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CONFORMATIONAL ANALYSIS OF ASYMMETRIC ETHANES

EXTRACTION OF ACYCLIC CONFORMATIONAL LIGAND CONSTANTS FROM TIME-AVERAGED GEMINAL FLUORINE ANISOCHRONISM

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Abstract—The syntheses and ambient-temperature ^{19}F NMR data are reported for 27 asymmetric ethanes of the general formula RCF_2CXYZ, including a complete series of 10 compounds with R = Cl and all combinations of the 5 ligands H, F, Cl, Br and Ph. Within the theoretical framework of a previously proposed heuristic mathematical model the geminal ^{19}F chemical shift differences are fitted to chirality functions $\chi = \rho_R(\lambda_X - \lambda_Y)(\lambda_Y - \lambda_Z)(\lambda_Z - \lambda_X)$ to yield acyclic conformational ligand constants λ and substituent parameters ρ. It is demonstrated that the λ constants already reported for an analogous series of 10 compounds with R = Br are transferable to the Cl series with $\rho_{Cl} = 0.63 \pm 0.07$. Crude first approximations are also reported for the normalised (according to $\rho_{Br} = 1$) ligand constants $\hat{\lambda}_{CH_3}$, $\hat{\lambda}_{OH}$, $\hat{\lambda}_{OCH_3}$ and $\hat{\lambda}_I$ and for the substituent parameter ρ_H. It is argued that the $\hat{\lambda}$ values thus extracted play a role in the conformational analysis of asymmetric ethanes that is conceptually analogous to the conformational free energies in monosubstituted cyclohexanes.

The solution-phase equilibria involving the three nonequivalent conformers about the C^{α}–C^{β} bond of amino acid derivatives $RCH_2CHNHR'COR''$ and their subtle interplay amongst each other and with the backbone in peptides are to a large degree responsible for the details of protein folding and for the conformational changes associated with enzymatic activity. Our present tentative knowledge of these factors stems almost exclusively from the combined evaluation of the three types of vicinal nuclear coupling constants $^3J_{HH}$, $^3J_{HC}$ and $^3J_{HN}$ and has been competently reviewed by Bystrov[1] (for some leading papers to more recent work, Refs. 2–7). This problem, which in Bystrov's well-reasoned judgement represents one of the most pressing ones of contemporary bio-organic chemistry, is part of the larger physical-organic problem of the conformational analysis of asymmetric ethanes.

There are three reasons why the conformational analysis of asymmetric ethanes is vastly less developed than that of 1,2-disubstituted ethanes or of carbocyclic and heterocyclic compounds. The first resides in the dearth of experimental methods. Most standard spectroscopic and physical-organic techniques of conformational analysis must capitulate to the complexity of the problem, with NMR remaining the virtually sole survivor. The second consists in the fact that unassailable quantitative conformational information, against which the indirect evidence extracted from the study of time-averaged vicinal coupling constants could be checked, is largely missing. This lack is, to our knowledge, complete for amino acid derivatives and, with the exception of our own work,[8] almost so for asymmetric ethanes in general. Finally, there is a conceptual problem, which appears to have gone largely unrecognised and which is connected with the circumstance that the conformational energetics in asymmetric ethanes of the type RCG_2CXYZ always depends, for constant geminal groups G, on the three variable ligands X, Y and Z and the substituent R *simultaneously*. What one would really like to have is some quantity characteristic of just one of these ligands, suitably averaged over a series of different compounds to which this ligand is common, with the hope that such a number might play a role in the conformational analysis of asymmetric ethanes that would be conceptually analogous to the familiar "A values" or "conformational energies" pertinent to cyclic compounds.

