Tetrahedron Vol. 33, pp 1745 to 1747 Pergamon Press 1977 Printed in Great Britain

RING INVERSION IN FLUORO-CYCLOHEXANES

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(*Received in the UK* 10 *December* 1976; *Accepted for publication* 3 *February* 1977)

Abstract—Rates of ring inversion in some isomeric octa- and deca-fluorocyclohexanes and in perfluorocyclohexane have been determined by dynamic ^{19}F NMR spectroscopy and compared with data for other compounds. $\Delta G^{\ddagger}_{cb}$ varies over the range 39–49 kJ mol^{-1}. Surprisingly the barriers in the diastereomeric octafluorocyclohexanes lie at opposite ends of the range. It seems that 1,3-diaxal interactions are less important than supposed hitherto; other factors which may affect the barriers are discussed.

Cyclohexane occupies a key position in conformational analysis and molecular stereodynamics. Following the first direct measurement of the rate of chair-chair interconversion in 1960,[1,2] a large number of cyclohexane derivatives have been investigated by dynamic NMR spectroscopy.[3-6] Apart from perfluorocyclohexane,[2,7,8] which was one of the first substituted cyclohexanes to be studied by dynamic NMR, there have been few studies of ring inversion in cyclohexanes containing more than one or two fluorine atoms. The available data indicate that the replacement of hydrogen by fluorine has little effect on the barrier to cyclohexane ring inversion. It is difficult to accept that fluorine introduces little perturbation into the bonding and non-bonding interactions of cyclohexane. Accordingly, it would seem that the similarity in the activation free energy for inversion in perfluorocyclohexane and cyclohexane may result from a coincidental calcellation of opposing effects in the former. It has been suggested that 1,3 diaxial interactions may destabilise the chair form of perfluorocyclohexane and compensate for higher vicinal CF_2–CF_2 interactions in the transition state for ring inversion.[2] On this basis it might be expected that in some partially fluorinated cyclohexanes the various interactions might not cancel and significant variations in the ring inversion barriers could result. We now present dynamic NMR data for some isomeric octa- and deca-fluorocyclohexanes.

EXPERIMENTAL

Dynamic ^{19}F NMR studies were performed on a Perkin–Elmer R-12B spectrometer operating at 56.45 MHz or on a Varian XL-100 instrument at 94.1 MHz. Samples were *ca.* 40% w/v in diethylether. Probe temperatures were measured with a copper-constantin thermocouple (digital readout) inserted into the sample at the level of the receiver coil. Exchange modified NMR bandshapes were analysed on the University ICL 1906A digital computer using the programme INMR[9] (for CFH signals) or SPECAB[10] (for CF_2 AB-systems). Vicinal coupling (often unresolved) was neglected since the signal separations were greater than the vicinal couplings by more than an order of magnitude.[11]

The fluorocyclohexanes have been previously prepared and characterised in this Department.[12,13] Samples for NMR analysis were purified by GLC on a 9 m column packed with dinonylphthalate on Celite (1:3).

RESULTS AND DISCUSSION

The fluoro-substituted cyclohexanes investigated have stereochemistry such that both chair forms are of equal energy (the stereochemistry is given in the Table). Thus at low temperature, two equally intense CFH signals were observed in the ^{19}F NMR spectrum corresponding to axial and equatorial fluorine in the slowly interconverting chair forms. Rate constants (k_{cc}) for chair-chair interconversion were determined by bandshape analysis near the coalescence temperature. The results are given in the Table together with literature data for other fluorocyclohexanes.

