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NUCLEAR MAGNETIC RESONANCE CONFORMATION ANALYSIS OF *CIS* AND *TRANS* ISOMERS OF 1,2-DICHLORO-2,3,3-TRIFLUOROCYCLOBUTANE AND RELATED MOLECULES

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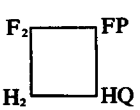
Abstract—The *cis* isomer of the title compound is found almost exclusively in the conformation with the 1-chlorine equatorial and the 2-chlorine axial whereas the *trans* isomer is a 3:2 mixture of the two allowed conformers in which both chlorines are either equatorial or axial.

A NMR study of cyclobutane in a liquid crystal and microwave and dipole moment studies of substituted cyclobutanes have shown that the cyclobutane ring is normally puckered by 20 to 30°.[1-3] This leads to pseudo axial (a) and pseudo equatorial (e) positions for each substituent. In analogy to cyclohexane, two stable conformations exist. The energy difference between the two forms is sufficiently low that interconversion is fast on the NMR time scale and chemical shifts and coupling constants are averaged over the relative populations of the two stable forms. The relative energies of the two stable forms is a function of the substituents. Lambert and Roberts used the dihedral angle dependence of hydrogen-fluorine coupling constants to show alkyl or monohalo substituted cyclobutanes prefer conformations in which the large substituent is locked in the equatorial position.[4] Similar results have been found by Hopkins in other substituted cyclobutanes.[5] Thus, a *trans* dialkyl cyclobutane should have both substituents equatorial and be found exclusively as one conformer whereas a *cis* dialkyl cyclobutane should have equal populations of the two possible conformations in which one substituent is axial and the other equatorial. Analysis of the spectrum of 1-chloro-2,3,3-trifluorocyclobutane (1) proved the 1-chlorine and 2-fluorine were *trans* and the conformer with both these substituents equatorial was greatly favored over the conformer with both substituents axial.[6] Thus, it appeared polar substituents also favored equatorial positions on the cyclobutane ring. Subsequently the spectrum of 1-chloro-2-iodo-2,3,3-trifluorocyclobutane (2) was analyzed to show both conformations were present in equal amounts in $CFCl_3$ solution.[7] It was assumed the material was the *cis* isomer because the *trans* isomer should have favored the conformation with both bulky substituents equatorial. The effect of the additional dipole moment of the iodine in 2 was expected to be insignificant compared to the three fluorines and chlorine already present in 1 and 2. The coupling constants in the NMR spectrum of 1,2-dibromo-2,3,3-trifluorocyclobutane (3) were similar to those found in 2 and the spectrum was first interpreted as indicating 3 was the *cis* dibromo isomer. However 3 was obtained from bromination of 2,3,3-trifluorocyclobutene and was expected to be the *trans* isomer since bromination of cyclobutene or perfluorocyclobutene goes *trans*.‡,[8,9]



1: P = H, Q = Cl
2: P = I, Q = Cl
3: P = Br, Q = Br
4: P = Cl, Q = Cl
5: P = Cl, Q = Br

The NMR spectra of the *cis* and *trans* isomers of 1,2-dichloro-2,3,3-trifluorocyclobutane (4) and 1-bromo-2-chloro-2,3,3-trifluorocyclobutane (5) have now been analyzed. From these data we show the *trans* isomers are approximately 3:2 mixtures of the two conformers whereas the *cis* isomers are found almost exclusively in the conformation with the 1-bromine or 1-chlorine equatorial. Unequivocal analysis of the

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‡Cullen and Singh prepared both *cis* and *trans* isomers of 1,2-dibromoperfluorocyclobutane by thermal codimerization of bromotrifluoroethylene.[8] Only one isomer, assumed *trans*, was obtained from bromination of perfluorocyclobutene.[8] Confirmation of this assignment is possible from chemical shift calculations based on the electric field influence of the fluorine and bromine chemical shifts following the procedure of Feeney *et al.*[10] The methine fluorine in the *cis* isomer is predicted to be 11·5 ppm upfield from the methine fluorine in the *trans* isomer. The observed difference is 16·4 ppm in the correct direction.

stereochemistry of the *cis* isomers was possible because these isomers existed in only one conformation; the fluorine chemical shifts and the coupling constants could be used to assign the stereochemistry. The similarity of the coupling constants of **2** and **3** to the *trans* isomers of **4** and **5** then indicates **2** and **3** were actually *trans*.

