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CONFORMATION, IN SOLUTION, OF c-4-t-BUTYL-1-PHENYL-r-1-(N-PIPERIDYL)CYCLOHEXANE HYDROCHLORIDE. THE CONFORMATIONAL ENERGY OF t-BUTYL

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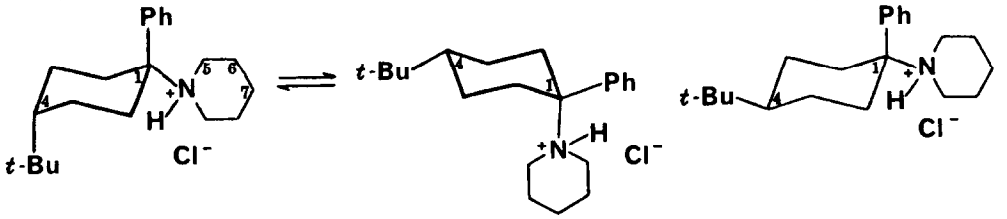
SUMMARY: Although the hydrochloride of c-4-t-butyl-1-phenyl-c-1-(N-piperidyl)cyclohexane crystallizes in the conformation with axial t-butyl, it exists as an almost equimolar mixture of the two chair conformers in CD_2Cl_2 solution. The position of equilibrium allows one to calculate $\Delta G°_{t\text{-Bu}}$ as -4.9 kcal/mol.

In 1981, Geneste et al.[1] showed that the title compound (1) crystallizes in the conformation 1A with axial t-butyl, presumably because of a high tendency of the protonated and ion-paired piperidinium moiety to avoid the axial position. Surprisingly, however, it was also reported[1] that, in solution, 1 has the phenyl and t-butyl groups equatorial, i.e. exists as 1B.



1A 1B 2

This claim was based on proton[2] and ^{13}C nmr[3] data and on the fact that the free base corresponding to 1 was shown,[2,3] in various ways, to be exclusively in the conformation with equatorial t-butyl, corresponding to B.

That a compound should exist entirely in one conformation in solution and in another in the crystal is quite unusual, at least in cyclohexane derivatives. Moreover, Geneste et al.[2] had shown that phencyclidine hydrochloride (1, H in lieu of t-bu) prefers conformation A with equatorial piperidinium by 4.4 kcal/mol; since it has been calculated[5] that the equatorial conformation of t-butyl has a rather similar preference of 4.7 kcal/mol, K for the equilibrium shown above should only be of the order of 2.

The comparison of 1 with the corresponding free base[1] is not instructive, since conformational equilibria in amines and their salts are often quite different.[6] As for the spectral evidence in 1 itself, it is difficult to draw conclusions from the published[2] proton spectra and the evidence from the ^{13}C spectra[3,7] is questionable. In fact, the large reported difference in chemical shift of C(4) as between 1 (42.06 ppm) and its diastereomer 2 (45.77 ppm)[3] speaks against both compounds existing with purely equatorial t-butyl but rather suggests that conformer 1A makes an important contribution to 1.

We have now succeeded in decoalescing the ^{13}C nmr spectrum of 1 in CD_2Cl_2 at -120°C. Room temperature and low-temperature shifts in CD_2Cl_2 are summarized in Table 1. Assignment of the C(1), C(4) and C(ipso) peaks (which are well split) is based on analogy of 1A with phencyclidine hydrochloride[3,8] and the reasonable assumption that C(4) in 1A should be upfield of that in 1B. The peak area ratio (B/A) is 1.81 for C(4) and 1.51 for C(1), corresponding to $\Delta G°$ of ca. -0.15 kcal/mol. Clearly, both conformations contribute about equally to 1 in solution, contrary to the earlier report.[1]

Table 1 - ^{13}C Signals of 1, 1A and 1B (ppm from Me_4Si)

	C(1)	C(2)	C(3)	C(4)	C(α)	C(ß)	C(5)	C(6)	C(7)	C(i)	C(o,m)		C(p)
1	70.6	29.4	22.4	43.1	33.3	28.4	48.3	22.9	22.7	134.5	129.0	129.5	129.7
1A	70.4	29.3	27.7	38.6	33.7	28.1	48.8	22.3	22.8	130.1	129.1	129.6	129.2
1B	69.0	32.9	22.3	47.1	33.2	28.1	48.2	22.1	22.8	136.3	128.7	129.1	130.1

If one accepts a value of $\Delta G° = -4.8$ kcal/mol[2,10] for the parent phencyclidine hydrochloride equilibrium (A/B, without the t-butyl substituent), the predominance of 1B over 1A by 0.1 kcal/mol signifies that $-\Delta G°$ for the t-butyl group is -4.9 kcal/mol. We believe that this is the first experimental measurement of $-\Delta G°_{t\text{-bu}}$ not involving escape of the cyclohexane ring into the twist form (for which we find no evidence in 1). The good agreement with the value of 4.7 kcal/mol calculated by molecular mechanics[5] supports the soundness of the argument, even though one must admit to some uncertainty inasmuch as the phencyclidine hydrochloride equilibrium was determined in aqueous methyl cellosolve[2] rather than in methylene chloride.

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References and Notes

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6. This point is, unfortunately, often overlooked, especially in the pharmacological literature.
7. See also J.M. Kamenka and P. Geneste in "PCP (Phencyclidine): Historical and Current Perspectives", E.F. Domino, ed., NPP Books, Ann Arbor, MI, 1981, p. 47ff.
8. G.A. Brine, E.E. Williams, K.G. Boldt and F.I. Carroll, J.Heterocyclic Chem., 16, 1425 (1979).
9. C(i) in 1A is overlapped with other aromatic signals and cannot be used to determine the A/B ratio. The assignment for C(2) and C(3) in 1A and 1B are not certain and these peaks are clustered with others. Little or no resolution (as between A and B) occurs for C(α), C(ß), C(5), C(6), C(7), C(o,m) and C(p). Our room temperature peak positions agree reasonably with those in ref. 3 as revised in ref. 7, considering the difference in solvent (CD_2Cl_2 vs. $CDCl_3$).
10. This value is corrected from that given in ref. 2 because the assumption there made that 1 in solution exists entirely as 1B and can therefore serve as a model for phencyclidine hydrochloride with axial piperidinium is not valid. If one takes into account the 1A/1B equilibrium here determined, the corrected pK_a for pure 1B becomes 5.635 which leads to a value of -4.78 kcal/mol for the phencyclidinium equilibrium.

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