Rate constants determined by dynamic NMR are usually quite accurate when measured by line-shape analysis close to the coalescence temperature. Indeed, the major sources of error in derived free energies of activation often lie in temperature measurement and temperature gradients over the sample volume. The $\Delta G^{\ddagger}$ values determined in this investigation are considered to be accurate to ±0.5 kJ/mol (corresponding to a ±2° precision in temperature or a 20% error in rate). Systematic errors can lead to much larger uncertainties in enthalpies and entropies of activation even where careful bandshape analyses are performed.[18] Thus $\Delta G^{\ddagger}$ values determined near coalescence are more precise than $\Delta H^{\ddagger}$ data evaluated over a limited temperature range by at least an order of magnitude. However, the former data can include a temperature dependent entropy term which affects the comparison of results obtained at different coalescence temperatures. The most reliable estimates indicate that $\Delta S^{\ddagger}$ is close to zero for cyclohexane ring inversion and for many other intramolecular stereodynamic processes;[6] therefore the comparison of $\Delta G^{\ddagger}$ values is justified. Allowance should first be made for statistical entropy factors, hence the $\Delta G^{\ddagger}$ values given in the Table refer to the chair-boat process. Similarly, if it is assumed that the twist-chair conformation is the transition state for inversion and that changes in vibrational entropy are negligible, $\Delta H^{\ddagger}$ can be estimated from $\Delta G^{\ddagger}_{cb} + RT \ln \sigma$ (where σ is an integer allowing for rotational symmetry and possible differences in the entropy of mixing).[3]

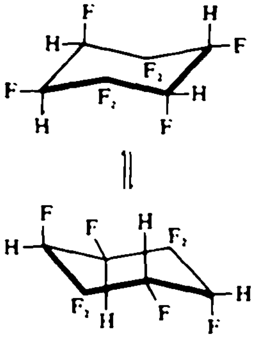
The $\Delta G^{\ddagger}_{cb}$ and $\Delta H^{\ddagger}_{cc}$ values for perfluorocyclohexane (Table 1) in diethyl ether solution are in very close agreement with previous measurements in other solvents. The barriers in the three isomeric decafluoro-compounds (**2**–**4**) are almost identical, and $\Delta H^{\ddagger}_{cc}$ is *ca.* 4 kJmol^{-1} lower than for perfluorocyclohexane but similar to cyclohexane. In contrast, the stereoisomeric octafluoro-compounds **5** and **6** have barriers that differ by 9 kJmol^{-1}. In view of this surprisingly large difference, rate constants for inversion were also determined from the collapse of the CF_2 AB-system (using a different spectrometer). The resulting $\Delta G^{\ddagger}_{cb}$ data are identical (within experimental error) with those derived from the

Table 1. Dynamic ^{19}F NMR data for ring inversion in fluoro-cyclohexanes

	Compound	Geometry[a]	Signals	T (°C)	k_{ce} (s^{-1})	$\Delta G^{\ddagger}_{ce}$[d] (kJ mol^{-1})	σ[g]	$\Delta H^{\ddagger}_{est}$[h] (kJ mol^{-1})	Ref[i]
1	C_6F_{12}		CF_2	-3	4160[b]	45.6	6	49.6	p.w.
				25	34600	45.5		49.9	2
				25		45.4		49.8	7
				-11		46.6		50.5	8
2	$C_6F_{10}H_2$	H1,H2	CFH	-20	999[c]	45.6	1	45.6	p.w.
3	$C_6F_{10}H_2$	H1 H3	CFH	-15	3142[c]	44.1	1	44.1	p.w.
4	$C_6F_{10}H_2$	H1,H4	CFH	-14	3081[c]	44.3	2	45.8	p.w.
5	$C_6F_8H_4$	H1,H2 H4,H5	CFH	+2	1566[c]	48.8	2	50.4	p.w.
			CF_2	-1	1596[b]	48.2		49.8	p.w.
6	$C_6F_8H_4$	H1,H4 H2,H5	CFH	-47	1412[c]	39.9	2	41.2	p.w.
			CF_2	-51	1020[b]	39.8		41.1	p.w.
7	$C_6F_4H_8$	F1,F2 F1,F2	CF_2	-29	11[illegible]	43.7	2	45.1	15
8	$C_6F_2H_{10}$	F1 F1	CF_2	-45	1660	40.0	2	41.8	16
				-46		39.3		41.1	15
9	C_6FH_{11}		CFH	-38	4000	39.5[e]	2	40.9	17
10	C_6H_{12}		CH_2	ca. -50		43.1[f]	6	46.4	6

