

Ellel E L. Conformational analysis in saturated heterocyclic compounds.

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This is a short review dealing mainly with my work on the quantitative conformational analysis of substituted 1,3-dioxanes and 1,3-dithianes. The methodology used involves acid-catalyzed equilibration combined with proton nuclear magnetic resonance spectroscopy; the most important conclusion is that unshared electron pairs are "smaller" than hydrogen atoms. [The *SCi*<sup>3</sup> indicates that this paper has been cited in over 180 publications.]

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Barton's pioneering papers on conformational analysis and earlier studies of its quantitative aspects dealt largely with saturated carbocycles. It was assumed that saturated heterocycles—important in the alkaloid and carbohydrate families—behaved similarly to cyclohexanes.

In the late 1960s, encouraged by conversations with S. J. Angyal (Sydney), I decided to test this assumption. By then it was clear that the best methods of quantitative analysis involved either equilibration<sup>1</sup> or nuclear magnetic resonance (NMR).<sup>2</sup> We chose the 1,3-dioxane system for study since it lent itself to application of both methods because of its facile synthesis (from 1,3-diols and aldehydes) and because cis and trans isomers of 2,4- (or 2,5-) disubstituted 1,3-dioxanes, being acetals, are readily equilibrated by acid.

The first experiments proved frustrating. Since the acid catalyst used in the condensation of acetaldehyde and 1,3-butanediol also produces equilibration, only the stable cis, diequatorial, 2,4-dimethyl-1,3-dioxane was obtained. Clearly, equatorial methyl was preferred much more than in methylcyclohexane, but we could not tell by how much!

Two circumstances saved the day. One was a suggestion by the late J. Sicher that we stop acetal

formation short of completion, thereby obtaining partial kinetic control, which might favor the equatorial-axial (trans) isomer. The other was the enormous patience and dedication of my collaborator, Sister Margaret Knoeber. Though only about 6 percent of the minor isomer was formed even under conditions of kinetic control, she managed to isolate enough of it for characterization by spending many hours in front of a gas chromatograph!

We then found that methyl at C(2) in 1,3-dioxane prefers the equatorial position by 4.0 kcal/mol;<sup>3,4</sup> the corresponding preference at C(4) is 2.9 kcal/mol. These values are much larger than the 1.7 kcal/mol value in methylcyclohexane, presumably because the shortness of the C-O bond (compared to C-C) leads to enhanced syn-axial CH<sub>3</sub>/H interaction in the oxygen systems.

Our next surprise came when we equilibrated 2R, 5-t-butyl-1,3-dioxanes (R = methyl, ethyl, isopropyl, t-butyl, phenyl) and found  $\Delta G^\circ$  to be constant (1.4 kcal/mol) in this series. NMR analysis confirmed that all the cis isomers had equatorial R and axial t-butyl and that the (small)  $\Delta G^\circ$  corresponded to equilibration of the 5-t-butyl group into the axial position! This was the first instance of a six-membered ring with axial t-butyl; evidently the latter's interaction with the syn-axial lone pairs on oxygen is much less than corresponding interactions with syn-axial hydrogen atoms. Shortly after publishing this result,<sup>5</sup> we learned that Riddell and Robinson at Oxford had arrived at the same conclusion.<sup>5</sup>

Subsequent work dealt with 1,3-dithianes.<sup>6</sup> Conformational energies in this system are smaller than in 1,3-dioxanes because of the much longer C-S-C (as compared to C-O-C) distances. For the same reason, the 1,3-dithiane system readily assumes the twist or boat conformation.

The account has been widely quoted presumably because it was one of the first to lay out the conformational factors particular to saturated heterocycles and to summarize the magnitude of such factors, including dipolar ones.

In 1980 an entire book dealing with conformational analysis in saturated heterocycles appeared.<sup>7</sup>

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5. Riddell F G & Robinson M J T. Conformational effects in compounds with six-membered rings—VI. Conformational equilibria in 5-alkyl-1,3-dioxanes. *Tetrahedron* 23:3417-25, 1967. (Cited 80 times.)
6. Ellel E L & Hutchins R O. Conformational analysis. XVIII. 1,3-dithianes. Conformational preferences of alkyl substituents and the chair-boat energy difference. *J. Amer. Chem. Soc.* 91:2703-15, 1969. (Cited 105 times.)
7. Riddell F G. *The conformational analysis of heterocyclic compounds*. New York: Academic Press, 1980. 153 p.