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Experimental determination of the conformational free energies (*A* values) of fluorinated substituents in cyclohexane by dynamic ^{19}F NMR spectroscopy. Part 1. Description of the method for the trifluoromethyl group†

Yvan Carcenac, Patrick Diter, Claude Wakselman and Marc Tordeux*

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The conformational free energy (*A* value) of the trifluoromethyl group was determined by variable temperature ^{19}F NMR studies of trifluoromethylcyclohexanes bearing a substituent at the 4 position. ^{19}F NMR chemical shifts for each conformer above the coalescence temperature were obtained by extrapolation from low temperature values, allowing the high precision determination of the equilibrium constants, and then the thermodynamic parameters (ΔG°, ΔH°, ΔS°). The validity of the hypothesis that substituent parameters are additive was discussed. Thermodynamic data of phenyl and cyclohexyl groups were also given.

Introduction

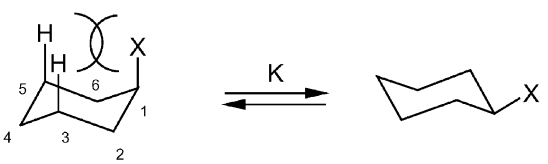
Since Barton's first works,[1] conformational analysis has been an important part of organic chemistry[2,3] and is used for the interpretation of many phenomena.[4] Understanding of the steric repulsions of a molecule often allows the correct prediction of the relative conformer stability, the reactivity or the stereochemistry of synthesised compounds.[5] Information on the steric effect of a substituent can be obtained from kinetic experiments: Taft defined in 1952 a steric parameter (E_S) based on the rate of acid-catalysed ester hydrolysis.[6,7] Twenty years later, Dubois *et al*. proposed revised Taft steric constants (E_S').[8] These two parameters provide a measure of steric hindrance relative to a proton. Computed parameters have also been derived from van der Waals radii (Charton ν values)[9,10] or from the volume of the portion of the substituent that is within 0.3 nm of the reacting centre (Meyer V^a values).[11]

Steric effects can also be estimated from the conformational energies of substituted cyclohexanes. In 1955, Winstein and Holness defined the *A* value of a substituent as the free energy difference between axial and equatorial isomers of monosubstituted cyclohexanes (Scheme 1).[12]

Repulsive steric interactions between axial X and the C (3,5) methylenes destabilise the conformer with the substituent in the axial position relative to the equatorial one. When the corresponding size of the substituent grows, the conformer with the substituent in the equatorial position becomes more and more predominant and the *A* values increase concomitantly.

This parameter has become a very useful resource to assess the steric size of a large variety of substituents. While many *A* values have been determined and compiled,[3,13] very few data concerning fluorinated groups are available. The only studied substituents are the fluorine atom[14] and the trifluoromethyl group. For this last substituent, exploratory work was performed by ^{13}C NMR and IR spectroscopy in the late 1960s.[15,16] Our purpose was to obtain more precise values for the trifluoromethyl group and to extend these data to other fluorinated groups. In this way, ^{19}F NMR spectroscopy is a very convenient tool. Only one signal for each isomer is observed, and the two conformer signals are very well separated below the coalescence temperature. Moreover, the natural abundance (100%) and the molar receptivity (0.83 rel. to ^{1}H) of the ^{19}F nucleus allow the registration of spectra in a short time at low concentration, even near the coalescence temperature when signals become very broad.

The aim of our work was to study by dynamic ^{19}F NMR spectroscopy the influence of the trifluoromethyl group on the cyclohexane equilibrium.[17] When the steric hindrance of a substituent is important, which is the case for the trifluoromethyl group, the axial conformer is extremely minor and the conformational equilibrium is not observable. In such a



$$A = -\Delta G^\circ = RT\ln K / 4186$$

(A values are given in kcal mol^{-1})

Scheme 1

SIRCOB, UMR CNRS 8086, Université de Versailles-Saint-Quentin en Yvelines, 45 Avenue des Etats-Unis, 78035 Versailles, France. E-mail: marc.tordeux@chimie.uvsq.fr