EXPERIMENTAL

Spectra were taken of **3** on a Varian HA-100 NMR spectrometer at the Univ. of Colo. The spectra of **4** and **5** were obtained on a Varian XL-100 NMR spectrometer at 3M. Nonlinearities in the recorder were corrected for by placing frequency markers approximately 1·0 Hz before and 1·0 Hz after each peak. The CFCl fluorine peaks were 3:1 doublets due to the ^{35}Cl:^{37}Cl isotope effect. The isotope shift is about 0·7 ppm with the ^{37}Cl peaks upfield.[11]

The iterative LAOCOON computer program was used to determine best values of the chemical shifts and coupling constants.[12] The root-mean-square deviation between the observed and calculated frequencies of at least 176 lines (out of a possible 192 lines) in each sample was less than 0·04 Hz. In several cases the line broadening from the ^{37}Cl isotope peaks rendered impossible the accurate determination of the frequencies of 16 of the 32 lines in the CFCl multiplet.

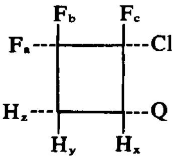
The syntheses of **4** and **5** will be reported by Park, Croft, and Gropelli.[13] Dr. R. O. Michael kindly prepared **3** for us by bromination of 2,3,3-trifluorocyclobutene following the procedure of Park *et al.*[14]

RESULTS AND DISCUSSION

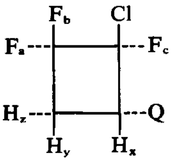
The chemical shifts and coupling constants are given in Table 1. Homonuclear and heteronuclear spin tickling experiments were performed in the standard manner on **4** to determine the signs of all the coupling constants relative to the known positive sign for the geminal J(FF).[15]

Fluorine homonuclear decoupling was performed on all the other samples to determine the signs of the J(HF) and J(FF) coupling constants that were not unambiguously determined by analogy to **4**. Spectra of all samples were obtained in $CFCl_3$. Spectra of **4** were also obtained in acetone-d_6, but the insignificant variation in the NMR parameters in this solvent (see Table 1) relative to $CFCl_3$ did not justify synthesis of additional pure sample for other solvent studies.

The chemical shifts are assigned as follows (*vide supra*):



a: *cis*



b: trans

4: Q = Cl
5: Q = Br

Whipple and Evanega have given the dependenc of the aa, ae, and ee vicinal J(HH) coupli constants in cyclobutanes on puckering angle usi the well known Karplus equation.[16] They show th the ee coupling is always small (under 3 Hz). F puckering angles under 30°, the J(ae) coupli should be greater than J(aa), but for angles abo 30°, J(aa) becomes larger than J(ae). Results compounds of known stereochemistry have show that vicinal J(HF) coupling constants follow t same general dihedral angle dependence as vicin J(HH) coupling constants.[4,17] Lambert and Rober found the vicinal J(HF) in 2,2 - dichloro - 1,1 difluoro - 3 - phenylcyclobutane (**6**) were 1·75, 8·5 12·59, and 20·52 Hz.[4] These couplings were a signed to ee, ea, ae, and aa positions of the fluori and proton, respectively, and show that, for J(HF the aa coupling is large and the ee coupling small cyclobutanes. Interconversion of the two confo mations of a conformationally mobile cyclobuta interchanges the axial and equatorial positions. T aa and ee couplings are thus averaged and all fo J(HF) in the CH_2–CF_2 fragment become near equal.

The spectrum of **4a** showed one large (18·49 H and one small (3·62 Hz) vicinal J(HF) indicati from the arguments above that only one conform is appreciably populated. We show this isomer *cis* by proving the 2-chlorine is axial and t 1-chlorine equatorial. If the 1-proton (H_x, s structure above) were equatorial, one of the vicin J(HH) in the –CH_2–CHCl– fragment would under 3 Hz.[16] Since the two vicinal J(HH) are ov 9 Hz, this proton must be axial and the 1-chlori equatorial. From the known dihedral angle depe dence of J(HF), J_{ay} is a diequatorial coupling and J is a diaxial coupling. Thus F_b is axial and equatorial. The chemical shift difference betwe the fluorines is determined principally by t electric field of the fluorine and chlorine in t CFCl group. This effect is quantitatively calculat using the electric field theory of Feeney *et al.*[10] F a cyclobutane puckered by 22°, the fluorine *cis* F_c should be about 11 ppm upfield from the fluori *trans* to F_c. The observed chemical shift differen is 17·7 ppm. Thus the upfield axial fluorine, F_b, *trans* to the vicinal 2-chlorine. This chlorine mu then be axial and the two chlorines are therefo *cis*. This result is in agreement with the chemic data reported by Park *et al.*[13]

