

CONFORMATIONAL EQUILIBRIA BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Ernest L. Eliel and Michael H. Gianni

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana

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RECENT publications on the conformational equilibrium constants and associated conformational free energy or enthalpy differences¹ of methoxyl,² carbethoxyl³ and acetoxyl,⁴ obtained by chemical methods, and of the sulfhydryl group,⁵ obtained by infrared spectroscopy, prompt us to record values of some of these and other related constants as derived by nuclear magnetic resonance spectroscopy.

The method used has been previously described.⁶ It is well known that axial and equatorial protons in appropriately substituted cyclohexanes resonate at different field strength.⁷ However, in as much as a monosubstituted cyclohexane, $C_5H_{10}\underline{CH}X$ undergoes rapid chair inversions, the proton underlined will be seen in an average field position rather than in the position appropriate for a purely axial or purely equatorial proton. If δ is the chemical shift of the marked proton, δ_e the corresponding shift of a purely axial proton in an equatorially substituted cyclohexane and δ_a

¹ E.L. Eliel, J. Chem. Educ. **37**, 126 (1960).

² D.S. Noyce and L.J. Dolby, J. Org. Chem. **26**, 3619 (1961).

³ E.L. Eliel, H. Haubenstein and R.V. Acharya, J. Amer. Chem. Soc. **83**, 2351 (1961).

⁴ N.B. Chapman, R.E. Parker and P.J.A. Smith, J. Chem. Soc. 3634 (1960).

⁵ G. Chiurdoglu, J. Reisse and M. Vander Stichelen Rogier, Chem. & Ind. 1874 (1961).

⁶ E.L. Eliel, Chem. & Ind. 568 (1959).

⁷ R.U. Lemieux, R.K. Kullnig, H.J. Bernstein and W.G. Schneider, J. Amer. Chem. Soc. **80**, 6098 (1958).

the shift of the equatorial proton in an axially substituted $C_6H_{11}X$, then $\delta = N_e \delta_e + N_a \delta_a$ or $K = (\delta_a - \delta) / (\delta - \delta_e)$ where N_e and N_a are the mole fractions of cyclohexyl-X in the equatorial and axial conformation, respectively, and K is the equilibrium constant between the two conformational isomers.¹

Two methods have been used to obtain δ_e and δ_a . In one,⁶ these shifts are measured in a 4-t-butylsubstituted cyclohexyl compound, 4-(CH₃)₃CCH(CH₂)₄CHX-1. The cis isomer gives δ_a and the trans isomer δ_e . In this method it is assumed that the 4-t-butyl group does not affect the chemical shifts in any other way than by biasing the molecule in favor of one conformation. In the other method, which is theoretically more secure but experimentally more difficult, δ_e and δ_a are obtained from the mono-substituted cyclohexane itself by recording the NMR spectrum at a temperature low enough to slow down the interconversion of the conformational isomers to the point where their individual spectra can be seen.⁸

Using the former method, we have recorded (on a Varian High-Resolution instrument), the chemical shifts and computed the conformational free energy differences shown in Table 1. Shifts were measured at 60 mc in ca. 10% carbon tetrachloride solution using tetramethylsilane as standard by means of side bands from a calibrated audio oscillator. The precision of the measurements is estimated at ± 2 c.p.s.

Although the method used here has been criticized,⁹ the data obtained are in good agreement with other data in the literature. Thus conformational free energy differences reported for hydroxyl range from 0.4 to 0.9 kcal/mole,¹ those for bromine from 0.2 to 0.7 kcal/mole.¹⁰ Other values

⁸ A.J. Berlin and F.R. Jensen, Chem. & Ind. 998 (1960); L.W. Reeves and K.O. Strømme, Canad. J. Chem. **38**, 1241 (1960).

⁹ F.R. Jensen and L.H. Gale, J. Org. Chem. **25**, 2075 (1960).

