This Week's Citation Classic


March 19, 1962

"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, C. 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 Winstein² and by us.¹ 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 Saika³ had already shown that the signal for a fast-exchanging nucleus (e.g., the acidic proton in CH₃CO₂H and H₂O) is found at the weighted average position corresponding to the two contributing structures (CH₃CO₂H and H₂O). It appeared that the same averaging should occur between the axial (a) and equatorial (e) CHBr protons of cyclohexyl bromide. Therefore, and considering that nₑ+nₐ=1 where nₑ and nₐ are the mole fractions of the conformations with equatorial and axial protons, respectively, the conformational equilibrium constant K=nₑ/nₐ could be determined from the equation δₑ=neδₑ+naδₐ provided one could measure not only δₑ (the chemical shift of the CHBr proton in cyclohexyl bromide) but also δₐ and δₑ. 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 a-hydrogen (CHBr) is equatorial and its shift should be δₑ whereas in the latter it is axial and should yield δₐ. Lemieux⁴ had already shown that such protons display substantially different chemical shifts and, indeed, the values for δₑ and δₐ were quite distinct and, along with the value for δₐ, led to the determination of nₑ and nₐ 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=(δₑ−δₐ)/(δₑ−δₐ), has become known as the 'Eliel equation.' See publications by H. Booth and me for more recent work in the field."³⁷