† Electronic supplementary information (ESI) available: Variable temperature ^{19}F NMR chemical shifts of *cis*- and *trans*-4-substituted 1-trifluoromethylcyclohexanes and 4-substituted 1-trifluoromethylcyclohexanols, coefficients *a*, *b* and *c* of the temperature dependence of the chemical shifts, equilibrium constants and free energies. See DOI: 10.1039/b516636e

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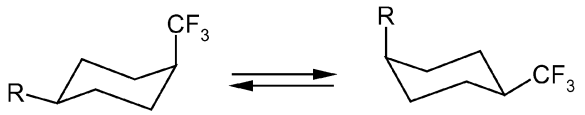

$$\Delta G^\circ = \Delta G^\circ_{CF_3} - \Delta G^\circ_R$$

(Where $\Delta G^\circ_{CF_3}$ and ΔG°_R are the conformational free energies in monosubstituted cyclohexanes).

Scheme 2

situation, the "counterpoise" method is used in studying disubstituted cyclohexanes.[18] In the case of *cis*-1,4-disubstituted cyclohexanes, conformational energies are considered to be additive,[3] if the bulkinesses of the two groups are close enough without interaction between them (Scheme 2).

In this paper, the study of the conformational equilibrium of *cis*-4-substituted trifluoromethylcyclohexanes by variable temperature ^{19}F NMR spectroscopy is reported. Part 2 will be devoted to the extrapolation of this method to other fluorinated groups.[40]

Results and discussion

The synthesis of *cis*-4-substituted trifluoromethylcyclohexanes and cyclohexanols from the corresponding cyclohexanones was previously described.[19] A mixture of the two isomers was used directly for the ^{19}F NMR studies. *trans*-Isomers were useful as an internal reference for chemical shift variations and for signal width without exchange (coupling constants are almost the same and relaxation times T_1 and T_2 should be similar if the exchange contribution is not taken into account). Trifluoromethylcyclohexane and 1,4-bis(trifluoromethyl)cyclohexane were also prepared by catalytic hydrogenation of the corresponding aromatic compounds.

The synthesised molecules were then studied by variable temperature NMR spectroscopy. For each compound, ^{19}F NMR spectra were registered from room temperature to 168 K in deutero THF. It appears that the trifluoromethyl group of trifluoromethylcyclohexane is highly based in the equatorial position and in the *cis*-4-*tert*-butyl-1-trifluoromethylcyclohexane, the CF_3 group is locked in the axial position at any temperature. In all other cases, an equilibrium was observed. The spectra showed one signal (singlet or doublet depending on proton irradiation) for each diastereoisomer at 298 K. The *trans*-isomer chemical shift δ_{trans} is characteristic of an equatorial CF_3 (around −72 ppm, Table 1). A broad band is observed for the *cis*-isomer, due to the conformational equilibrium (between −66 and −71 ppm, depending on the axial or equatorial preference of the trifluoromethyl group). The spectra were then registered in 5 K steps. The *cis*-isomer signal vanished completely around 240 K and the separated signals of the two conformers appeared below the coalescence temperature (220 K): the trifluoromethyl group in the equatorial position near the signal of the *trans*-isomer and the axial one around −63 ppm. Then, the spectra were simulated with the WINDYN (Bruker) program in order to calculate chemical shifts, populations, and equilibrium rates according to temperature.

The first method to determine the equilibrium constant K and the associated free energy ΔG° used the signal integrations below the coalescence temperature. However, margins of error were too great, due to the relative inaccuracy of the