¹⁰ E.L. Eliel, Stereochemistry of Carbon Compounds. McGraw-Hill, New York (1962).

are 1.1 kcal/mole for carbethoxyl³ and 0.74 kcal/mole for methoxyl.² Our value for thiophenoxyl agrees in magnitude, but not in sign with that (-0.4 kcal/mole) recently reported for sulfhydryl (-SH).⁵ This discrepancy

TABLE 1

Group	δ_a	δ_e	δ	K	$-\Delta F$, kcal/mole
OH	236	202	211	2.8	0.6
OAc	299	268	275	3.4	0.7
OCH ₃	200	177	183	2.8	0.6
OTs	273	243	251	2.8	0.6
SPh	211	171	179	4.0	0.8
CO ₂ Et	148	93	101	5.9	1.1
Br ^a	(185)	(153)	(167)	1.3	0.2

^a Data obtained at 40 mc in the absence of solvent; ref. 6.
There is a misprint in ref. 6: Cyclohexyl bromide contains
60±3% of the equatorial (not axial) isomer.

will be discussed further in the following letter. The value for tosyloxyl (0.6) is in agreement with the value of Eliel and Ro¹¹ (0.7) but not with that of Winstein and Holness (1.7).¹² The value for acetoxyl is slightly larger than that (0.4) reported by Lemieux and Chu¹³ but much smaller than that (1.5) reported by Chapman and coworkers.^{4*}

* The values for ΔF_{OAc} in ref. 4 are internally inconsistent. A value of 0.8 kcal/mole may be derived from the reported ΔG for trans-3-methyl-cyclohexyl acetate or a value of 1.1 kcal/mole from ΔG for the cis-4-methyl isomer.

¹¹ E.L. Eliel and R.S. Ro, *J. Amer. Chem. Soc.* **79**, 5995 (1957).

¹² S. Winstein and N.J. Holness, *J. Amer. Chem. Soc.* **77**, 5562 (1955).

¹³ R.U. Lemieux and P. Chu, Abstracts, San Francisco Meeting, Amer. Chem. Soc., p. 31N (1958).

Further support for the method comes from the near identity in signal position between cyclohexanol (211 c.p.s.) and 4,4-dimethylcyclohexanol (209 c.p.s.) which we also measured. The two compounds are conformationally analogous and the near identity of the shifts indicates that the equatorial and axial 4-methyl substituents exert no appreciable disturbing influence.

Musher¹⁴, in a footnote to a paper on NMR spectra of decalols, has claimed that the chemical shifts for the carbinol protons in cyclohexanol and trans-4-t-butylcyclohexanol are the same, and that the method here described is therefore not valid. We have measured the shifts for both the above compounds numerous times* and find them different, as indicated in Table 1. The cyclohexanol value varied between 210 and 211 c.p.s. and the trans-4-t-butylcyclohexanol value (sample pure gas-chromatographically) between 201 and 203 c.p.s.

Although the values reported here are not highly accurate, mainly because of the difficulty of measuring precisely chemical shifts involving bands which are often quite broad, and possibly also because of a very minor disturbing effect of the t-butyl group, the NMR method gives correct orders of magnitude for conformational free energy differences and allows one to make decisions between conflicting data in the literature obtained by other means. Since the equation used to calculate K involves a quotient of differences, the precision of the method decreases as δ approaches δ_e . As a result, the method as described here is not suited for large X-substituents, the practical limit being reached at approximately $\Delta F_X = 1$ kcal/mole. However, the method may be extended by applying it to disubstituted cyclohexanes with one equatorial and one axial substituent, such as a

¹⁴ J. Musher, J. Amer. Chem. Soc. **83**, 1146 (1961), footnote 16.

* We are grateful to Dr. Thomas Williams for checking these measurements.

cis-4-methylsubstituted cyclohexyl-X.

The compounds required in this investigation were prepared by standard methods. The epimeric 4-t-butylcyclohexyl acetates were obtained by fractionating the commercial cis-trans mixture ("Dorisyl", Dow) through a 100-plate Podbielniak column at reduced pressure and were saponified to obtain the alcohols from which the tosylates,¹¹ bromides,¹⁵ and thiophenyl ethers¹¹ were prepared as described earlier. The methyl ethers were prepared from the alcohols by treatment with diazomethane and boron trifluoride.¹⁶ The ethyl cyclohexanecarboxylates were available from another investigation.³

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¹⁵ E.L. Eliel and R.G. Haber, J. Org. Chem. **24**, 143 (1959).

¹⁶ W. Hückel and J. Kurz, Ann. **645**, 194 (1961).