When we contemplated these questions some 10 years ago it occurred to us that the chances of establishing a solid foundation in this area depended critically on the correct choice of a sensor nucleus for the geminal groups G, and for a variety of reasons[8,9] it became clear that this could not be hydrogen but had to be fluorine. In 14 representatives of the structural type RCF_2CXYZ we indeed succeeded[8] in arresting the internal rotation on the NMR time scale by recording the ^{19}F NMR spectra at temperatures as low as $-160°$. Out of the 42 possible conformers the spectra of 40 could not only be detected, analysed, integrated and assigned, but we also managed to assign all 80 fluorine nuclei individually, with some residual doubt remaining in only two or three cases. With this information it was possible to calculate the absolute sign of the geminal fluorine anisochronism at ambient temperature, and that in turn permitted the extraction of acyclic conformational ligand constants on the basis of a heuristic mathematical model.[9]

Our original sample included a complete series of 10 compounds with R = Br and all possible combinations of the 5 ligands H, F, Cl, Br and Ph. The heuristic mathematical model predicts that the ligand constants extracted from that series should be transferable, within a scaling factor, to other series with a different R. Before venturing into the amino acid field it was therefore considered desirable to test this point explicitly by synthesising a complete set of 10 compounds containing the same ligands but with R = Cl, and also to enlarge the collection of ligand constants by investigating a few additional, easily accessible compounds containing new ligands. The results of this study are reported in the present paper.

Syntheses

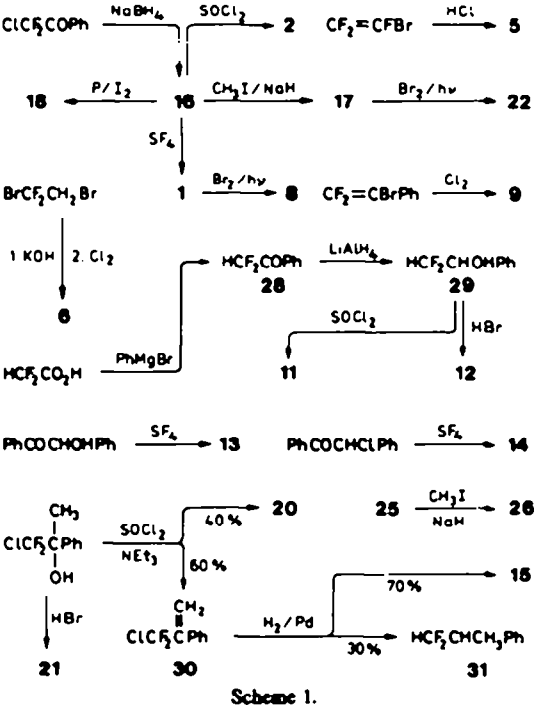
The asymmetric ethanes investigated in this work are enumerated in Table 1. They include the four compounds

Table 1. Compound key for the asymmetric ethanes RCF_2CXYZ

Compound	R	X	Y	Z	Compound	R	X	Y	Z
1	Cl	H	Ph	F	14	Ph	H	Ph	Cl
2	Cl	H	Ph	Cl	15	Cl	H	CH_3	Ph
3	Cl	H	Ph	Br	16	Cl	H	Ph	OH
4	Cl	H	F	Cl	17	Cl	H	Ph	OCH_3
5	Cl	H	F	Br	18	Cl	H	Ph	I
6	Cl	H	Cl	Br	19	Cl	H	F	I
7	Cl	Ph	F	Cl	20	Cl	CH_3	Ph	Cl
8	Cl	Ph	F	Br	21	Cl	CH_3	Ph	Br
9	Cl	Ph	Cl	Br	22	Cl	Ph	OCH_3	Br
10	Cl	F	Cl	Br	23	Cl	CF_3	F	Cl
					24	Cl	F	Cl	I
11	H	H	Ph	Cl	25	Br	H	Ph	OH
12	H	H	Ph	Br	26	Br	H	Ph	OCH_3
13	Ph	H	Ph	F	27	Br	CF_3	F	Br

2, 3, 7 and 19 for which NMR data have already been reported.[8] Together with the ten compounds[8] homologous to 1–10 but with R = Br this makes up a list of 37 asymmetric RCF_2CXYZ ethanes all told.

The reaction sequences used for preparing the compounds not previously described in the literature are summarised in Scheme 1. Also included are two known compounds synthesised by novel routes. The remaining compounds of Table 1 not listed in Scheme 1 could either be purchased or were made according to literature procedures.



Scheme 1.