Although over 50 percent larger than predicte the good agreement between calculated and o served chemical shift differences in a variety perhalogenated groups of this type makes extremely improbable the assignment of the C fluorines should be reversed. Furthermore, t difference between the observed and calculat shift is approximately equal to the downfield shi 7·7 ppm, observed for the equatorial fluori relative to the axial fluorine in 2,2 - dichloro - 1,1

Table 1. Chemical shifts[a] and coupling constants[b] of 1,2 - dihalo - 2,3,3 - trifluoro - cyclobutanes, $CF_aF_b–CF_cP–CH_xQ–CH_yH_z$. See structures **4** and **5** in text for stereochemical assignments.

	cis Isomers			*trans* Isomers				
	4a[c]	**4a**[d]	**5a**[c]	**2**[c]	**3**[c]	**4b**[c]	**4b**[d]	**5b**[c]
P	Cl	Cl	Cl	I	Br	Cl	Cl	Cl
Q	Cl	Cl	Br	Cl	Br	Cl	Cl	Cl
δF_a	99·85	99·13	98·17	108·53	107·29	108·85	108·43	107·47
δF_b	117·54	116·76	118·62	87·95	97·30	104·63	104·16	105·03
δF_c	113·22	112·90	111·45	129·72	121·02	130·73	129·42	123·95
δH_x	4·52	4·97	4·49	4·57	4·48	4·35	4·81	4·33
δH_y	3·06	3·35	3·03	3·09	3·25	3·16	3·47	3·22
δH_z	2·55	2·68	2·57	2·77	2·84	2·74	2·90	2·83
J(FF)								
J_{ab}	200·35	198·68	198·65	197·62	198·48	202·16	200·44	200·66
J_{ac}	4·23	3·94	4·31	−8·92	−10·09	−9·06	−9·00	−9·90
J_{bc}	−7·38	−7·71	−6·96	−5·56	−0·40	1·65	1·48	0·76
vicinal	J(HF)							
J_{ay}	3·62	4·36	3·18	10·23	9·78	8·40	9·35	7·97
J_{az}	9·93	10·72	9·12	13·23	12·67	12·79	13·68	12·05
J_{by}	13·44	13·93	13·37	8·45	9·66	10·59	11·09	10·73
J_{bz}	18·49	18·45	18·55	11·71	12·00	13·81	13·87	13·96
J_{cx}	13·27	13·73	13·55	6·85	7·73	7·00	7·44	8·53
cross	ring	J(HF)						
J_{ax}	1·02	1·05	0·75	1·13	0·65	0·83	0·81	0·54
J_{bx}	4·61	4·70	4·40	5·56	5·67	5·49	5·63	5·31
J_{cy}	7·94	8·24	7·63	−2·53	−2·40	−2·28	−2·45	−2·26
J_{cz}	−2·70	−2·74	−2·65	5·92	5·25	5·71	6·11	4·87
J(HH)								
J_{xy}	9·42	9·53	9·52	8·39	8·98	8·91	9·09	9·17
J_{xz}	9·53	9·38	10·03	6·09	6·73	7·19	7·11	7·61
J_{yz}	−14·12	−14·45	−13·99	−14·38	−14·55	−14·47	−14·92	−14·47
p_e[e]	0·78	0·77	0·79	0·52	0·54	0·60	0·59	0·61
ΔG[f]	0·76	0·72	0·79	0·05	0·10	0·31	0·22	0·27

[a] Fluorine chemical shifts are in ppm upfield from $CFCl_3$ and proton chemical shifts are in ppm downfield from tetramethylsilane.

[b] In Hz.

[c] $CFCl_3$ solvent.

[d] Acetone-d_6 solvent.

[e] Fractional populations of conformer with 3-chlorine equatorial.

[f] Free energy difference between conformations, in kcal/mole.

difluoro - 3 - methyl - 3 - phenylcyclobutane;[18] the fluorine chemical shifts should be within 2 ppm of each other based on the electric field theory. Ernst has attributed the intrinsic downfield shift of equatorial fluorines to the anisotropy of the puckered ring system.[19]

Since the fluorine assignment based on the chemical shift argument above is critical, confirmation of this assignment is desirable from the FF coupling constants. Ernst found the *cis* coupling (approximately 20° dihedral angle) ranges between −6·3 and −9·2 Hz in five 1,1,2 - trifluoro - 2 - chlorocyclobutanes containing methyl, nitrile, vinyl, or phenyl substituents at the 3 position, whereas the *trans* coupling varies from −1·3 to +7·3 Hz.[19] Thus, the −7·38 Hz coupling constant between F_a and F_c must be the *cis* coupling, in agreement with the chemical shift argument outlined above; J_{bc}, +4·23 Hz, is consistent for the *trans* coupling (140° dihedral angle).