Table 1 Coefficients a, b and c of the chemical shift temperature dependence

R		δ/ppm[a]		a/ppm	b/ppm K^{-1}	c/ppm K^{-2}
Me			δ_{ax}	−62.22	-7.31×10^{-3}	—
	δ_{cis}	−70.34	δ_{eq}	−70.54	-6.75×10^{-3}	—
	δ_{trans}	−71.85	δ_{trans}	−69.57	-1.38×10^{-2}	1.99×10^{-5}
Et			δ_{ax}	−62.07	-7.56×10^{-3}	—
	δ_{cis}	−70.29	δ_{eq}	−70.43	-6.93×10^{-3}	—
	δ_{trans}	−71.85	δ_{trans}	−69.41	-1.46×10^{-2}	2.14×10^{-5}
c-Hex			δ_{ax}	−62.04	-7.69×10^{-3}	—
	δ_{cis}	−69.35	δ_{eq}	−70.56	-6.19×10^{-3}	—
	δ_{trans}	−71.89	δ_{trans}	−69.53	-1.42×10^{-2}	2.10×10^{-5}
*i*Pr			δ_{ax}	−61.89	-8.69×10^{-3}	—
	δ_{cis}	−69.18	δ_{eq}	−70.42	-7.18×10^{-3}	—
	δ_{trans}	−71.87	δ_{trans}	−69.41	-1.49×10^{-2}	2.23×10^{-5}
*t*Bu	δ_{cis}	−66.4	δ_{cis}	−64.05	-7.09×10^{-3}	-2.71×10^{-6}
	δ_{trans}	−71.37	δ_{trans}	−68.97	-1.45×10^{-2}	2.15×10^{-5}
Ph			δ_{ax}	−62.04	-7.49×10^{-3}	—
	δ_{cis}	−66.97	δ_{eq}	−70.7	-5.99×10^{-3}	—
	δ_{trans}	−71.83	δ_{trans}	−69.71	-1.26×10^{-2}	1.84×10^{-5}
CF_3			δ_{ax}	−70.39	-7.27×10^{-3}	—
	δ_{cis}	−68.3	δ_{eq}	−62.48	-6.77×10^{-3}	—
	δ_{trans}	−71.92	δ_{trans}	−69.59	-1.36×10^{-2}	1.94×10^{-5}

[a] δ at 298 K.

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integration. Moreover, the results were obtained at low temperatures and it is very hazardous to extrapolate them to room temperature. The application of Winstein–Holness and Eliel–Ro theory [eqn (1)] to chemical shifts provides more precise data:[12,20] conformational composition can be calculated from balanced averages of chemical shifts of each conformer in a system in fast equilibrium.

$$K = x_{eq}/x_{ax} = (\delta_{ax} - \delta_{obs})/(\delta_{obs} - \delta_{eq}) \quad (1)$$

Where δ_{obs} is the chemical shift observed for the molecule in fast equilibrium, x_{ax} and x_{eq} are the molar fractions and δ_{ax} and δ_{eq} are the chemical shifts of the axial and equatorial conformers, respectively.

δ_{ax} and δ_{eq} were measured below the coalescence temperature. In order to apply eqn (1), conformer chemical shifts have to be determined at each temperature. Indeed, the chemical shifts cannot be considered as similar below and above the coalescence temperature: their temperature dependence can be described as a binomial function [eqn (2)]:[21]

$$\delta = a + bT + cT^2 \quad (2)$$

We first applied the method described by Abraham and Ribeiro:[22] the temperature dependences of the chemical shifts were determined from conformational homogeneous reference molecules. Using the parameters of the *trans*-isomers as a reference, we assumed the same chemical shift variations for the two *cis*-conformers and the *trans*-isomer (respective equality of coefficients *b* and *c*). We obtained a non-linear variation of free enthalpy as a function of the temperature which is not in agreement with eqn (3).

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -RT\ln(K) \quad (3)$$

Studies described by Abraham and Ribeiro were carried out by ^{13}C NMR spectroscopy with only one value under the coalescence temperature, due to the long acquisition time. In our case, we had the possibility to register six or seven ^{19}F NMR spectra between the coalescence and the solvent crystallisation. We were also able to use the experimental low temperature δ_{ax} and δ_{eq} values in order to extrapolate the chemical shifts of each *cis*-conformer above the coalescence temperature. The coefficients *a*, *b* and *c* are listed in Table 1.

Calculated coefficients *b* are close but not similar for the two *cis*-conformers, and they are smaller than that for the *trans*-isomer. Moreover, second coefficient $c(T^2)$ values are negligible since they are less than 10^{-6} ppm K^{-2} and the margin of error is of the same order. We obtained from these values the equilibrium constants (given in the supporting information†) and the free energies as a linear function of the temperature (Fig. 1 and supporting information†). From these values, we deduced the associated ΔH° and ΔS° (Table 2). The validity of the method was verified in the case of *cis*-1,4-bis(trifluoromethyl)cyclohexane since $K = 1$ at all temperatures.