In two cases mixtures of products were obtained, which could be quantitatively separated by preparative glc; the percentages cited in Scheme 1 refer to relative yields. We also mention that the starting material for the preparation of 9, α-bromo-β,β-difluorostyrene, previously obtained[9] in poor yield by hydrogen chloride elimination from 3, could be prepared in good yield by hydrogen bromide elimination from 1,2-dibromo-1,1-difluoro-2-phenylethane.[10] All the other details of the syntheses are not of sufficient interest in the context of the present paper to be discussed here explicitly and are relegated to the Experimental. The same applies to the structure proofs, which in all cases followed unambiguously from the elemental analyses, the mass and IR spectra and the ^1H and ^{19}F NMR data.

RESULTS AND DISCUSSION

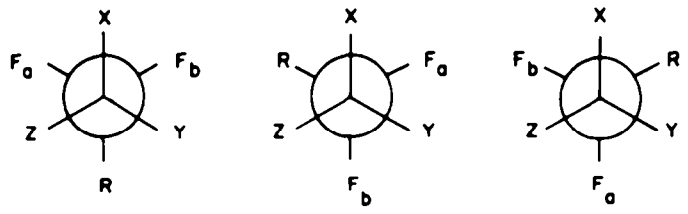
When talking about the sign of the time-averaged geminal fluorine chemical shift difference (anisochronism) we shall adhere to the convention depicted in the following drawing, where the clockwise arrangement of the ligands X, Y and Z at the asymmetric carbon follows the decreasing order of priority in the Cahn–Ingold–Prelog sequence. The anisochronism $\langle\Delta\rangle$ is then defined as the population-weighted average

$$\langle\Delta\rangle = \sum_r^{\infty} p_r(\delta_r^a - \delta_r^b)$$

and is to be fitted in the least-squares sense to the corresponding chirality functions[9]

$$\chi = \rho_R(\lambda_X - \lambda_Y)(\lambda_Y - \lambda_Z)(\lambda_Z - \lambda_X)$$

involving the dimensionless substituent parameter ρ, normalized to $\rho_{R_r} = 1$, and the acyclic conformational



ligand constants λ, referred to the origin $\lambda_H = 0$. The latter thus have the formal "dimension" of the cubic root of a chemical shift, but are of course really also dimensionless quantities if the chemical shifts are expressed in ppm.

Unless noted otherwise, the ^{19}F NMR data refer to 0.4 M solutions in $CFCl_3$ and have been extracted from the spectra by standard computer analysis. The λ constants for the bromine series, reported[9] for vinyl chloride solutions, have been recalculated for the $CFCl_3$ solutions. Our previously used[9] computer program was augmented by a statistics package, developed for another purpose,[11] and we can therefore now also specify the standard deviations for the bromine-series λ constants.

The ambient-temperature ^{19}F NMR data for **1–10** are collected in Table 2, from which the absolute magnitudes of the geminal chemical shift differences of Table 3 can be calculated. The signs of $\langle\Delta\rangle$ for **2**, **3** and **7** are known from the previous low-temperature work.[8] Obviously, no sign information is required for **9**. On the basis of the extensive qualitative and semiquantitative information about chemical shift trends gathered and discussed earlier[9] the correct signs can be deduced for **4**, **5** and **6** beyond doubt. Arguments of that type also strongly suggest the listed signs for **1**, **8** and **10**, but are not altogether conclusive in these cases owing to the relatively small magnitudes of the numbers. We have therefore performed separate least-squares calculations with all possible sign combinations for **1**, **8** and **10** and have found that only the combination (− − +) gives rise to an acceptable fit to the chirality functions and to standard deviations in the ligand constants comparable to those extracted from the bromine series, where direct sign information was available for all 10 compounds.[8]

The unscaled ligand constants extracted from both series are given in Table 4, together with their standard deviations, and the theoretical values of the chirality functions back-calculated from the ligand constants are listed in columns 3 and 6 of Table 3.

