted cyclohexanes show in general only three ring methylene carbon resonances owing to the magnetic equivalence of C-2 and C-6 and of C-3 and C-5 (Scheme 1). However, as with the isopropyl methyl groups, C-2 and C-6 linked to the prochiral C-1 could be diastereotopic and, therefore, anisochronous when the C-1 substituent bears an asymmetric center. In addition, C-3 and C-5 should also exhibit non-equivalent chemical shifts in the presence of an asymmetric center in the substituent. Thus, cyclohexanes monosubstituted with a group bearing a chiral center should provide another opportunity to study the effect of nearby molecular asymmetry on ^{13}C chemical shifts. The ^{13}C chemical shift non-equivalence observed for the ring methylene carbons of monosubstituted cyclohexanes is reported in this paper.



1 : X=CH_3, Y=COPh
2 : X=CH_3, Y=CO_2CH_3
3 : X=CF_3, Y=CO_2CH_3
4 : X=CH_3, Y=CN
5 : X=CF_3, Y=Ph
6 : X=H, Y=CO_2CH_3
7 : X=H, Y=Ph

Scheme 1

* Author to whom correspondence should be addressed.

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RESULTS AND DISCUSSION

The 'mercury method' developed by Giese[16] is a convenient way of synthesizing ethylcyclohexanes (Scheme 1). Olfefins with electron-withdrawing substituents react with the electron-rich cyclohexyl radical more readily. When $X \neq Y \neq H$ (**1–5**) an asymmetric center is introduced into the carbon β to C-1 although the products are racemic mixtures, while monosubstituted vinyl monomers (X = H, $Y \neq H$, **6** and **7**) do not give rise to any asymmetry centers in the products.

As the ^{13}C DEPT NMR[17] spectrum shown in Fig. 1 clearly demonstrates, the cyclohexyl adduct with perdeuteriated methyl methacrylate (MMA) (**2-*d***) gives five CH_2 resonances which apparently belong to the cyclohexane ring. The reason for the use of the perdeuteriated monomer was to distinguish C-7 derived from the terminal CH_2 of MMA from the ring methylene carbons. It is clear that C-2 and C-3 are not magnetically equivalent to C-6 and C-5, respectively, in **2** (and **2-*d***).

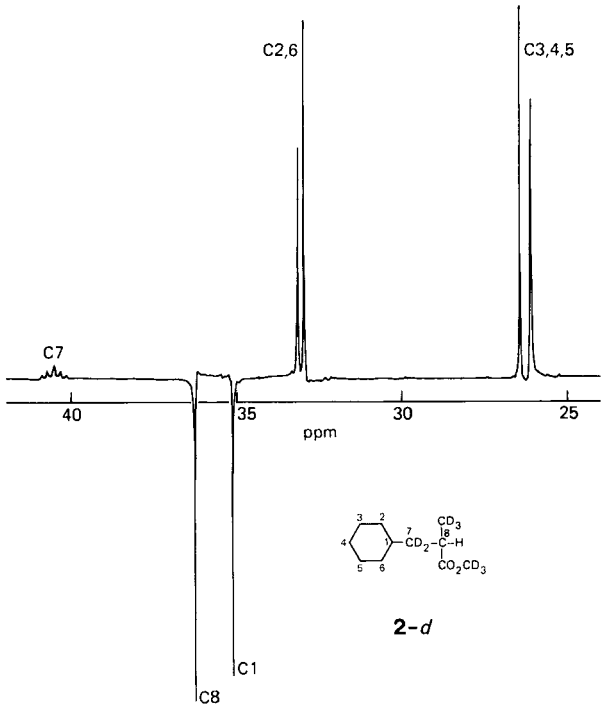


Figure 1. ^{13}C DEPT spectrum of **2-*d*** in $CDCl_3$ showing five distinct cyclohexane methylene carbon resonances.

