Conformational *gem*-Effect in Disubstituted Cyclohexanes

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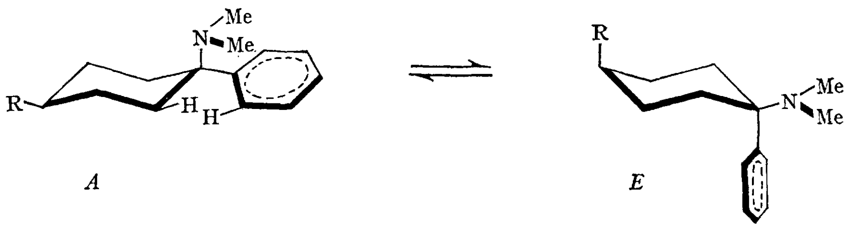
IT has previously been reported, that the conformational free-energy difference ΔG of 4-t-butylcyclohexyl monothioketals is in good agreement with the known values of ΔG_{S-R} and ΔG_{O-R}.[1] Accordingly it is accepted that in the 1,1-disubstituted cyclohexanes, the substituent having the larger ΔG-value would exist in a predominantly equatorial position.[2a]

However, in a recent paper, on the cyclisation of geminally-substituted β-phenylglutaric monoesters, the ΔG-value of the phenyl group seems to be dependent on the size of the second substituent.[3] In this Communication we confirm the dependence of the ΔG-value of the phenyl group on the second substituent in the geminally substituted cyclohexane derivatives.

For our study, compounds (I), (II), and (III) were readily prepared by the known Grignard



(I) R = Bu^t (II) R = Me (III) R = H

p*K* 7·05 7·45 7·89 (in Methylcellosolve)

reaction.[4] The p*K*-values were measured in Methylcellosolve (80%).[5]

On the one hand it is expected that substance (I), having an equatorial t-butyl group[6] has exclusively conformation *A*, but on the other hand conformation *A* of the compound (II) is stabilized by $\Delta G_{\text{Me}} = 1{\cdot}7$ kcal./mole.[2b] On this basis we calculated the free-energy difference of the conformational equilibrium of compound (III). The calculations were based on the p*K*-values of these three compounds using Stolow's[7] or Sicher's[8] equation.

Surprisingly it was found that conformation *E* is more stable than conformation *A* by 0·9 kcal./mole. For the corresponding ammonium salt this value is increased to 2·2 kcal./mole. These data disagree completely with the known values of ΔG, [2b]: Ph, 2·0, 2·6, or 3·6, NMe_2; 2·1 $HNMe^+$, 2·4 kcal./mole.

The following explanation may be offered for this discrepancy: (1) ΔG_{Ph} decreases with a diminution of the equatorial conformation stability: the presence of the second substituent, such as dimethylamino, hinders the free rotation of the phenyl group in the equatorial conformation and consequently the nonbonded interaction of the *ortho*- and equatorial hydrogens as shown in *A* is increased. Such an *ortho*- and 2-equatorial interaction has already explained the preferential axial conformation of the *ortho*-t-butylphenyl group.[9] The stability increase of *E*-form is much higher (1·3 kcal./mole) than the known 0·3 kcal./mole difference between ΔG ($HNMe_2^+$) and $\Delta G(NMe_2)$. This may result from the overlap of the H–N^+ bond by the π-electron system of benzene nucleus. The interaction between π-electron system and the hydrogen of OH in the case of benzyl alcohol has also been reported.[10]

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