Absence of a small vicinal J(HF) in the CH_2CF_2 fragment of **4b** indicates both possible conformers are present in significant amounts. However, both vicinal J(HH) are large (7·19 and 8·91 Hz), indicating the conformer with the chlorine equatorial is the major component. The smaller vicinal J(HF), J_{ay}, is attributed to nuclei which are equatorial in the major component. The upfield methylene fluorine, F_a, shows a −9·06 Hz coupling to F_c. As in **4a**, this fluorine must be *cis* to F_c. In contrast to **4a**, the upfield fluorine is equatorial. Thus, both chlorines are equatorial in the predominant *trans* conformer. The possibility that the *trans* isomer exists as an nonequilibrating planar isomer is excluded by the large values of J_{xy} and J_{xz}. One of these vicinal J(HH) would be under 4 Hz in a planar conformation.[16]

In conformationally mobile systems the observed coupling constants are weighted averages of the couplings in the conformers. For the vicinal J(HF) discussed above,

$$J_{ay} = p_e J_{ee} + p_a J_{aa}; \quad J_{bz} = p_a J_{ee} + p_e J_{aa}$$

where p_e and p_a are the relative populations of the conformers with the 1-chlorine equatorial and axial, respectively $(p_e + p_a) = 1$. From the temperature dependence of the fluorine chemical shifts Lambert and Roberts showed **6** is an 86:14 mixture of the phenyl equatorial:axial isomers at 31°C.[3] Since $J_{ay} = 1{\cdot}75$ and $J_{bx} = 20{\cdot}52$ Hz in **6**,[4] values of J_{ee} and J_{aa} can be calculated from the above pair of simultaneous equations: $J_{ee} = -1{\cdot}90$; $J_{aa} = 24{\cdot}17$ Hz. Relative populations of the two conformers and their free energy differences, $\Delta G° = RT \ln p_e/p_a$, could then be calculated for **2–5** (Table 1). These calculations are no more than semi-quantitative because the large substituents could change the dihedral angle of the two possible conformations from those in the reference and the calculated values of J_{ee} and J_{aa} given above are clearly approximate. However, all the cyclobutanes discussed contain the same basic $-CH_2-CF_2-$ fragment so that electronegativity and bond angle effects on J(HF) should be insignificant.

The coupling constants in the two isomers of **5** are very similar to those in **4**. The 2-bromine has negligible effect on the conformational equilibrium compared to the 2-chlorine substituent.

The coupling constants of **2** and **3** are similar to those found in **4b** and **5b**. Calculation shows these cyclobutanes are roughly 50:50 mixtures of two conformers. The similarity of J_{cx}(6·85 and 7·73 Hz, respectively, in **2** and **3**) to the values observed in **4b** and **5b** (7·00 and 8·53 Hz) indicates **2** and **3** are also *trans* isomers. In the *cis* isomers J_{cx}, an ae coupling, is 13·5 Hz. This coupling in the *trans* isomers is an average of aa and ee vicinal coupling constants.

The decrease in the chemical shift of F_b in **2** and **3** compared to **4b** or **5b** is attributable to the effect of the larger polarizability and ionization potential of the *cis* halogen. Assuming a planar cyclobutane to represent the time average of the two conformations, electric field theory calculations analogous to those performed above for **4** predict downfield shifts of 4·2 ppm in **3** and 10·0 ppm in **2** for the *cis* fluorine, compared to **4b**, but downfield shifts of only 0·8 and 1·8 ppm, respectively, for the fluorine *trans* to the iodine.

CONCLUSIONS

The NMR results show the *cis* isomers, **4a** and **5a**, prefer the conformation in which the chlorine or bromine in the CHX is always equatorial and the CFCl chlorine is axial. The *trans* isomers are rapidly interconverting between about equally populated conformations with diequatorial ar diaxial halogens. These results are contrary those expected for bulky halogen substituen which were expected, based on **1**, to prefer t equatorial conformation. However, it is known th *trans* 1,2 - dibromocyclohexane and 1 - chloro - 2 iodocyclohexane prefer the diaxial to the di quatorial conformation in order to minimize t dipole moment of the molecule.[20] The results for and **5** indicate interactions between the dipo moments of the five electronegative substituen are the prime factor in determining the relati stabilities of the conformers in each isomer. T effect of solvent polarity on the equilibrium do not appear significant.

The NMR results in this paper and chemic results of Park, Croft and Gropelli[13] prove t stereochemistry of **2** was incorrectly assigned Park *et al.*[7] The ICl addition to 2,3,3 - trifluorocy lobutene goes *trans*, not *cis*.

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