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CONFORMATIONAL STUDIES XIV. DESTABILIZATION OF CHAIR CONFORMATIONS OF CYCLOHEXANONES BY t-BUTYL-HYDROXYL AND t-BUTYL-METHOXYL GAUCHE INTERACTIONS.[1]

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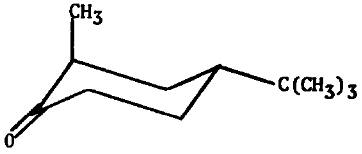
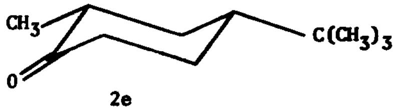
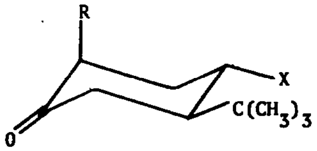
Chemical equilibrations of trans- and cis-4-t-butyl-2-methylcyclohexanones (1 and 2) have shown that 2 is more stable than 1, $\Delta G^\circ = -1.7 \pm 0.1$ kcal/mole at 40°.[4,5] The equilibrations 1e $\rightleftarrows$ 2e and 3e $\rightleftarrows$ 4e, if exclusively between the chair conformations shown, should give nearly the same free energy difference. We find for 3 $\rightleftarrows$ 4, $\Delta G^\circ = -0.13 \pm 0.05$ kcal/mole at 40° (Table I). The large difference between ΔG° for 1 $\rightleftarrows$ 2 and ΔG° for 3 $\rightleftarrows$ 4, $\Delta\Delta G^\circ = (-0.13) - (-1.7) = 1.6$ kcal/mole, clearly demonstrates that conformations significantly more stable than chair 3e must be populated for hydroxyketone 3.

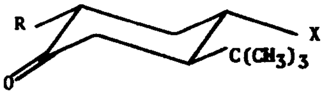


1e



2e

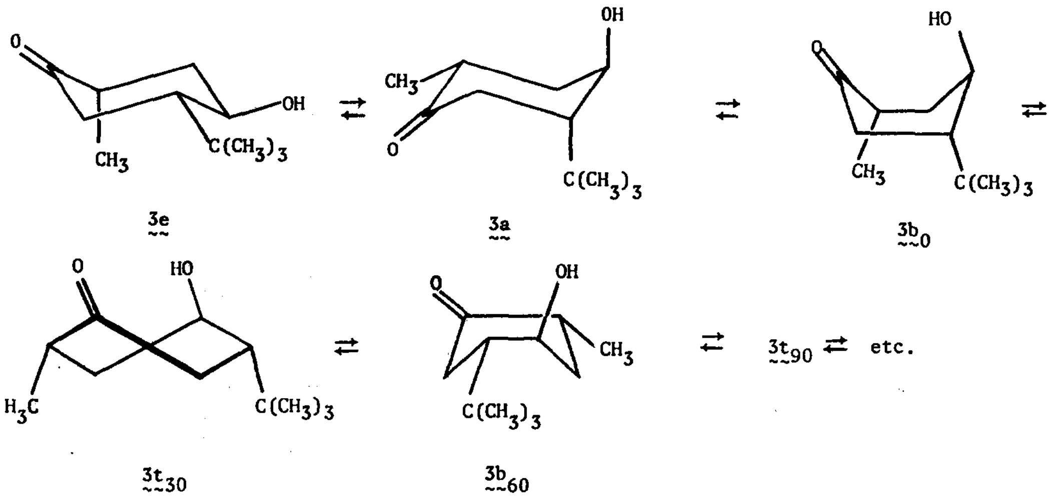




3e R = CH_3, X = OH
5e R = H, X = OH
6e R = $C(CH_3)_3$, X = H
8e R = $C(CH_3)_3$, X = OH
10e R = $C(CH_3)_3$, X = OCH_3

4e R = CH_3, X = OH
7e R = $C(CH_3)_3$, X = H
9e R = $C(CH_3)_3$, X = OH
11e R = $C(CH_3)_3$, X = OCH_3

Gauche interactions between trans vicinal groups (such as $C(CH_3)_3$ and OH in 3) can introduce strong destabilization into a chair conformation (such as 3e) relative to nonchair



