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 SCF indicates that this paper has been cited in over 180 publications.

Evel E. Eliel
Department of Chemistry
University of North Carolina
Chapel Hill, NC 27514

January 2, 1986

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 St Angyal (Sydney), I decided to test this assumption. Barton had found that the best methods of quantitative analysis involved either equilibration of nuclear magnetic resonance (NMR).

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- and 3,4-disubstituted 1,3-dioxanes, being acyclic, 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 methyacyclohexanes, 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, the corresponding preference at C(4) is 2.9 kcal/mol. These values are much larger than the 1.7 kcal/mol value in methyacyclohexane, presumably because of the shortness of the C-O bond (compared to C-C) and the enhanced syn-axial CH3 interaction in the oxygen systems.

Our next surprise came when we equilibrated 2R, 5-t-buty1-1,3-dioxanes (R = methyl, ethyl, isopropyl, t-buty1, phenyl) and found AG to be constant (1.4 kcal/mol) in this series. NMR analysis confirmed that all the cis isomers had equatorial R and axial 1-buty1 and that the (small) AG corresponded to equilibration of the 2-t-buty1 group into the axial position! This was the first instance of a six-membered ring with axial t-buty1; 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, we learned that Riddell and Robinson at Oxford had arrived at the same conclusion.

Subsequent work dealt with 1,3-dithianes. Conformational energies in this system are smaller than in 1,3-dioxanes because of the much longer C-S-C (as compared to C-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.