We are now in a position to test the prediction[9] of the heuristic mathematical model concerning the transferability of the ligand parameters from one series to another. From the theory[9] it follows that

$$\chi_i^{Cl} = \rho_{Cl}\chi_i^{Br}/\rho_{Br}$$

and with the normalisation definition $\rho_{Br} = 1$ we simply have

$$\chi_i^{Cl} = \rho_{Cl}\chi_i^{Br}$$

Table 2. Ambient-temperature ^{19}F NMR data for **1–10**

	Chemical shifts (ppm)[a,b,c]			Coupling constants (Hz)[a,d]					
Compound	$\langle\delta_A\rangle$	$\langle\delta_B\rangle$	$\langle\delta_M\rangle$	$\lvert\langle J_{AB}\rangle\rvert$	$\lvert\langle J_{AM}\rangle\rvert$	$\lvert\langle J_{BM}\rangle\rvert$	$\lvert\langle J_{AQ}\rangle\rvert$	$\langle J_{BQ}\rangle$	$\langle J_{MQ}\rangle$
1	-65.407	-66.573	-167.338	169.2	16.9	16.6	7.1	7.2	44.0
2	-58.165	-61.316		163.1			7.4	10.3	
3	-53.357	-59.725		161.7			6.0	14.1	
4	-67.292	-69.888	-148.197	170.9	15.0	15.1	3.7	4.6	48.0
5	-65.195	-68.209	-151.488	170.0	18.9	18.1	4.2	6.5	47.2
6	-60.152	-61.992		160.8			5.7	6.5	
7	-66.177	-66.757	-120.887	168.9	10.0	10.2			
8	-63.049	-63.864	-122.001	167.3	13.0	12.0			
9	-58.914	-58.914							
10	-65.815	-66.675	- 71.094	163.5	11.9	11.2			

[a] A and B refer to the downfield and upfield geminal fluorine chemical shifts, respectively, M to the fluorine and Q to the hydrogen atom at the asymmetric carbon.

[b] Chemical shifts are relative to internal $CFCl_3$.

[c] Standard deviations are <4 units in the last digit listed.

[d] Standard deviations are <2 units in the last digit listed.

Table 3. Time-averaged geminal fluorine anisochronism and theoretical chirality function values for the complete chlorine and bromine series

Compound	$\langle\Delta\rangle_{obsd}$	$\langle\Delta\rangle_{calcd}$	Compound[a]	$\langle\Delta\rangle_{obsd}$	$\langle\Delta\rangle_{calcd}$
1	-1.166	-0.551	1'	-1.883	-1.087
2	3.151	3.082	2'	4.872	4.649
3	6.368	4.844	3'	9.762	7.783
4	2.596	2.872	4'	3.878	4.075
5	3.014	4.112	5'	4.388	5.919
6	1.840	2.251	6'	3.311	3.866
7	0.580	-0.761	7'	0.0	-1.661
8	-0.815	-1.283	8'	-2.037	-2.951
9	0.0	0.489	9'	0.0	0.732
10	0.860	0.274	10'	1.674	0.716

[a] The primed compound labels refer to the series with R = Br and the same ligands as for the unprimed labels; see ref. 8.

Table 4. Unscaled acyclic conformational ligand constants extracted from the data of Table 3

R	λ_H	λ_P	λ_{Ph}	λ_{Cl}	λ_{Br}
Br	0	-0.80	-1.63	-2.69	-3.15
		±0.19	±0.47	±0.17	±0.12
Cl	0	-0.82	-1.33	-2.32	-2.68
		±0.26	±0.49	±0.16	±0.13

for all compound indices i; in other words, the ratios χ_i^{Cl}/χ_i^{Br} should be constant and equal to the substituent parameter ρ for chlorine. There are two ways to check this hypothesis. One could use the experimental anisochronism values (columns 2 and 5 of Table 3) directly or form the ratios from the back-calculated chirality function values (columns 3 and 6 of Table 3). The second method is clearly preferable, not only because the experimental information occurs in these quantities already in properly averaged form, but also because pathological situations (i.e. division by zero as would be required for the experimental pairs **7**/**7'** and **9**/**9'**) are much less likely to arise. Still, some care is necessary in such calculations and it will not do to perform them thoughtlessly. This caveat follows from an error analysis of a quotient $q = a/b$. Standard techniques of error propagation lead to

