The Nature of the Constraining Effect of a t-Butyl Group upon Some Cyclohexane Compounds

By SAUL WOLFE* and JOHN R. CAMPBELL

(*Department of Chemistry, Queen's University, Kingston, Ontario, Canada*)

QUANTITATIVE conformational analysis of mobile cyclohexyl systems relies heavily upon the postulate that a property of a monosubstituted cyclohexyl compound will be the weighted average of the properties of the axial and equatorial forms, and that these can be obtained by reference to the *cis*- and *trans*-4-t-butylcyclohexyl systems. The conditions which must exist for this postulate to be valid have been clearly stated.[1] If any of these conditions is not met, the method fails and it must be questioned whether thermodynamic or kinetic data could then have any real meaning. Cornubert[2] cautioned in 1956 that t-butyl should cause some flattening of a cyclohexane ring, but most workers have decided to ignore the possible consequences of such deformation. Recently, failures of the t-butyl postulate in systems examined by both kinetic and thermodynamic methods have been described.[3]

What is the contribution to such failures of ground-state differences between cyclohexyl and t-butylcyclohexyl compounds? The difficulty is that t-butyl systems are conformationally homogeneous, whereas the cyclohexyl systems are not, and at ordinary temperatures one cannot compare directly one unique species with another. At low temperatures, however, ring inversion of cyclohexyl systems can be slowed sufficiently so that, on the n.m.r. time scale, the properties of individual conformations can be seen. Provided that the n.m.r. parameters under consideration are temperature-independent, which for the data described below was found to be the case, then it is possible to compare cyclohexyl compounds "constrained" by t-butyl with the same cyclohexyl compounds lacking the t-butyl group but constrained by the use of a low temperature. Clearly, if the effect of the t-butyl group is negligible, chemical shifts and coupling constants should be the same. The chemical shift criterion is perhaps less meaningful since it would be dangerous to relate a diamagnetic anisotropic effect of t-butyl to what takes place during a chemical reaction. But if the anisotropy of t-butyl causes a change in

chemical shifts, then the n.m.r. method of conformational analysis is invalid.

We summarize the results of a study, made under the conditions described above, of the n.m.r. parameters of each diastereoisomer of the series of compounds (I) and (II) (X = Cl, OH, OAc, CO_2H, CO_2Me). These compounds were selected for study because the low-temperature data can readily be obtained and because, for the *trans*-compounds of series (II), two conformations can be seen. The compounds were prepared by standard methods[4] from the deuterated olefinic precursors.[5] Since a 4-t-butyl group does affect chemical shifts of protons in the 1- and 2-positions, the series (III) was also prepared in order to permit identification of the 1- and 2- protons.

(I)   (II)   (III)
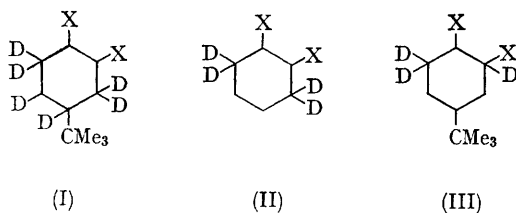
For all *eq,eq*-isomers of series (I), the tertiary protons were equivalent; for all *ax,ax*-isomers these protons were nonequivalent, chemical shifts and coupling constants varying with the nature of the substituent. [In series (II) the tertiary protons of the *ax,ax*- and *eq,eq*-isomers are, of course, equivalent.]

The three straight lines of Figure 1 were obtained by a least-squares fit of $J_{ax,eq}$ (negative slopes) and $J_{eq,eq}$ (positive slope) against substituent electronegativity.[6] For the *cis*-isomers there is a constant effect of 4-t-butyl at the 1- and 2-positions, independent of the electronegativity of X, which increases $J_{ax,eq}$ by 0·4 c./sec. This would correspond to a flattening of the side of the ring remote from t-butyl by less than 5° if a Karplus relationship of the usual form existed.[7] Thus the effect of 4-t-butyl upon the ground-state structure at the opposite end of the ring is negligible. However, the effect upon a transition state is likely to be significant since flattening at the 1- and 2-positions is the result of increased steric compression from the axial 3- and 5-protons;[2,3a] increased interference from these protons would certainly make the ease of entry of a reagent or departure of a leaving group more difficult in the t-butyl systems.