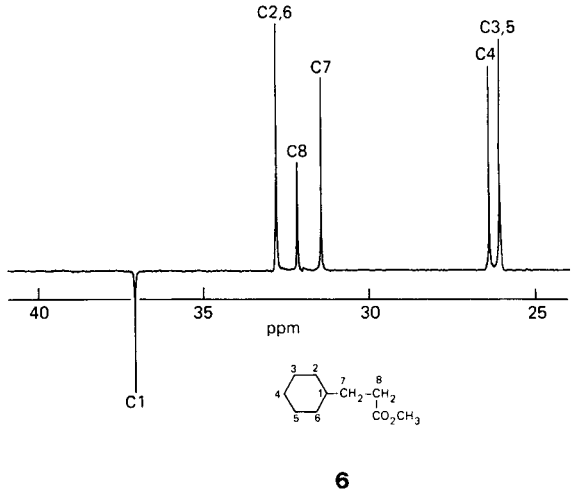


Figure 2. ^{13}C DEPT spectrum of **6** in $CDCl_3$ showing isochronism in the cyclohexane ring.

In contrast, the adducts **6** and **7** with monosubstituted vinyl compounds, such as methyl acrylate (MA), exhibit only five CH_2 resonances, although these compounds have seven methylene carbons, indicating that C-2 is magnetically equivalent to C-6 and C-3 to C-5 (Fig. 2). The C-1 in these compounds is prochiral but there is a plane of symmetry bisecting the C-2—C-1—C-6 angle. Thus, C-2 and C-6 are enantiotopic and isochronous and so are C-3 and C-5.

As summarized in Table 1, the cyclohexyl adducts with unsymmetrically α,α-disubstituted olefins (**1–5**) exhibit six CH_2 resonances while the adducts with monosubstituted olefins (**6** and **7**) show five CH_2 resonances. In the case where $X = CF_3$ (**3** and **5**), the coupling with F assisted the assignment of the C-8 resonances. The carbon adjacent to CN in **4** resonates at very high field (22.71 ppm), which has also been reported elsewhere.[18] The assignment shown in Table 1

Table 1. ^{13}C chemical shifts of cyclohexyl adducts in $CDCl_3$ at room temperature

No.	Substituent X	Substituent Y	CH_2 C-3, -4, -5			CH_2 C-2, -6		CH_2 C-7	CH C-1	CH C-8
1	CH_3	COPh	26.16	26.24	26.49	33.05	33.84	41.25	35.36	37.64
2	CH_3	CO_2CH_3	26.09	26.15	26.44	32.95	33.16	40.52	35.11	36.29
3	CF_3	CO_2CH_3	25.63	25.76	26.00	31.84	33.15[a]	33.22[a]	34.87	47.62[b]
4	CH_3	CN	23.77	25.84	26.16	32.29	33.18	41.59	35.21	22.71
5	CF_3	Ph	25.85	26.06	26.43	31.85	34.16	36.09	34.01	47.31[b]

			CH_2 C-3, -5	CH_2 C-4	CH_2 C-2, -6	CH_2 C-7	CH_2 C-8	CH: C-1
6	H	CO_2CH_3	26.05	26.37	32.79	31.45[a]	32.16[a]	37.04
7	H	Ph	26.33	26.69	33.28	33.28	39.41	37.31

[a] Assignment may be reversed.
[b] Quartet due to coupling with F.

