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CONFORMATIONAL ENERGY AND ENTROPY DIFFERENCES OF THE t-BUTOXY GROUP AND IMPLICATIONS IN STEREOCHEMISTRY AND STEREOELECTRONICS¶

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Abstract. The conformational energy and entropy differences of the t-butoxy group were determined using ^{1}H- and ^{13}C-NMR variable temperature techniques and ΔE_{conf} was calculated by molecular mechanics (MM2). Strikingly small values were observed and discussed in conjunction with the alleviated anomeric effect in 2-t-butoxytetrahydropyran systems.

In the variegated literature on conformational free energies accumulated over more than 25 years[1a,2-5], there was a missing link among the available data: the t-butoxy group.

We became aware of this deficiency in the course of an investigation of the role of the trimethylsilyloxy (TMSO) and t-butoxy (TBO) vis-a-vis that of other, simple alkoxy (RO) groups in the alleviation of the *anomeric effect*.[6,7]

To assess the magnitude of the latter, we needed the A-values, i.e., $-\Delta G^o_{conf}$ of RO-groups. Some of these were available[2], as was also that of TMSO[8] but not that of TBO and we decided to determine it.

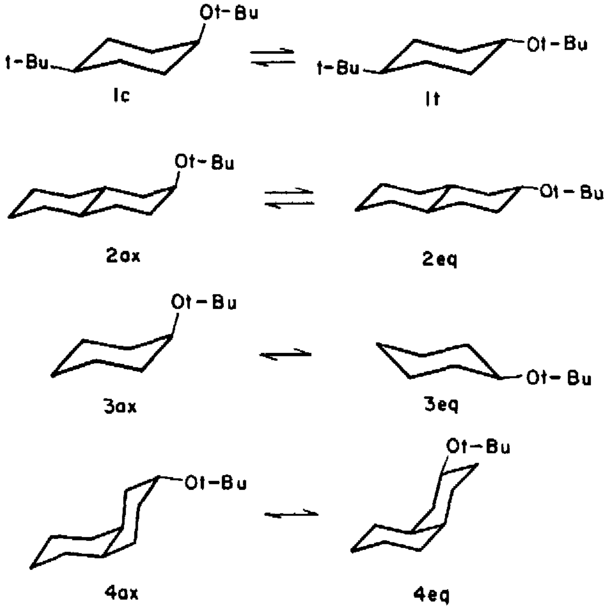
The methods we considered at first were chemical equilibration of cis/trans-4-t-butyl-t-butoxycyclohexane (1 c&t) and of cis/trans-2-t-butoxy-trans-decalin (2 c&t), which were prepared by reaction of the corresponding alcohols with isobutylene under acid catalysis and were spectroscopically well characterized and related to published data whenever available.

In this chemical approach we met, however with severe difficulties because of the sensitivity of t-butyl ethers to even weak acid catalysis, causing massive elimination to iso-butylene during isomerization. However, a second approach, namely, variable temperature NMR spectroscopy of t-butoxycyclohexane (3) and of trans-2-t-butoxy-cis-decalin (4) was successful and the data are depicted in the Figure.

It has been established long ago[9-11] that the t-butyl fixating group affects somewhat the cyclohexane geometry and the ^{1}H-NMR chemical shifts. On the other hand, ^{13}C-NMR chemical shifts were found to be largely unaffected in similar circumstances.[12]