The positive slope of the $J_{eq,eq}$–electronegativity plot is opposite to that predicted theoretically.[8] The theoretical treatment attributes

substituent-induced changes in J_{vic} to changes in hybridization of the HCC'H fragment carbon
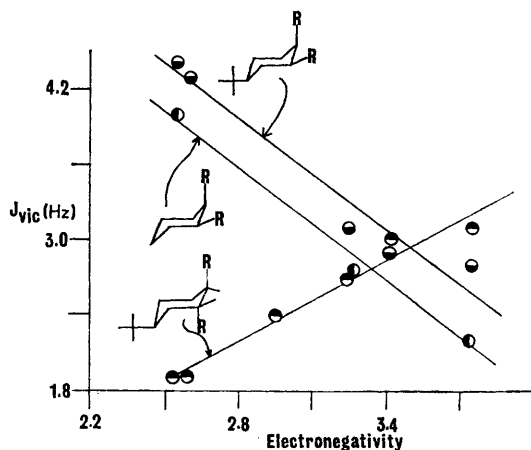

FIGURE 1. *Vicinal coupling constant plotted against substituent electronegativity for three series of 1,2-disubstituted cyclohexanes.*

atoms and direct inductive effects upon the polarities of the C–H bonds. Our observations are most concisely explained by the assumption that, in the t-butylcyclohexyl system, direct substituent effects are small and substituents operate indirectly by causing a change in the dihedral angle. An increase in the XCCX dihedral angle with increasing electronegativity of X would increase the $H_{ax}CCH_{eq}$ dihedral angle and decrease the $H_{eq}CCH_{eq}$ dihedral angle and
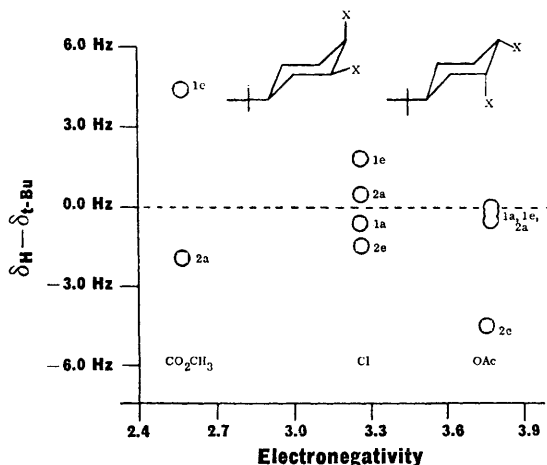

FIGURE 2. *The effect of 4-t-butyl upon the chemical shifts of the 1- and 2-protons for the cis-1,2-disubstituted cyclohexanes.*

produce the trends shown in Figure 1. This conclusion that direct substituent effects are small can be tested through a determination of J_{CH} for these compounds and such studies are being initiated.

Figure 2 shows directly the chemical-shift differences as a function of substituent electronegativity between the tertiary protons of *cis*-1,2-disubstituted cyclohexyl compounds constrained by low temperature and by a t-butyl group. It is very clear that the assumption that

t-butyl has no effect upon the chemical shift of a remote proton is not correct. Attempts to obtain conformational parameters by relating the averaged chemical shift of a proton in a mobile cyclohexyl system to those observed for t-butylcyclohexyl systems are, therefore, unjustified.

[1] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, 1965, p. 50.

[2] R. Cornubert, *Bull. Soc. chim. France*, 1956, 996.

[3] (a) F. Shah-Malak and J. H. P. Utley, *Chem. Comm.*, 1967, 69; (b) J. L. Mateos, C. Perez, and H. Kwart, *Chem. Comm.*, 1967, 125; (c) H. Kwart and T. Takeshita, *J. Amer. Chem. Soc.*, 1964, **86**, 1161; (d) E. A. S. Cavell, N. B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1960, 1413; (e) E. L. Eliel and F. J. Biros, *J. Amer. Chem. Soc.*, 1966, **88**, 3334.

[4] J. R. Campbell, J. K. N. Jones, and S. Wolfe, *Canad. J. Chem.*, 1966, **44**, 2339.

[5] S. Wolfe and J. R. Campbell, unpublished; S. Wolfe and P. G. C. Campbell, *Canad. J. Chem.*, 1965, **43**, 1184.

[6] J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, 1961, **34**, 1099; K. L. Williamson, *J. Amer. Chem. Soc.*, 1963, **85**, 516; P. Laszlo and P. R. Schleyer, *J. Amer. Chem. Soc.*, 1963, **85**, 2709.

[7] N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964, p. 49.

[8] M. Karplus, *J. Amer. Chem. Soc.*, 1963, **85**, 2870.