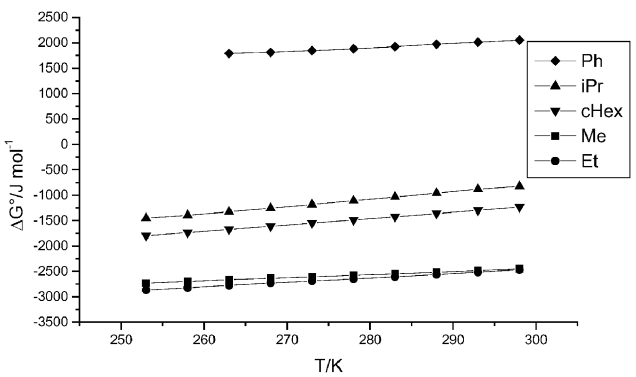
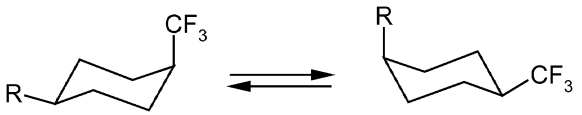


Fig. 1 Free energies at various temperatures of *cis*-4-substituted 1-trifluoromethylcyclohexanes.

Table 2 Enthalpies and entropies of *cis*-4-substituted 1-trifluoromethylcyclohexanes



R	ΔH°/kJ mol^{-1} (ΔH°/kcal mol^{-1})[a]	ΔS°/J mol^{-1} K^{-1} (ΔS°/cal mol^{-1} K^{-1})[b]	ΔG°_{298K}/kJ mol^{-1} (ΔG°_{298K}/kcal mol^{-1})
Me	−4.28 (−1.0)	−6.11 (−1.46)	−2.45 (−0.58)
Et	−5.08 (−1.21)	−8.74 (−2.09)	−2.47 (−0.59)
c-Hex	−4.98 (−1.19)	−12.56 (−3.00)	−1.23 (−0.30)
*i*Pr	−5.19 (−1.24)	−14.67 (−3.50)	−0.82 (−0.20)
Ph	−0.37 (−0.09)	−8.11 (−1.94)	2.05 (0.49)

[a] The average precision of ΔH° is 0.05 kJ mol^{-1}. [b] The average precision of ΔS° is 0.10 J mol^{-1} K^{-1}.

These variations appear logical taking the counterpoise substituent bulkinesses into account. The equatorial preference of the trifluoromethyl group is significantly larger than those of methyl and ethyl, slightly larger than those of cyclohexyl and isopropyl, and smaller than the phenyl one. The thermodynamic parameters of the counterpoise groups[23] are listed in Table 3. Parameters of the trifluoromethyl group are deduced from the additivity of thermodynamic values (Table 4). A very good agreement of the results is obtained, whatever the counterpoise group may be. The averaged values of enthalpy, entropy and free energy were found to be, respectively −2.78 kcal mol^{-1}, −1.38 cal mol^{-1} K^{-1} and −2.37 kcal mol^{-1}. These studies also allowed the determination of the thermodynamic parameters of phenyl and cyclohexyl groups that were not known (Table 3, bold letters).

The polarity of the solvent could influence the conformational preference of polar substituents.[25,26] We examined the influence of the nature of the solvent on the thermodynamic parameters of the trifluoromethyl group by studying the

Table 3 Thermodynamic parameters of the counterpoise groups

R	ΔH°/kJ mol^{-1} (ΔH°/kcal mol^{-1})[a]	ΔS°/J mol^{-1} K^{-1} (ΔS°/cal mol^{-1} K^{-1})[b]	ΔG°_{298K}/kJ mol^{-1} (A/kcal mol^{-1})
Me[24]	−7.32 (−1.75)	−0.03 ± 0.25	−7.28 (1.74)
Et[24]	−6.69 (−1.60)	0.64 ± 0.35	−7.49 (1.79)
c-Hex	**−6.66 (−1.59)**	**6.79 (1.62)**	**−8.63 (2.07)**
*i*Pr[24]	−6.36 (−1.52)	9.67 (2.31)	−9.25 (2.21)
Ph[3]	**−11.27 (−2.69)**	**2.34 (0.56)**	−12.00 (2.87)

[a] The average precision of ΔH° is 0.25 kJ mol^{-1}. [b] The average precision of ΔS° is 1.10 J mol^{-1} K^{-1}.

