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EQUILIBRATION OF CIS- AND TRANS-2-t-BUTYL-4-HYDROXYCYCLOHEXANONE

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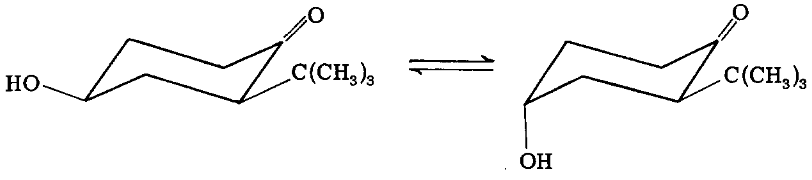
Equilibrations of the stereoisomeric cis- and trans-2-t-butyl-4-hydroxycyclohexanones (I and II), catalyzed by hydrogen chloride in benzene solution (Table I), show that the trans isomer (II) is more stable than the cis isomer (I).



I II

TABLE I

Equilibration Data for I $\rightleftharpoons$ II in Benzene Solution

T, °C[a]	% trans (II)[b]	-ΔG°, cal/mole[c]
45.2	53.4 ± 0.1	86 ± 3
65.0	53.2 ± 0.1	86 ± 3
85.0	52.9 ± 0.2	83 ± 6
105.0	52.6 ± 0.1	78 ± 3

[a] ±0.3°.

[b] The equilibrium mixtures were analyzed by gas chromatography in direct comparison with known mixtures of I and II. Four separate samples, two starting from pure I, and two starting from pure II, in sealed tubes, were equilibrated at each temperature.

[c] ΔH°, -130 ± 30 cal/mole; ΔS°, -0.13 ± 0.1 eu; from a graph of log K vs. 1/T. Estimated absolute error limits are given.

From the results of infrared and nmr studies, we have concluded that chair conformations with t-butyl axial, as well as nonchair conformations of I and II, are not populated significantly (1). Therefore, it would appear reasonable to interpret the equilibration results for I $\rightleftharpoons$ II in terms of the chair conformations with t-butyl equatorial, illustrated above (2).

The effect produced by introduction of a carbonyl group at C_4 of cis- and trans-3-t-butylcyclohexanol (III and IV), to give I and II, respectively, is sufficient to reverse the equilibrium position for epimerization of III $\rightleftharpoons$ IV, reported ΔG_1°, +0.81 kcal/mole in benzene solution at 80° (3), giving for I $\rightleftharpoons$ II, ΔG_2°, -0.08 ± 0.01 kcal/mole, also in benzene solution at 80° (interpolated from Table I). The difference, $\Delta\Delta G^\circ = \Delta G_1^\circ - \Delta G_2^\circ =$ 0.89 kcal/mole, may be taken as a measure of the significant influence of the transannular carbonyl group upon the conformational energy of the hydroxyl group. As a result of the influence of the transannular carbonyl group, the hydroxyl group is more stable in the axial position than it is in the equatorial position in benzene solution.

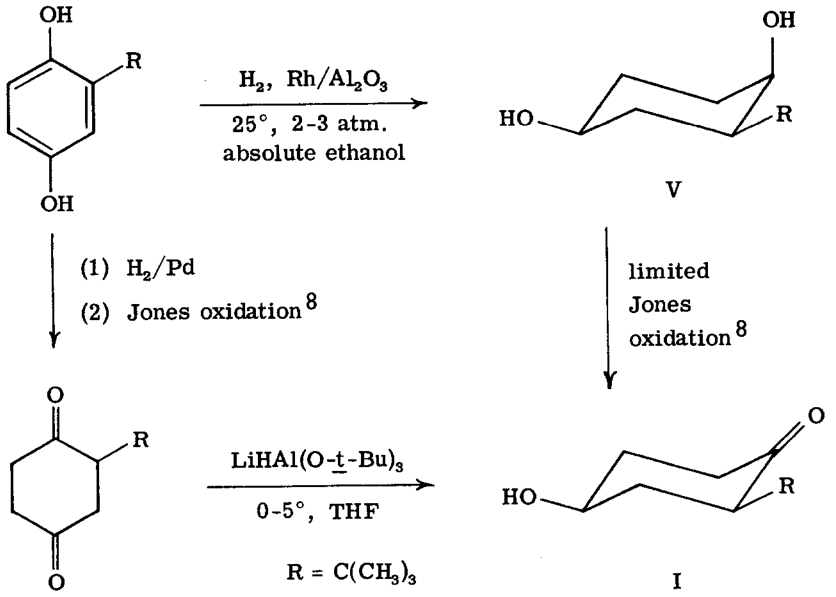
The carbonyl group can exert its influence upon the hydroxyl group by (a) an indirect steric effect resulting from slightly altered ring geometry, and (b) a polar effect, such as a transannular dipole-dipole interaction. In the absence of accurate geometries and energy calculations for I - IV, such as those reported recently for hydrocarbons by Hendrickson (4), and by Allinger (5), further experimental work would be needed in order to determine whether a steric effect or a polar effect is the dominant factor. However, a crude calculation of the transannular carbonyl-hydroxyl dipole-dipole interaction energy for I and II is suggestive. By use of the equation (6),

