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CONFORMATIONAL STUDIES. XIII. FAILURE OF t-BUTYL AS A CONFORMATION-HOLDING GROUP IN TRANS-3-t-BUTYL-4-HYDROXYCYCLOHEXANONE: t-BUTYL-HYDROXYL GAUCHE INTERACTIONS[1]

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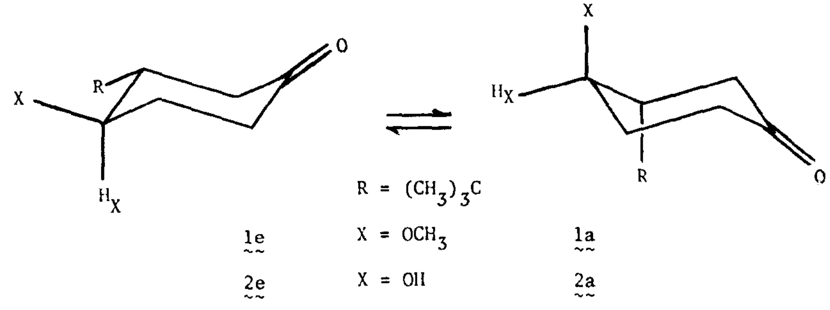
Mere presence of a t-butyl substituent cannot be relied upon to render a cyclohexane derivative conformationally homogeneous. For example, Portnova, et al., concluded that trans-3-t-butyl-4-methoxycyclohexanone (**1**) is conformationally homogeneous;[2] extensive addition reaction results were interpreted as if the chair, **1e**, were the only conformation populated for **1**.[2,3] We report here infrared and nmr results which lead us to the opposite conclusion; for both trans-3-t-butyl-4-hydroxycyclohexanone (**2**) and its methyl ether (**1**) in solution, nonchair conformations probably predominate.



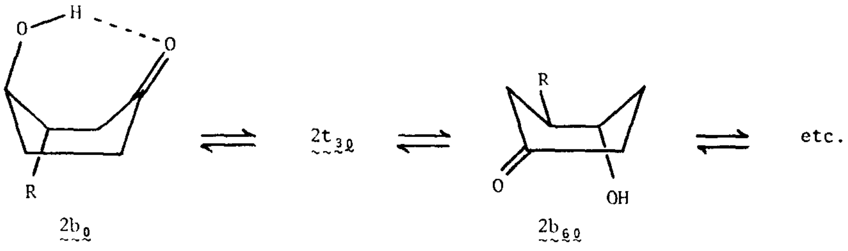
1e **2e**

R = $(CH_3)_3C$

X = OCH_3

X = OH

1a **2a**



$2b_{\ell}$ **$2t_{3\ell}$** **$2b_{6\ell}$**

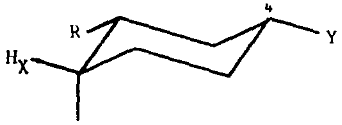
In **1a** and **2a**, destabilization caused by the axial t-butyl group is easily recognized. We emphasize here that gauche interactions between trans vicinal groups (such as R and X in **1** and **2**) can also introduce strong destabilization into a chair conformation (such as **2e**) relative to nonchair conformations in which the gauche interaction is relieved (such as **$2b_{6\ell}$**).

Molecular models suggest that the repulsive gauche interaction in 2e should be comparable to a 1:3 diaxial methyl-hydroxyl interaction, reported as *ca.* 2.2 kcal/mole.[4] Taking the energy difference between chair and nonchair conformations of 4-hydroxycyclohexanone as *ca.* 2.5 kcal/mole,[5] the net difference in energy predicted for $2e \rightleftharpoons 2b_{6\ell}$ would be very small, *ca.* 0.3 kcal/mole. The nonchair population found for 2 in this work appears to be even *greater* than the very crude calculation above would predict.