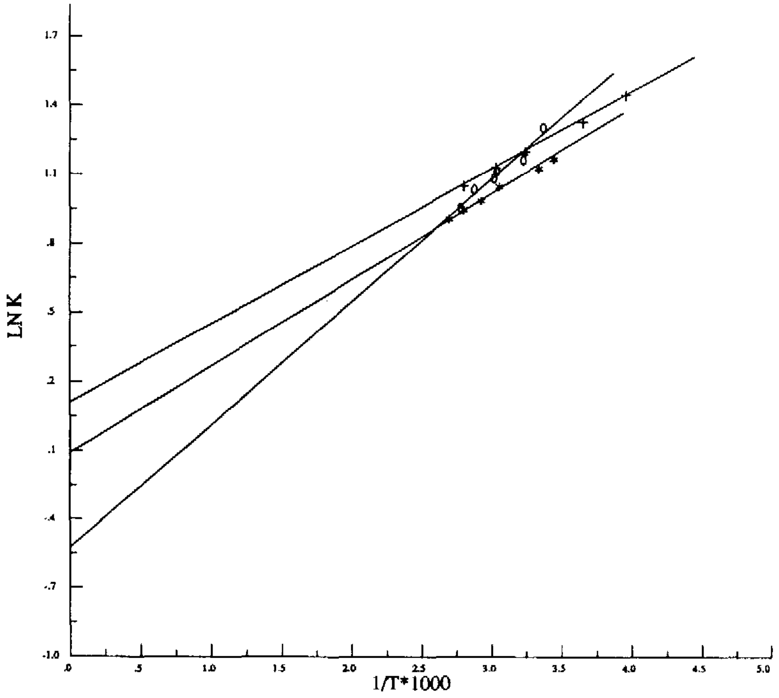
We considered, hence, the most precise and reliable method to be that based on ^{13}C-chemical shifts. The center of scrutiny was the C1 ring-carbon in 3 and the variation of its ^{13}C chemical shift with temperature. This was related to the corresponding values of the C1 chemical shifts in 4-t-butyl-t-butoxycyclohexane. In addition to that, similar ^{1}H-NMR coupling constants measurements were performed on t-butoxycyclohexane (3) and trans-2-t-butoxy-cis-decalin (4)[13]; these were related to the corresponding values of the coupling constants in cis and trans-4-t-butyl-t-butoxycyclohexane (1 c&t) and of trans-2-t-butoxy-trans-decalin.[13] Notably, both reference systems exhibited similar coupling constants in the C1H-C2H$_2$ grouping, viz. $^3J_{axax}$= 10.9 and $^3J_{eqeq}$= 2.9 Hz.

¶ Dedicated to Professor Ernest L. Eliel.



Figure

Plots of ln K vs. 1/T for t-butoxycyclohexane (1) by ^{13}C-NMR (crosses) and by ^{1}H-NMR (circles) as well as of *trans*-2-t-butoxy- *cis*-decalin (4) by ^{1}H-NMR (stars).



The ^{13}C-NMR data (see Figure) yield ΔG^{o}_{conf} = -0.75 kcal/mol at 36°C, ΔH^{o}_{conf} = - 0.68±0.04 kcal/mol and ΔS^{o}_{conf} = 0.2±0.1 cal/K.mol. The less precise ^{1}H-NMR $^{3}J(C1H\text{-}C2H_2)$ measurements (see Figure) gave a similar A-value (0.72 kcal/mol) but lower, albeit less reliable ΔH= -1.0±0.1 kcal/mol and ΔS=-1.0±0.8 cal/K.mol. Similarly, ^{1}H-NMR work on the fused bicyclic six-membered ring system, <u>trans</u>-2-t-butoxy-<u>cis</u>-decalin (<u>4</u>) (see Figure) gave ΔG^{o}_{conf} = -0.67 kcal/mol, ΔH^{o}_{conf} = -0.75±0.1 kcal/mol and ΔS^{o}_{conf} = -0.2±0.2 cal/K.mol. In view of the uncertainty inherent in this type of determination of enthalpy and entropy differences,[14] we conclude on the following set for the t-butoxy group: ΔG^{o}_{conf} = -0.75 kcal/mol at 36°C, $\Delta H^{o}_{conf} \simeq$ -0.7 kcal/mol and $\Delta S^{o}_{conf} \simeq$ 0 cal/K.mol.

The above described experimental work was actually preceded by molecular mechanics (MM2-82[15]) calculations of t-butoxycyclohexane and some related compounds. Their steric energies are given in the Table, as deduced from Boltzmann distributions in their three conformations (a,g^{+},g^{-}) of each, axial and equatorial forms. The calculated values of the conformational energy differences, compare very well with the experimental ones, listed therein.