[a] Substituents before the slash are on one side of the ring, those after are on the other; commas separate *cis*-substituents [see Refs. 13 and 14 for this stereochemical nomenclature]. [b] Spectra recorded at 94.1 MHz. [c] Spectra recorded at 56.45 MHz. [d] $\Delta G^{\ddagger}_{ce} = \Delta G^{\ddagger}_{cc} - RT \ln 2$. [e] Average of the ax.–eq. and eq.–ax. processes. [f] Average from several investigations. [g] Symmetry factor [see ref. 5]. [h] $\Delta G^{\ddagger}_{ce} + RT \ln \sigma$. [i] See reference list in main text; p.w. = present work.

coalescing CFH signals (Table). It is surprising that the inversion barriers in these two diastereomers are the highest and lowest respectively for all the compounds in Table 1. Furthermore these compounds have identical numbers of 1,3 diaxial FF and FH interactions (see Fig. 1), so contrary to literature suggestions, it would seem that these effects do not play a major role in determining the magnitude of the barrier to ring inversion.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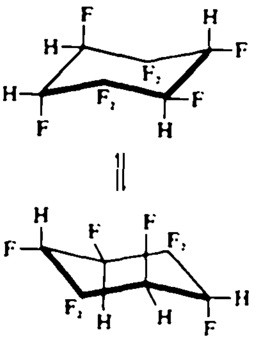
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Additionally, compounds **2** and **4** respectively have *cis*-1,2 and *trans*-1,4 hydrogen interactions similar to those in **5** and **6** respectively, yet the barriers for the former pair are virtually identical. One is therefore tempted to conclude that *cis*-1,2 HH or FF interactions are also not associated with the enhanced barrier in **5** relative to **6**. However, the inversion process need only involve part of the cyclohexane ring, i.e. two of the ring atoms remain staggered in the twist-chair conformation. Therefore compound **2** could attain the twist conformation without *cis* CHF–CHF eclipsing interactions, whereas compound **5** cannot readily avoid perturbing one of the two staggered *cis* CHF–CHF fragments. The low barrier in **6** might be associated with the *trans* CHF–CHF geometry which is absent in compounds **1**–**5**. Ring inversion in **6** involves a *trans-gauche* interconversion around the CHF–CHF linkage whereas in **5** the twisting process is *gauche-gauche*; possibly the former is more favourable. Some support for this suggestion can be derived from microwave studies on 1,2-difluoroethane which indicate that the *trans-gauche* and *gauche-gauche* torsional potentials are 8.4 and 19.2 kJ mol⁻¹ respectively.[19] Recent *ab initio* molecular orbital calculations are also indicate that the *trans-gauche* barrier in 1,2-difluoroethane is considerably lower than the *gauche-gauche* barrier (13.5 and 32.4 kJ mol⁻¹ respectively).[20]

The low reported inversion barriers in monofluoro and 1,1-difluoro-cyclohexane (relative to cyclohexane) might also suggest that twisting around CHF–CH_2 and CF_2–CH_2 linkages can be somewhat more facile than twisting about CH_2–CH_2 bonds. The available estimates[21] of the torsional potential in ethane and 1,1-difluoroethane (12.0 and 13.3 kJ mol⁻¹ respectively) would not appear to support this suggestion, though the comparison may not be appropriate. There is considerable evidence from *ab initio* molecular orbital calculations that polar substituents can greatly perturb the potential function for torsion around C–C single bonds.[22] The bonding and repulsive interactions are markedly dependent on the relative orientation of the *vicinal* substituents, and clearly these factors could affect the chair-chair interconversion barrier in fluoro-cyclohexanes. It is, of course, also possible that subtle changes of shape away from the ideal cyclohexane chair or twist-chair forms are occurring in the polyfluorocyclohexanes. Such changes are not easily deducable from the usual qualitative factors of the type discussed here; they need not be uniform between the various polyfluorocyclohexanes and could obviously lead to asymmetry within molecules **2**-**9**.

Acknowledgement—We thank the Science Research Council for a maintenance grant to J.C.H.

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