This Week's Citation Classic

Eliel E L. Conformational equilibria by nuclear magnetic resonance spectroscopy.
Chem. Ind. London (18):568, 1959.
[Gates and Crellin Labs., California Institute of Technology, Pasadena, CA]

The conformational equilibrium between an equatorially and axially substituted cyclohexane (here cyclohexyl bromide) is determined by proton NMR spectroscopy from the (averaged) position of the CHX proton in $C_6H_{11}X$ and the positions of corresponding equatorially and axially locked protons in appropriate model compounds (here *cis-* and *trans-*4-*t*-butylcyclohexyl bromides). [The $SCI^®$ indicates that this paper has been cited in over 105 publications since 1961.]

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"In the fall of 1958, I spent my sabbatical leave in the laboratory of J.D. Roberts at Caltech to learn about the then burgeoning field of proton NMR spectroscopy. Roberts himself was away on sabbatical at Harvard, but his postdoctoral collaborators M. Caserio, G. Fraenkel, and A. Loewenstein taught me the experimental aspects of NMR after I had learned about the theory from the page proofs of Roberts's book *Nuclear Magnetic Resonance.*[1] They were willing to give me time on the 40/60 MHz Varian HR instrument then available in Roberts's lab.

"We had, during 1953-1957, worked on the determination of conformational equilibria in monosubstituted cyclohexanes by a kinetic method developed both by the late Saul Winstein[2] and by us.[3] I was looking for a way to confirm the results independently and my reading at Caltech suggested that this might be done by proton NMR spectroscopy. Gutowsky and Saika[4] had already shown that the signal for a fast-exchanging nucleus (e.g., the acidic proton in CH_3CO_2H/H_2O which exchanges between the acid and the water) is found at the weighted average position corresponding to the two contributing structures (CH_3CO_2H and H_2O). It appeared that the same averaging should occur between the axial (a) and equatorial (e) $CHBr$ protons of cyclohexyl bro-

mide. Therefore, and considering that $n_e + n_a = 1$ where n_e and n_a are the mole fractions of the conformations with equatorial and axial protons, respectively, the conformational equilibrium constant $K = n_e/n_a$ could be determined from the equation $\delta_H = n_e \delta_e + n_a \delta_a$ provided one could measure not only δ_H (the chemical shift of the $CHBr$ proton in cyclohexyl bromide) but also δ_e and δ_a. The method to do that was at hand, since, in work on the conformational equilibrium of cyclohexyl bromide by the kinetic method, my collaborator Ralph Haber had synthesized *cis-* and *trans-*4-*t*-butylcyclohexyl bromide. In the former, the α-hydrogen ($CHBr$) is equatorial and its shift should be δ_e whereas in the latter it is axial and should yield δ_a. Lemieux[5] had already shown that such protons display substantially different chemical shifts and, indeed, the values for δ_e and δ_a were quite distinct and, along with the value for δ, led to the determination of n_e and n_a and hence K. Thus a new method to obtain conformational equilibrium constants was developed.

"It is interesting that this paper is so highly cited, for several reasons. 1) It is only one page long. 2) The use of *t*-butylcyclohexyl compounds as conformationally locked models gives only approximate results for conformational equilibria, since the *t*-butyl group affects the shift. Better NMR methods (based on low-temperature measurements) are now available. 3) Even apart from this problem, because of the primitive state of experimentation and the fact that the $CHBr$ signals are broadened by multiple coupling, the 1959 results were not very precise. 4) Because of the confused referencing of NMR shifts in 1959, the paper is hard to read.

"Nevertheless, the 1959 method was conceptually important and, in view of the enormous importance NMR has had in conformational studies, related methods have frequently been used. As a result, a variation of the above equation, $K = (\delta_a - \delta)/(\delta - \delta_e)$, has become known as the 'Eliel equation.' See publications by H. Booth and me for more recent work in the field."[6,7]

1. Roberts J D. *Nuclear magnetic resonance: applications to organic chemistry.* New York: McGraw-Hill, 1959. 118 p.
2. Winstein S & Holness N J. *t*-Butylcyclohexyl derivatives: quantitative conformational analysis.
   J. Amer. Chem. Soc. 77:5562-78, 1955.
3. Eliel E L & Lukach C A. Conformational analysis. II. Esterification rates of cyclohexanols.
   J. Amer. Chem. Soc. 79:5986-92, 1957.
4. Gutowsky H S & Saika A. Dissociation, chemical exchange and the proton magnetic resonance in some aqueous electrolytes. *J. Chem. Phys.* 21:1688-94, 1953.
5. Lemieux R U, Kullnig R K, Bernstein H J & Schneider W G. Configurational effects on the proton magnetic resonance spectra of six-membered ring compounds. *J. Amer. Chem. Soc.* 80:6098-105, 1958.
   [Citation Classic. *Current Contents/Physical, Chemical & Earth Sciences* 20(26):10, 30 June 1980.]
6. Booth H. Applications of ¹H nuclear magnetic resonance spectroscopy to the conformational analysis of cyclic compounds. *Progr. Nucl. Magn. Res. Spectrosc.* 5:149-381, 1969.
7. Eliel E L. Conformational analysis—the last 25 years. *J. Chem. Educ.* 52:762-7, 1975.

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