The outcome of this investigation is very interesting: (i) the conformational free energy of the t-butoxy group is actually inbetween those of the ethoxy and methoxy groups[2] and enthalpy similar to that of methoxy[14a]; (ii) the conformational entropy difference is all but nil (albeit with a rather low confidence level), similar to that of the methyl group but not of ethyl or i-propyl.[24] This behaviour is even more striking than that of the neopentyl group,[16] the A-value of which is also quite similar to (and calculated lower than) that of the methyl and ethyl substituents. A possible explanation (based on a cursory examination of the van der Waals energies and inter-atomic distances in the MM2 calculations) is that equatorial 1,4-gauche interactions of the neopentyl group counterweigh some of the 1,3-diaxial interactions and that this effect stronger as the (C-O) bond lengths become shorter.

Be this as it may, it is compelling to relate the obtained results to the above mentioned alleviation of the *anomeric effect* by R=t-butyl in 2-(R)oxy-tetrahydropyran[17-20] (cf. <u>5</u>ax&eq) or 1,4-dioxan[6,21] systems. Following the established quantitation of the *anomeric effect*[1b], $\Delta G^{o}{}_{(\underline{5}eq\text{-}ax)} - \Delta G^{o}{}_{(\underline{3}eq\text{-}ax)}$ i.e., 0.3[17]- 0.7 = 1.0 kcal/mol. This is considerably less than the accepted value for O-alkyl (1.3-1.5[22]) by any standards.[23]

We conclude, therefore, that the observed relative stabilization of the equatorial t-butoxy group in anomeric systems are not due to simple steric effects, since these act just oppositely; an electronic, hyperconjugative effect has been invoked,[6] instead. To be sure, this does not mean that we deal with an open and shut case; rather, it remains still to be explained <u>why</u> the t-butoxy group exhibits its peculiar behaviour in such circumstances.

5ax **5eq**

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Table

Molecular mechanics (MM2[15]) calculations of t-butoxycyclohexane and some selected R-cyclohexanes[a] vs. experimental ΔG^{o}_{conf} values.[b]

	E									
	axial			equatorial						
R	*a*	g^-	g^+	*a*	g^-	g^+	Eax	Eeq	ΔE	exp[b]
Me		8.7			6.9		8.7	6.9	-1.8	-1.7
Et	10.4 (0.5)	10.4 (0.5)		8.5 (0.45)	8.5 (0.45)	9.4 (0.1)	10.4	8.6	-1.8	-1.75
Neopentyl	15.9 (0.5)	15.9 (0.5)		14.2 (0.5)	14.2 (0.5)	16.6	15.9	14.2	-1.7	-2.0
OH	8.2 (0.45)	8.2 (0.45)	9.1 (0.1)	7.6 (0.42)	7.6 (0.42)	8.3 (0.16)	8.3	7.7	-0.6	-0.52
OMe	12.7 (0.5)	12.7 (0.5)		12.1 (0.485)	12.1 (0.485)	14.2 (0.03)	12.7	12.2	-0.5	-0.60
OEt	13.1 (0.5)	13.1 (0.5)		12.6 (0.495)	12.6 (0.495)	14.7 (0.01)	13.1	12.7	-0.5	-0.90
Ot-Butyl	19.9 (0.5)	19.9 (0.5)		19.4 (0.5)	19.4 (0.5)	23.9	19.9	19.4	-0.5	-0.75[d]
-"- [c]									-0.7	-0.7[d]

a) Steric energies (E) in kcal/mol; numbers in parenthesis stand for Boltzman populations of the various conformers (*a*=anti, *g*=gauche in the R-O-C1-C2 torsional angle).

b) ΔG^{o}_{conf} ("best values") taken from ref. 2.

c) using trans-2-t-butoxy-cis-decalin (4)

d) this work

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