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THE CONFORMATIONAL PREFERENCE OF THE TRIFLUOROMETHYL GROUP

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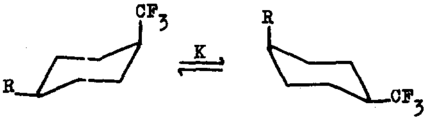
Studies in the field of conformational analysis have led to the assignment of conformational free energy differences ($-\Delta F_x$) to a large number of substituents.[1] No information has appeared on the conformational equilibrium of the trifluoromethyl group, which is of interest compared with other symmetrical substituents (CH_3, NH_3^+, and t-Bu) because $-\Delta F_{CF_3}$ may be influenced by attractive hydrogen-fluorine interactions. An evaluation of the conformational preference of the trifluoromethyl group by infrared spectroscopy is now reported, the method adopted being essentially that described by Pickering and Price.[2]

Judging from models it seemed likely that $-\Delta F_{CF_3}$ would be at least as great as $-\Delta F_{CH_3}$ (and probably also $-\Delta F_{NH_3^+}$) but somewhat lower than $-\Delta F_{t\text{-}Bu}$, so that trifluoromethylcyclohexane (I) should exist predominantly if not exclusively as conformation (Ie). This proved to be the case, and accordingly the mobile equilibrium of cis-4-methyltrifluoromethylcyclohexane (IIa $\rightleftharpoons$ IIe) was studied in the expectation that the additional methyl group would alter conveniently the position of equilibrium.

Additivity of conformational energies is assumed, an assumption made previously[3] which appears to be generally valid.[4]

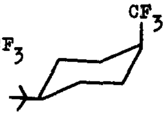


Ia, R=H Ie, R=H

IIa, R=CH_3 IIe, R=CH_3

III, R=CH_3

IV, R=t-Bu



V

Compounds (II-V) were synthesised* in good yield from the corresponding carboxylic acid by reaction with sulphur tetrafluoride at 70°.[5] At this temperature the conversion ($RCOOH \rightarrow RCF_3$) occurred with little, if any, epimerisation in contrast to the significant epimerisation that occurred when fluorination was conducted at 130°. Trifluoromethylcyclohexane was prepared by published methods and had physical constants identical with recorded values.[6]

The trifluoromethyl group has been shown[7] to have a number of characteristic infrared absorbance bands between 1100-3500 cm^{-1} and between 680-750 cm^{-1}. The infrared spectra of compounds (I-V) contained strong absorption peaks in the higher frequency range, some of which are associated with CF_3 stretching vibrations. The compounds also absorbed between 685-720 cm^{-1}, the region ascribed to CF_3 symmetrical deformation.[7] In view of the sharpness of the bands, and the lack of extraneous absorptions, the latter region was examined in greater detail (see Table) with a Perkin-Elmer 21 spectrometer.

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* All these new compounds gave satisfactory analyses for C, H and F, and were stereochemically pure (vpc).

TABLE

Compound	Concentration[a,b]	λ_{max} (ε)[c]	
		$^{e}CF_3$	$^{a}CF_3$
I	0.237 M	684 cm^{-1} (67.0)	-
I	0.300 M	684 cm^{-1} (68.1)	-
II	0.245 M	692 cm^{-1} (43.0)	711 cm^{-1} (9.8)
II	0.329 M	692 cm^{-1} (42.5)	711 cm^{-1} (9.7)
III	0.247 M	692 cm^{-1} (64.0)	-
III	0.311 M	692 cm^{-1} (62.7)	-
IV	0.276 M	687 cm^{-1} (64.0)	-
IV	0.340 M	687 cm^{-1} (62.5)	-
V	0.303 M	-	703 cm^{-1} (32.2)
V	0.514 M	-	703 cm^{-1} (31.0)

[a] KBr prism and (0.2 mm) cells.

[b] Mole/litre, cyclohexane solution at 25°.

[c] Analytical bands. ε = molar extinction coefficient. Average of triplicate measurements.

The bands in trifluoromethylcyclohexane (I), trans-4-methyltrifluoromethylcyclohexane (III) and trans-4-t-butyltrifluoromethylcyclohexane (IV) must clearly represent symmetrical deformation of the equatorial CF_3 group as compounds (III) and (IV) are both expected to exist completely in the conformation shown (cf. I as Ie). The added 4-alkyl substituent evidently has only a slight effect on both the frequency and the ε-value.

cis-4-t-Butyltrifluoromethylcyclohexane (V) had a single absorption at a higher frequency and this was assigned to axially positioned CF_3.

The spectrum of cis-4-methyltrifluoromethylcyclohexane (II) contained a band at 692 cm^{-1} and another at 711 cm^{-1}. The former is undoubtedly due to the equatorial CF_3 group (IIe) on the basis of its coincidence with the band observed in the spectrum of the trans-epimer. It seems likely that the peak at 711 cm^{-1} corresponds to that at 703 cm^{-1} in compound (V) and is due to conformation (IIa). Calculation of the constant, K, for the equilibrium ($IIa \rightleftharpoons IIe$) from the two independent coefficients (εe and εa) gave values in remarkably good agreement and which average to 2.1. Thus the free energy difference, $-\Delta Fo$, between IIa and IIe ($-\Delta Fo = -\Delta F_{CF_3} + \Delta F_{CH_3}$) is found to be 0.4 Kcal/mole. Substituting 1.7 Kcal/mole[8] for $-\Delta F_{CH_3}$ gives 2.1 Kcal/mole for the conformational preference of the trifluoromethyl group.

Criticism has been levelled at the practice of assuming that band intensities of axial (or equatorial) substituents in cyclohexyl and 4-alkylcyclohexyl derivatives are necessarily the same. The very small discrepancy between the intensity of e_{CF_3} in compounds (I, III, and IV) clearly shows that the assumption is valid in this case.[9] Frequency assignments have also been criticised, but those made here are justified by previous work.[7] Using the εe- and εa- values already mentioned in determining the position of the equilibrium ($IIa \rightleftharpoons IIe$) gave K values in excellent agreement, and it is doubtful that the assigned bands are due to anything but CF_3 absorptions.

The value (2.1 Kcal/mole) for $-\Delta F_{CF_3}$ appears a little lower than might be expected from comparison of values for CF_3, CH_3, NH_3^+ and t-Bu groups. This may indicate that the axially placed CF_3 substituent has favourable H......F attractions which offset to some extent other highly unfavourable non-bonded interactions. These and similar implications will be discussed more fully in a later paper.

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