$$E. = \frac{\mu_1 \mu_2}{r^3 D} (\cos \chi - 3 \cos \alpha_1 \cos \alpha_2),$$

taking D, the dielectric constant of the medium between the dipoles as unity, it would appear that the interaction energy is slightly stabilizing for II (axial hydroxyl), $E_{II} =$ -0.08 kcal/mole, but for I (equatorial hydroxyl), considerable destabilization is calculated, $E_I = 0.68$ kcal/mole (7). The difference, $\Delta E = E_I - E_{II} = 0.76$ kcal/mole, may be taken as a crude estimate of the maximum influence of the carbonyl group, through its dipole-dipole interaction alone, upon the energy difference between I and II. This value of ΔE, 0.76 kcal/mole, could account for most of the observed free energy difference, $\Delta\Delta G^\circ =$ 0.89 kcal/mole, defined above. We conclude that the transannular dipole-dipole interaction requires serious consideration as the dominant factor responsible for the observed value of $\Delta\Delta G^\circ$.

Stereoselective reduction of 2-*t*-butyl-1,4-cyclohexanedione, mp 53-54°, with excess lithium tri-*t*-butoxyaluminohydride in tetrahydrofuran solution at 0-5° gave 75% of *cis*-2-*t*-butyl-4-hydroxycyclohexanone (I), mp 66.5-67.5°, and 15% of its *trans* isomer (II), mp 67-68°, plus 10% of diols. The *cis* isomer (I) was isolated by crystallization. The *trans* isomer (II) was separated from the equilibrium mixture of I and II by preparative thin layer chromatography on silica gel. Jones oxidation of *cis*, *cis*-2-*t*-butyl-1,4-cyclohexanediol (V), mp 152.5-153.5°, with one equivalent of chromium trioxide, gave I as the major product, confirming assignment of the *cis* configuration to I (8).

Assignment of the *cis*, *cis* configuration to diol V on the basis of its C_1 and C_4 ring proton nmr band widths, 7 and 28 Hz, respectively, is considered to be unequivocal. The four racemic 2-*t*-butyl-1,4-cyclohexanediols (V-VIII) have been prepared. The nmr spectrum of diol V is consistent only with the *cis*, *cis* configuration; diols VI-VIII give nmr spectra clearly inconsistent with the *cis*, *cis* configuration.



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2. Structures I and II represent racemic mixtures. Change in configuration at C_2, not C_4, would be the expected path during equilibration under these conditions (*via* keto $\rightleftharpoons$ enol equilibria). Therefore, enantiomer I (drawn above) would actually equilibrate with the mirror image of enantiomer II (drawn above), and *vice versa*, a process thermodynamically equivalent to I $\rightleftharpoons$ II.
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6. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Interscience Publishers, Inc., New York, N. Y., 1965, pp. 460-462.
7. Hydroxyl rotamer populations have been taken as 80% gauche for I and 100% gauche for II. Since E_I (gauche) = 0.64 kcal/mole and E_I (anti) = 0.84 kcal/mole, E_I is not very sensitive to hydroxyl rotamer population.
8. See J. Meinwald, J. Crandall, and W. E. Hymans, Org. Syn. **45**, 77 (1965), and reference cited. Jones oxidation gives negligible epimerization of I to II; less than 0.6% of II was present in the total product.