$$\sigma_q^2 = (\sigma_a/b)^2 + (a\sigma_b/b^2)^2$$

from which one obtains for the relative errors

$$(\sigma_a/q)^2 = (\sigma_a/a)^2 + (\sigma_b/b)^2.$$

The error in the quotient will therefore blow up if either the numerator or the denominator become very small. For that reason it makes no sense to include compound **10** in the test. Restricting the calculations to **1**–**9** one obtains an average ratio of 0.59 with a maximum scatter of +0.11 and −0.17, thus indeed confirming the postulated constancy within the precision of the model. As suggested by the above error considerations, a better method for actually calculating ρ_{Cl} is to average all individual ratios with the weighting factors

$$w_i = \frac{[(\chi_i^{Br})^{-2} + (\chi_i^{Cl})^2/(\chi_i^{Br})^4]^{-1}}{\sum_j [(\chi_j^{Br})^{-2} + (\chi_j^{Cl})^2/(\chi_j^{Br})^4]^{-1}}$$

which leads to $\rho_{Cl} = 0.63 \pm 0.07$, and it is this value which will be used for the subsequent calculations. It is now possible to convert the unscaled ligand parameters directly extracted from the chlorine series (Table 4, bottom row) to normalized (i.e. according to the convention $\rho_{Br} = 1$) values by means of the relationships[9]

$$\hat{\lambda}_L = \lambda_L^{Br} = (\rho_{Cl})^{-1/3}\lambda_L^{Cl}$$

where

$$(\rho_{Cl})^{-1/3} = 1.17 \pm 0.04$$

and thereby effect a further averaging of the normalised ligand constants $\hat{\lambda}$ over more than one series.

With this point established for the two complete series **1**–**10** and **1'**–**10'** we can now proceed to the determination of $\hat{\lambda}$ constants for new ligands and of ρ parameters for new substituents. Naturally, it would be desirable to do this by investigating complete series of asymmetric ethanes with an enlarged set of ligands, since this would not only furnish further ligand parameters but would also place the already determined ones on a firmer basis, but the labor in such an enterprise increases as $n!/(3!(n-3)!)$, where n is the number of ligands. As a sensible first approach we therefore decided to be satisfied with approximate non-least-squares determinations. Such a policy demands that only *one* new ligand be introduced at a time for compounds with R = Cl or R = Br, and that the old ligand set be used for compounds with a different R. It will be noticed that the molecules listed in Table 1 were all designed with this point in mind. By the same token, the compounds **29** and **31** of Scheme 1, although being asymmetric fluoroethanes also, were not included in the present study.

The ^{19}F NMR data for **11**–**27** are collected in Tables 5–7. There is no experimental sign information for the time-averaged geminal fluorine anisochronism in these cases, except for **19**,[8] and we will therefore have to rely on internal consistency arguments in the calculations. Luckily, no sign information is needed for **11**, **12**, **15**, **20**, **21** and **22**.

No ambiguity exists for the methyl ligand occurring in **15**, **20** and **21**. The vanishing anisochronism in all three instances rigorously demands $\hat{\lambda}_{CH_3} = \hat{\lambda}_{Ph}$, although this accidental degeneracy would no doubt be lifted on suitable enlargement of the compound set. For the three molecules **18**, **19** and **24** containing iodine the sign of the anisochronism is known[8] for **19** and can be deduced unequivocally[8] for **18** to be positive. A formal least-squares fit to the sign combinations (+ + +) and (+ + −) yielded λ_I values of -3.61 ± 0.30 and $-3.20 + 0.64$, respectively, of which the former must obviously be the correct one. Similarly, only the sign combinations (+ 0 +) for (**17**, **22**, **26**) and (+ +) for (**16**, **25**) led to consistent results for $\hat{\lambda}_{OCH_3}$ and $\hat{\lambda}_{OH}$. From **11** and **12** one obtains $\rho_H = 0$. A very small value of ρ_H is indeed expected theoretically,[9] but its exact equality to zero is undoubtedly again a consequence of the limited compound set.