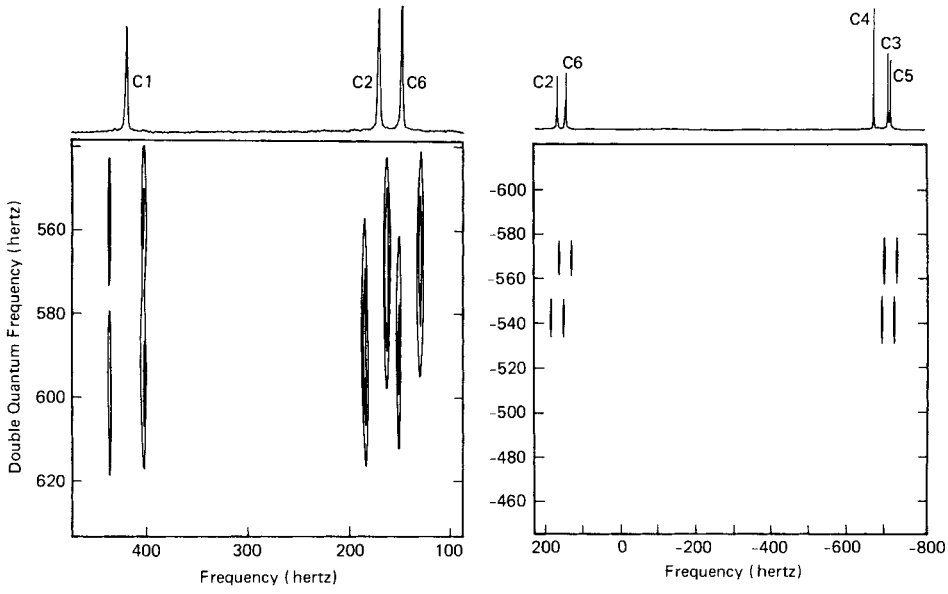


Figure 3. Carbon INADEQUATE map of **2**-*d* obtained at 125.7 MHz.

was accomplished by mutual comparison of the spectra, in addition to the use of DEPT, deuteriated monomer, coupling with F and the known chemical shift values. Table 1 clearly indicates that introduction of an asymmetric center into the carbon β to C-1 destroys the symmetry of the cyclohexane ring and renders C-2 and C-3 non-equivalent with C-6 and C-5, respectively, even though these ring carbons are three and four C—C bonds away from the asymmetric center. The effect is, of course, smaller on C-3/5 than on C-2/6. Whereas **2** gives the smallest chemical shift difference between C-2 and C-6 (0.21 ppm), **5** exhibits the largest difference, amounting to 2.31 ppm; **4** possessing small substituents (CH_3 and CN), shows a significant separation between the C-2 and C-6 resonances (0.89 ppm).

Kroschwitz *et al.*[3] observed the effect of the bulkiness of substituents on the magnetic non-equivalence of the methyl carbons of isopropylalkylcarbinols, $(CH_3)_2CHCH(OH)R$, with the anisochronism ranging from 0.2 ppm for R = CH_3 to 6.9 ppm for R = t-C_4H_9, and found a very large isopropyl methyl group non-equivalence of 7.2 ppm in $(CH_3)_2CHCH(CH_3)C(CH_3)_3$. They also studied the dependence of the isopropyl non-equivalence on the proximity to the asymmetric carbon in $(CH_3)_2CH(CH_2)_nCH(CH_3)C_2H_5$, and ascribed the monotonic decline of the anisochronism with increasing n to the attenuation of the steric effect with increasing distance;[3] while a non-equivalence of 2.2 ppm was observed with $n = 0$, the degree of the anisochronism was 1.0 and 0.2 ppm for $n = 1$ and 2, respectively. The former ($n = 1$) and the latter ($n = 2$) correspond to C-2/6 and C-3/5 in our cyclohexanes. Hence some of the chemical shift differences observed in the cyclohexane derivatives are significant, especially when X = CF_3 (1.31 and 2.31 ppm). The anisochronism of C-3/5 may be smaller (0.06 ppm in **2**) than in the Kroschwitz *et al.*'s compounds, which presumably reflects the longer distance between C-3/5 and the asymmetric C-8 in the rigid cyclohexane structure than the more flexible alkane structure.

The absolute assignment of the C-3, -4 and -5 resonances is difficult owing to their close proximity. We utilized the ^{13}C INADEQUATE technique[18] to accomplish the assignment of **2** (Fig. 3). The C-1 resonance of 35.11 ppm is connected with the resonances at 33.16 and 32.95 ppm, indicating that these resonances around 33 ppm are from the carbons adjacent to C-1, which are C-2 and C-6. The signal at 33.16 ppm was arbitrarily assigned to C-2, which shows a connection with the resonance at 26.15 ppm. The C-6 resonance is, in turn, connected with the resonance at 26.09 ppm. Hence the signals at 26.15 and 26.09 ppm can be assigned to the adjacent C-3 and C-5, respectively. Although we did not attempt to assign C-2/6 and C-3/5 in the absolute configuration, the INADEQUATE experiment unequivocally indicates that the assignment of C-3 and C-5 must be reversed simultaneously if C-2 and C-6 are to be interchanged in chemical shift.