conformations in which the gauche interaction is relieved (such as $\mathbf{3b_{60}}$).[1] That **3e** is but a very minor conformation of **3** can be calculated from ΔG° for **3** ⇄ **4** (Table I) plus the value for the "2-methyl ketone effect,"[7] taken as $G^\circ_{\mathbf{3e}} - G^\circ_{\mathbf{4e}} = G^\circ_{\mathbf{1}} - G^\circ_{\mathbf{2}} = 1.7 \pm 0.1$ kcal/mole at 40°.[4,5] For hydroxyketone **3** in benzene solution at 40°, the population of chair **3e** must be less than 9%.[8] It is unlikely that chair **3a**, with *t*-butyl axial, could be the major conformation of hydroxyketone **3**.[9] Therefore, we conclude that nonchair conformations predominate for hydroxyketone **3** in benzene solution. Further evidence supporting this conclusion may be derived from the striking similarity between results for hydroxyketones **3** and **8** (Tables I and II). There is no doubt that for hydroxyketone **8** one would expect nonchair conformations to predominate.

TABLE I

EQUILIBRATION OF **3** ⇄ **4** IN BENZENE SOLUTION[a]

T, °C	% **4**	ΔG°, cal/mole
40.0 ± 0.3	55.2 ± 2	-130 ± 50
80.9	55.5	-155
100.6	55.2	-155
121.4	56.4	-202

[a] 5α-*t*-Butyl-2α-methyl-4β-hydroxycyclohexanone (**3**), mp 50.5-52.0°, and 5α-*t*-butyl-2β-methyl-4β-hydroxycyclohexanone (**4**), mp 98.8-99.1°, were equilibrated by the procedure of ref. 6.

TABLE II

EQUILIBRATIONS[6] OF 8 $\rightleftarrows$ 9 IN BENZENE SOLUTION[a]

T, °C	% 8	ΔG°, cal/mole[b]
30.0 ± 0.3	51.5 ± 0.6	36 ± 18
65.0	51.9	51
100.0	52.1	62

[a] 2α,5α-di-*t*-Butyl-4β-hydroxycyclohexanone (8) mp 142.8-143.3° and 2β,5α-di-*t*-butyl-4β-hydroxycyclohexanone (9), mp 158.7-158.9°.

[b] ΔH = -80 ± 150 cal/mole,ΔS = -0.4 ± 0.5 eu.

TABLE III

EQUILIBRATIONS[6] OF 10 $\rightleftarrows$ 11 IN BENZENE SOLUTION[a]

T, °C	% 10	ΔG°, cal/mole[b]
40.06 ± 0.05	74.2 ± 0.3	657 ± 12
60.08	72.5	641
80.27	71.9	660
100.71	70.4	643

[a] 2α,5α-di-*t*-Butyl-4β-methoxycyclohexanone (10); 2β,5α-di-*t*-butyl-4β-methoxycyclohexanone (11).

[b] ΔH = 690 ± 150 cal/mole, ΔS = 0.1 ± 0.4 eu.