On the other hand, an analogous approach to the two pairs (**13**, **14**) and (**23**, **27**) did not permit the resolution of the ambiguities. For instance, three of the four possible sign combinations for (**23**, **27**) led to widely differing $\hat{\lambda}_{CF_3}$ values, but with comparable formal "errors". We must therefore refrain from citing numbers for $\hat{\lambda}_{CF_3}$ and ρ_{Ph}. Clearly, in these cases one has to await the results from a larger collection of compounds to fix the parameters even approximately.

The essential results of the present paper are now presented in Table 8, where the normalised acyclic conformational ligand constants are juxtaposed to the corresponding conformational free energies (in kcal mol^{-1}) in the cyclohexane system.[12] To the extent that the intrinsic contribution to the geminal anisochronism may be neglected,[8] the heuristic model demands[9] that the differences in the $\hat{\lambda}$ constants be *proportional* to the energy differences between the conformers, and since the ligand parameters are referred to $\hat{\lambda}_H = 0$, they themselves represent quantities characteristic of hypothetical *binary* equilibria in which each ligand is individually balanced against hydrogen; in other words, the heuristic model provides the desired theoretical framework for condensing the disparate conformational information contained in a large collection of individual compounds into a few numbers which play, in an averaged fashion and within a scaling factor, a role in the conformational

Table 5. Ambient-temperature ^{19}F chemical shifts (ppm) for **11**–**27**[a–c]

Compound	$\langle\delta_A\rangle$	$\langle\delta_B\rangle$	$\langle\delta_M\rangle$	Compound	$\langle\delta_A\rangle$	$\langle\delta_B\rangle$
11	-121.172	-121.172		20	-61.347	-61.347
12	-117.966	-117.966		21	-57.508	-57.508
13	-105.722	-109.494	-121.186	22	-61.232	-61.232
14	-100.170	-102.560		23	-64.735	-65.734
15	- 56.280	- 56.280		24	-62.301	-65.190
16	(2.122)[d]			25	(3.540)[d]	
17	- 61.447	- 63.552		26	-54.920	-58.236
18	- 46.169	- 55.191		27	-57.105	-59.026
19	- 62.813	- 65.288	-158.387			

[a–c] See Table 2.

[d] The individual ^{19}F chemical shifts are strongly concentration dependent. Only the absolute chemical shift differences extrapolated to infinite dilution from measurements at 6 different concentrations are listed.

Table 6. Ambient-temperature ^{19}F coupling constants (Hz) for some of the compounds 11–27[a,c]

Compound	$\lvert\langle J_{AB}\rangle\rvert$	$\lvert\langle J_{AM}\rangle\rvert$	$\lvert\langle J_{BM}\rangle\rvert$	$\lvert\langle J_{AQ}\rangle\rvert$	$\lvert\langle J_{BQ}\rangle\rvert$	$\lvert\langle J_{AP}\rangle\rvert$	$\lvert\langle J_{BP}\rangle\rvert$	$\lvert\langle J_{MQ}\rangle$
11				10.6	10.6	55.1	55.1	
12				11.1	11.1	55.1	55.1	
13	256.9	13.4	13.4	8.4	8.0			44.5
14	242.2			10.0	11.1			
15				10.9	10.9			
17	165.6			7.2	8.0			
18	158.2			5.1	17.5			
19	169.4	26.1	5.1	22.2	9.4			47.3
26	163.8			7.3	9.2			

[a] See Table 2.

[b] P refers to the hydrogen atom bound to the same carbon as A and B.

[c] Standard deviations are <2 units in the last digit listed.

Table 7. Absolute magnitudes of the time-averaged geminal fluorine anisochronism for 11-27

Compound	$\lvert\langle\Delta\rangle\rvert$	Compound	$\lvert\langle\delta\rangle\rvert$
11	0.0	20	0.0
12	0.0	21	0.0
13	3.772	22	0.0
14	2.390	23	0.999
15	0.0	24	2.889
16	2.122	25	3.540
17	2.105	26	3.316
18	9.022	27	1.921
19	2.475		

Table 8. Normalized acyclic conformational ligand constants and conformational free energies pertinent to the corresponding monosubstituted cyclohexanes[a]

L	$-\hat{\lambda}_L$	$-\Delta G^{\circ}_L$
H	0	0
F	0.84 ± 0.16	0.15
Ph	1.60 ± 0.36	3.0
CH_3	1.6	1.7
OH	2.5	0.52
OCH_3	2.5	0.6
Cl	2.70 ± 0.13	0.43
Br	3.15 ± 0.10	0.38
I	3.6	0.43

[a] The values for which standard deviations are given represent weighted averages of the two complete series with R = Br and R = Cl; the errors were obtained by full error propagation.

analysis of asymmetric ethanes that is conceptually analogous to that of the conformational free energies pertinent to the cyclohexane system.