Significant intramolecular hydrogen bonding, possible only in a small range of nonchair conformations, has been detected by infrared spectroscopy for 2. A 0.0040 *M* solution of 2 in carbon tetrachloride showed absorption bands at 3618 ± 2 cm^{-1} (strong), 3535 ± 5 cm^{-1} (very weak), and 3422 ± 5 cm^{-1} (very weak). Upon dilution to 0.002 *M*, all three peak intensities were halved; all three absorption bands may be attributed to monomeric 2. Upon partial replacement of OH by OD, the bands at 3618 and 3535 cm^{-1} were reduced in intensity. The band at 3422 cm^{-1}, unaffected by deuterium exchange, is attributable to the first overtone of the carbonyl stretching vibration. Therefore, we assign the strong band at 3618 cm^{-1} to the free hydroxyl group in nonhydrogen bonded conformations of 2,[6] and the very weak band at 3535 cm^{-1} to conformations of 2 in which a transannular intramolecular hydrogen bond exists between the hydroxyl and carbonyl groups.[7] The peak intensity ratio of 20:1 suggests that the population of intramolecularly hydrogen bonded nonchair conformations is small. However, they may represent only a small fraction of the total nonchair population of 2.

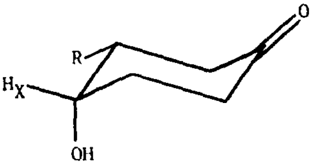
To explore this point further, nmr X-proton band widths[8] (W) of 2 and related compounds may be compared. *cis*-2-*t*-Butylcyclohexanol (3), W_3 = 7.7 ± 0.5 Hz, would be expected to exist almost entirely in the chair conformation with *t*-butyl equatorial. Remote substituents would not be expected to influence W significantly unless the dihedral angles about the C_1-C_2 and C_1-C_6 bonds were affected, that is, unless substitution produced a detectable change in conformational equilibria. Thus, substitution of a hydroxyl group into 3 at C_4 to give *cis*-2-*t*-butyl-*cis*-1,4-cyclohexanediol (4) [9] leaves the band width of the C_1 X-proton essentially undisturbed; W_4 = 7.2 ± 1 Hz, as expected. Similarly, introduction of a carbonyl group into 3 at C_4 gives *cis*-3-*t*-butyl-4-hydroxycyclohexanone (5),[10] W_5 = 8.2 ± 1 Hz, essentially the same as W_3, as expected.[11]

Consider next *trans*-2-*t*-butylcyclohexanol (6), W_6 = 22.3 ± 0.5 Hz, expected to exist almost entirely in the diequatorial chair conformation. While substitution of a hydroxyl group into 6 at C_4 to give *trans*-2-*t*-butyl-*cis*-1,4-cyclohexanediol (7), mp 156.5 - 157.7°,



3 Y = H

4 Y = OH



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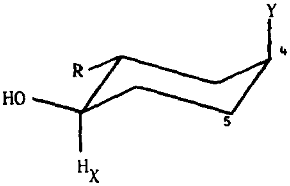
R = $C(CH_3)_3$



6 Y = H

7 Y = OH

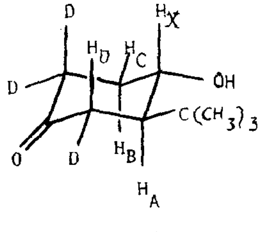
results in no detectable change, $W_7 = 22.0 \pm 1$ Hz, introduction of a carbonyl group into **6** at C_4 to give *trans*-3-*t*-butyl-4-hydroxycyclohexanone (**2**), mp 30 - 31°, produces a striking decrease in the X-proton band width. The X-proton of **2** gives $W_2 = 15 \pm 0.5$ Hz, clearly documenting the failure of the *t*-butyl group to hold **2** in the diequatorial chair conformation, **2e**.

Since $W_2 = \sum_i N_{2i}W_{2i}$,[8] where N_{2i} is the mole fraction and W_{2i} is the band width of the i th conformation of **2**, a limiting value for N_{2e}, the relative population of the diequatorial chair conformation of **2**, can be estimated by taking $W_{2e} = 22$ Hz (by analogy with W_6 and W_7) and $W_{2t_{30}} > 5$ Hz, the minimum calculated[8] band width for any accessible conformation of **2**. Then, the relation, $W_2 = 15 = N_{2e}(22) + (1 - N_{2e})(>5)$, gives $N_{2e} < 0.6$ as the limiting value. Therefore, the population of **2e** is less than 60%, possibly much less.[12]

Four vicinal coupling constants have been extracted from nmr spectra of **2**-2,6,6-d_3 and **2**-2,2,6,6-d_4 in fluorotrichloromethane solution at 31°. The spectra were recorded at 100 MHz with irradiation of deuterium.[13] The results (Table) fit *no single conformation*; a mixture

TABLE. J_{HCCH} PREDICTED[a] FROM MODEL COMPOUNDS FOR FOUR OF THE POSSIBLE CONFORMERS OF **2**.