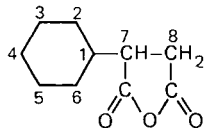
In order to study the effect of temperature on the chemical shift of **1**, ^{13}C NMR spectra were obtained in DMSO-d_6 at room temperature and at 120 °C, as summarized in Table 2. Although there are slight shift differences observed at the higher temperature, six CH_2 resonances are still observed even at 120 °C. The separation between the C-2 and C-6 resonances is smaller at 120 °C (0.55 ppm) than at room temperature (0.65 ppm) and in DMSO (0.65 ppm) than in $CDCl_3$ (0.79 ppm). Although the chemical shift non-equivalence may be subject to the rotation around C-1—C-7 and C-7—C-8 and to the flipping of the cyclohexane ring, the molecular asymmetry appears to be of primary importance in the anisochronism observed in the cyclohexane derivatives.

In **8**, prepared by the reaction of the cyclohexyl radical with maleic anhydride (MANH), an asymmetric center is located on C-7, closer to the cyclohexane ring than the previous cases. This compound exhibits five CH_2 resonances at 25.63 (two carbons), 25.81, 28.24, 30.07 and 31.13 ppm. The C-3 and C-5 resonances have collapsed into one peak located at 25.63 ppm, while C-2

Table 2. ^{13}C chemical shifts of 1 in DMSO-d_6

Temperature	CH_2 C-3, -4, -5			CH_2 C-2, -6		C-7	CH C-1	CH C-8
Room	25.67	25.72	26.00	32.58	33.23	40.85	34.92	36.89
120 °C	24.96	24.99	25.37	32.14	32.69	40.19	34.57	37.16

and C-6 resonate at different chemical shifts (30.07 and 31.13 ppm). The small anisochronism (0.06 ppm for C-2 and C-6, 0 ppm for C-3 and C-5) observed in **8** is surprising, as one would expect a proximity effect in this case.



8

EXPERIMENTAL

Materials

MMA, MA, styrene, methacrylonitrile and MANH were obtained commercially and purified by a conventional method. Syntheses of methyl α-(trifluoromethyl)acrylate (MTFMA),[19] α-trifluoromethylstyrene (TFMST)[20] and isopropenyl phenyl ketone (IPPHK)[21] have been reported previously.

Synthesis of monosubstituted cyclohexanes

The monosubstituted cyclohexanes for this study were prepared by the 'mercury method' (Scheme 1),[16] as reported previously for MTFMA[22,23] and TFMST.[20] Other cyclohexanes were synthesized in a similar fashion and purified by distillation. The purity of the adducts was assayed by gas chromatography, elemental analysis and NMR. The cyclohexyl adducts, **2**, **4**, **6**, **7** and **8**, have been reported previously by Giese *et al.*[24,25] The adduct with IPPHK (**1**) boiled at 109–110 °C/1.5 mmHg and the high-resolution mass spectrometry of **1**, performed by Shrader Laboratories, exhibited an *m/e* of 230.1698 ($m^{+\cdot}$) corresponding to $C_{16}H_{22}O$ (230.3517).

^{13}C NMR measurements

^{13}C NMR spectra were recorded in deuteriochloroform ($CDCl_3$, ca 30 mg ml^{-1}) at 23 °C on an IBM Instruments WP-200 (50 MHz) or Varian XL-400 (100 MHz) spectrometer. Spectra were also obtained for the adduct of the cyclohexyl radical with IPPHK (**1**) in dimethyl sulfoxide-d_6 (DMSO-d_6) at 120 °C. The DEPT experiment was performed to assist assignment of the resonances. The chemical shifts reported in this paper are in ppm downfield from tetramethylsilane (TMS). ^{13}C NMR spectra for the 2D INADEQUATE experiment were collected on a Bruker AM-500 NMR spectrometer, operating at 125.7 MHz at 25 °C. The pulse sequence for the INADEQUATE experiment was that of Mareci and Freeman[18] with a mixing pulse of 135°. In the observe dimension, a sweep width of 3086 Hz was defined by 4096 complex points, and a sweep width of 3000 Hz was defined by 128 points zero-filled to 256 points in the double quantum dimension.

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