Equilibrations of *cis*- and *trans*-2,5-di-*t*-butylcyclohexanones (6 and 7) have shown that 7 is more stable than 6, ΔG° = 1.83 ± 0.06 kcal/mole at 30°.[10] However, substitution of a hydroxyl group at C-4 of 6 and 7 to give 8 and 9, reduces this free energy difference to ΔG° = 0.04 kcal/mole at 30° (Table II). The value, ΔΔG° = (+0.04)-(-1.83) = 1.87 kcal/mole at 30°, limits the population of 8e to < 5%.[11]

Substitution of a methoxyl group at C-4 of 6 and 7 to give 10 and 11, produces an even larger change. Although 11 can exist in an all equatorial chair conformation (11e), 10 is 660 cal/mole more stable than 11 (Table III). Therefore, it is clear that chair 11e is strongly destabilized by its *t*-butyl-methoxyl gauche interaction. The value ΔΔG°, (+0.66)-(-1.79) = 2.45 kcal/mole limits the population of 10e to < 2.5% at 40°.[11] The free energy difference (ΔΔG°= +0.66 - 0.04 = 0.6 kcal/mole) between 8 $\rightleftarrows$ 9 and 10 $\rightleftarrows$ 11 suggests that the methoxy-*t*-butyl gauche interaction in 11e is greater than the hydroxyl-*t*-butyl gauche interaction in 9e.

The results are consistent with the predominance of nonchair conformations for ketones 3, 8, and 10. Even for ketones 4, 9, and 11, each all-equatorial chair conformation is destabilized by a strong gauche interaction, and significant populations of nonchair conformations cannot be excluded.[12]

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8. We have derived the equation, $(1 - N_{3e})\ln[(1 - N_{3e})/N_{3e}] - (1 - N_{4e})\ln[(1 - N_{4e})/N_{4e}] = [(G^\circ_{3e} - G^\circ_{4e}) - (G^\circ_{3} - G^\circ_{4})]/RT$, and by use of an IBM 1130 computer and a program adapted for this purpose by John and Virginia Morris, solved for the maximum possible value of N_{3e}, the mole fraction of **3e**, 0.08 ± 0.01 at 40°. Considering possible values for N_{4e} at 40°, if $1 \geqslant N_{4e} \geqslant 0.5$, then N_{3e} would be 0.07 ± 0.02; but if $0 < N_{4e} < 0.5$, then $N_{3e} < 0.07$.
9. The population of **5a** is reported[1] to be small (10 ± 10%) and introduction of a methyl group at C-2 of **5** to give **3** would be expected to change the energies of conformations $\mathbf{5t}_{30}$, $\mathbf{5b}_{60}$, $\mathbf{5t}_{90}$, and **5a** comparably. By comparison with **5**, a conservative limit of 20 ± 20% may be set for the expected population of **3a**. Thus, **3a**, with t-butyl axial, may be more stable than **3e**, but nonchair conformations in the range $\mathbf{3t}_{30}$ to $\mathbf{3t}_{90}$ probably predominate for **3**.
10. D. Pasto, private communication, Feb. 20, 1969, found $G^\circ_{6} - G^\circ_{7} = 1.83$ kcal/mole at 30° (or 1.79 at 40°).
11. The limit was set by assuming $(G^\circ_{6} - G^\circ_{7}) = (G^\circ_{6e} - G^\circ_{7e}) = (G^\circ_{8e} - G^\circ_{9e}) = (G^\circ_{10e} - G^\circ_{11e})$, and solving an equation analogous to that in ref. 8 above. The populations of **8e** and **10e** are probably much less than the limits set here, since the population of chair **6e** is expected to be small, so that $(G^\circ_{6} - G^\circ_{7}) < (G^\circ_{6e} - G^\circ_{7e})$.
12. The near zero values of ΔS observed for equilibrations **8** ⇄ **9** and **10** ⇄ **11** (Tables II and III) contrast sharply with ΔS = -3.8 eu for the parent ketones, **6** ⇄ **7**.[10] Ketones **6**, **8**, and **10** probably exist as conformational mixtures. If **7**, **9**, and **11**, each existed only in chair conformation **e**, then values like -3.8 eu might be expected in each case. But the results, ΔS = -0.4 ± 0.5 for **8** ⇄ **9**, and 0.1 ± 0.4 eu for **10** ⇄ **11**, suggest that **9e** and **11e** may not be the only populated conformations of **9** and **11**.