Conformer	J_{AX}	J_{BX}	J_{CX}	J_{AD}
Chair **2a**	2.5	3.5	2.5	3
Chair **2e**	10.5	10.5	4.5	12
Twist **2t$_{3\ell}$**	0	3	3	9
Boat **2b$_{60}$**	3	3	3	12
4:4:2 **2e**:**2b$_{6\ell}$**:**2t$_{3\ell}$**[b]	5.4	6.0	3.6	11.4
FOUND[13] for **2**[c]	5.5	5.8	3.6	11.1



2e-2,6,6-d_3

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[a] Probably ± 1 Hz. [b] One of several hypothetical conformational mixtures that fit the data. [c] ± 0.1 Hz, **2**-2,6,6-d_3 in fluorotrichloromethane solution at 31°.

must be present. The possible population of 2a (t-butyl axial) is limited since J_{AB} observed, 11.1, is near its upper limit. A mixture of 40% of 2e, 40% of $2b_{6\ell}$, and 20% of $2t_{3\ell}$, for example, would be expected to give the observed coupling constants (Table). Although other hypothetical conformational mixtures also fit the data, a satisfactory fit of the vicinal coupling constants for 2 is obtained only for conformational compositions which include less than 50% of 2e.[14]

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6. Compare trans-2-t-butylcyclohexanol (6), free hydroxyl absorption band, 3617 ± 2 cm^{-1} (0.004 M in carbon tetrachloride).
7. No band near 3535 cm^{-1} could be detected for 4-hydroxycyclohexanone itself. Compare (a) R. D. Stolow, J. Am. Chem. Soc., 84, 686 (1962); (b) R. D. Stolow, T. Groom and M. Gerace, ibid., 90, 3290 (1968).
8. N. C. Franklin and H. Feltkamp, Angew. Chem. Internat. Edit., 4, 774 (1965). The sum of the vicinal coupling constants equals the experimental X-proton band width. Expected changes in vicinal coupling constants with changes in HCCH dihedral angle (ω), were estimated taking: $J = A\cos^2\omega - B\cos\omega + C$, $A = 10$, $B = 1$, and $C = 0$. See C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, Tetrahedron, 23, 2265 (1967).
9. R. D. Stolow and T. Groom, Tetrahedron Letters, 4069 (1968).
10. Infrared spectra of 4 and 5 showed no evidence of intramolecular hydrogen bonding.
11. Molecular models show that gauche interactions between two cis vicinal groups (such as t-Bu and OH in 5), although introducing strong destabilization into the chair conformation, cannot be relieved significantly in any accessible nonchair conformation. Therefore, since there is no net destabilization of the chair relative to any accessible nonchair conformation, unlike 2, nonchair populations of 5 should be comparable to cyclohexanone itself (ca. 1%), too small to be detected in the experiments reported here.
12. Although its significance was not recognized in the literature, like 2, 1 is reported[2] to have an X-proton band width intermediate between those values expected for 1e and 1a, as judged by comparison with all the other "H_4" X-proton band widths reported. We conclude from the data reported,[2] and by close analogy with 2, that 1 exists as a mixture of conformations. The reduced stereoselectivity reported for addition reactions to 1 relative to 3-t-butylcyclohexanone (8) may reflect the greater conformational heterogeneity of 1 relative to 8.[3]
13. Spectra from a Varian HA-100 Spectrometer equipped with an NMR Specialties HD60B Heteronuclear Spin Decoupler were analyzed by use of the LAOCN3 program of A. A. Bothner-By and S. M. Castellano, run on the CDC-6600 Computer, Control Data Corp., Waltham, Mass.
14. The results for 2 suggest that the chair conformation shown above for diol 7 might be destabilized sufficiently by substitution of an axial methyl group at C-5 so that an appreciable nonchair population could then be detected. This has been confirmed here by James Marini. These and other examples of the conformational consequences of strong gauche interactions of substituents are under further investigation.