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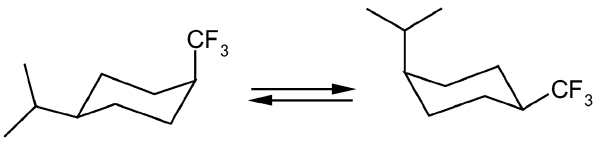
Table 4 Thermodynamic parameters of the conformational equilibria and *A* values for the trifluoromethyl group

Counterpoise used	ΔH°/kJ mol^{-1} (ΔH°/kcal mol^{-1})[a]	ΔS°/J mol^{-1} K^{-1} (ΔS°/cal mol^{-1} K^{-1})[b]	*A*/kcal mol^{-1}
Me	−11.60 (−2.77)	−6.24 (−1.49)	2.33
Et	−11.77 (−2.81)	−6.06 (−1.45)	2.38
*i*Pr	−11.55 (−2.76)	−5.00 (−1.19)	2.41
Ph	—	—	2.38
Averaged values	**−11.64 (−2.78)**	**−5.77 (−1.38)**	**2.37**

[a] The average precision of ΔH° is 0.25 kJ mol^{-1}. [b] The average precision of ΔS° is 1.50 J mol^{-1} K^{-1}.

Table 5 Solvent influences on the conformational equilibrium of *cis*-4-isopropyl-1-trifluoromethylcyclohexane

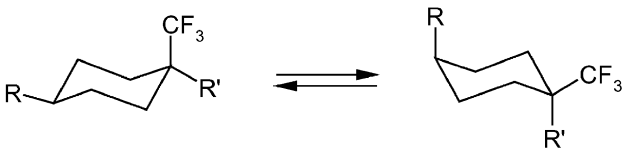


Solvent	ΔH°/kJ mol^{-1} (ΔH°/kcal mol^{-1})[a]	ΔS°/J mol^{-1} K^{-1} (ΔS°/cal mol^{-1} K^{-1})[b]	ΔG°_{298K}/kJ mol^{-1} (ΔG°_{298K}/kcal mol^{-1})
Toluene	−6.18 (−1.48)	−17.88 (−4.27)	−0.85 (−0.20)
THF	−5.19 (−1.24)	−14.67 (−3.50)	−0.82 (−0.20)
Methanol	−6.10 (−1.46)	−18.19 (−4.35)	−0.68 (−0.16)

[a] The average precision of ΔH° is 0.05 kJ mol^{-1}. [b] The average precision of ΔS° is 0.20 J mol^{-1} K^{-1}.

conformational equilibrium of *cis*-4-isopropyl-1-trifluoromethylcyclohexane in three deuterated solvents: methanol, tetrahydrofuran and toluene. In this case, the solvent influence on the *A* value appears to be small (Table 5). Indeed, the interactions between the trifluoromethyl group or the alkyl counterpoise group and the solvent are weak. The values obtained in THF can be generalised to other solvents.

Table 6 Conformational equilibria of 4-alkyl-1-trifluoromethylcyclohexanols



R	R′	ΔH°/kJ mol^{-1} (ΔH°/kcal mol^{-1})[a]	ΔS°/J mol^{-1} K^{-1} (ΔS°/cal mol^{-1} K^{-1})[b]	ΔG°_{298K}/kJ mol^{-1} (ΔG°_{298K}/kcal mol^{-1})
Me	H	−4.28 (−1.02)	−6.11 (−1.46)	−2.45 (−0.58)
Me	OH	−4.67 (−1.12)	−7.45 (−1.78)	−2.45 (−0.58)
*i*Pr	H	−5.19 (−1.24)	−14.67 (−3.50)	−0.82 (−0.20)
*i*Pr	OH	−5.78 (−1.38)	−15.94 (−3.81)	−1.10 (−0.26)

[a] The average precision of ΔH° is 0.20 kJ mol^{-1}. [b] The average precision of ΔS° is 0.07 J mol^{-1} K^{-1}.

We also studied the conformational equilibria of 4-methyl- and 4-isopropyl-1-trifluoromethylcyclohexanols. The isomer bearing trifluoromethyl and alkyl groups in *cis*-positions exhibited a conformational equilibrium, as in the case of trifluoromethylcyclohexanes. For the second isomer, the hydroxy group is blocked in the axial position. ΔG°, ΔH° and ΔS° were compared with those of the corresponding alkanes (Table 6). The steric bulkiness obtained due to the hydroxy group is almost zero. It is known however that the conformational energy of an hydroxy group is about 0.60–1.0 kcal mol^{-1} [26] and the additivity of the *A* value was observed by Kost *et al.* with trisubstituted 1,2,4-cyclohexanes.[27] So the presence of a quaternary carbon certainly induces a bond angle modification and the additivity of the conformational energies is no longer valid.

Conclusion

The size of the trifluoromethyl group has been determined by various methods[8,28–37] and it has been estimated in the past, as being as large as very different substituents such as methyl, isopropyl, trimethylsilyl or *tert*-butyl groups. The *A* value obtained by variable temperature ^{19}F NMR spectroscopy (*A* = 2.37) is slightly smaller than Della's data (*A* value = 2.4–2.5)[15,16] which is usually assumed. This early work was performed by dynamic ^{13}C NMR spectroscopy and we showed through comparison with Abraham and Ribeiro's work[22] that this method was not highly accurate. They only registered one value below the coalescence temperature and the variation of the chemical shifts had to be extrapolated from the variation of the *trans*-isomer. We have shown that this approximation was not reliable. Even the two *cis*-conformer chemical shifts were not defined by the same coefficients *a*, *b* and *c* in eqn (2): $\delta = a + bT + cT^2$. With advances in computing technology, we can now generate simulated spectra by WINDYN. Moreover ^{19}F NMR spectroscopy allows the generation of much more reliable data. The importance of the determination of the variation of chemical shifts as a function of temperature for each compound was shown. ^{19}F NMR studies with short relaxation times, good molar receptivity and very large splitting of the signals at variable temperature allow the generation of precise data. Hence, the thermodynamic parameters of the trifluoromethyl were deduced from a series of experiments with several counterpoise groups. The *A* value of the trifluoromethyl group is greater than that of the isopropyl group (2.37 *versus* 2.21), but smaller than that of the *tert*-butyl group (4.87). Finally, the method was also used to determine the thermodynamic parameters of cyclohexyl and phenyl groups. This is a good, accurate method to determine *A* values of certain substituents and steric interactions between groups on a molecular framework.[38] It has been extended to other fluorinated groups (see Part 2).[40]

Experimental

Variable temperature ^{19}F NMR spectra were recorded at 282.4 MHz on a Bruker AC-300 spectrometer. Chemical shifts are quoted relative to $CFCl_3$ used as an internal reference at room temperature, then the lock was not removed and all spectra

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were registered using the same absolute frequency. The registration of the $CFCl_3$ at low temperature was not done and the *cis*-disubstituted cyclohexane was used as an internal reference. The studies were performed in THF-d_8, toluene-d_8 or CD_3OD using diluted solutions ($\sim$0.1 mol L^{-1}). A 5.7 μs pulse width (90° pulse angle) was used, with a recycle delay of 1 s. The spectra were proton-decoupled and were obtained using 128 K of points. The spectral widths are 11.4 kHz (from −50 to −90 ppm for trifluoromethylcyclohexanes, and from −60 to −100 ppm for trifluoromethylcyclohexanols). The spectra were recorded every 5 K between 298 K and 168 K. Before each record a ten minute delay was applied in order to stabilise the temperature.[39] A calibration with methanol was made in the same conditions and allowed to estimate the temperature accuracy to 0.2 K.

The studied products have been previously described.[19]

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