Comparison between columns 2 and 3 of Table 8 reveals some remarkable differences. In the cyclohexane series the heavy halogens exhibit virtually the same "size", which is a frequently discussed and allegedly well understood phenomenon (see, however, Ref. 13), whereas their acyclic conformational ligand constants follow more closely the van der Waals radii. It is of course well known, though sometimes slighted, that sheer "size" of a substituent may have little to do with the position of conformational equilibria; polar effects can play a comparable role and, even more importantly, conformational equilibria may depend critically on the structural framework to which the ligand is attached. This is particularly true for substituents devoid of axial symmetry. A striking demonstration of this point is provided by the phenyl group, which heads the list of Table 8 for the cyclohexane system, but ranges far below the heavy halogens in the asymmetric ethanes. The reason for this difference is presumably that the phenyl group can assume a bisected orientation in the latter system, but not in the former.

In view of the vast amount of effort invested in the quantitative conformational analysis of cyclohexanes and their heterocyclic analogues, the present work on asymmetric ethanes must be regarded as a mere beginning. It is believed, however, that the foundations of the heuristic mathematical model and its practical usefulness are by now sufficiently well established that we can, with

some degree of confidence, proceed to apply it to problems of biological interest.

EXPERIMENTAL

Measurements. The ^{19}F NMR spectra were recorded at 56.4 MHz in CW mode, using a Varian HA-60-IL/620i spectrometer-computer system and degassed 0.4 M solns in $CFCl_3$, which also served as internal standard; the spectra of **16** and **25** were measured at 6 different concentrations in the range from 0.2 to 0.8 M. The chemical shifts and coupling constants represent averages from 5 spectra in each case and were extracted by standard iterative computer analysis for patterns more complex than AB. All samples were purified by preparative glc, using a Varian Aerograph Model 1440 chromatograph and a 5m × 3/8 in. 10% Silicon OV-17 on Varaport 30 80/100 mesh column.

2 - *Chloro* - 2,2 - *difluoro* - 1 - *phenylethanol* (**16**) was obtained in 80% yield by sodium borohydride reduction of α-chloro-α,α-difluoroacetophenone, using a procedure completely analogous to that described for the bromo derivative:[8] b.p. 104–106°/8 mm (lit.[14] b.p. 85–86°/5 mm); ^1H NMR ($CDCl_3$): δ 3.78 (s, 1H), 4.94 (t, J = 8.1 Hz, 1H), 7.37 (s, 5H).

1 - *Chloro* - 1,1,2 - *trifluoro* - 2 - *phenylethane* (**1**). A mixture of 5 g (25.9 mmol) of **16**, 14 g (129 mmol) of sulfur tetrafluoride and 40 ml of CH_2Cl_2 was shaken in an autoclave for 15 hr at room temp. The excess reagent and the solvent were removed in an aspirator vacuum, the residue taken up in CH_2Cl_2, washed with $NaHCO_3$aq and water and dried (Na_2SO_4). Distillation yielded 4.1 g (78%) of **1**: b.p. 95–97°/10 mm; ^1H NMR ($CDCl_3$): δ 5.50 (dt, J = 7.1 and 44.0 Hz, 1H), 7.40 (s, 5H); MS: *m/e* 194 (M^+), 159, 140, 109. (Found: C, 49.33; H, 3.02. Calc. for $C_8H_6ClF_3$: C, 49.37; H, 3.11%).

1 - *Bromo* - 2 - *chloro* - 1,2,2 - *trifluoro* - 1 - *phenylethane* (**8**). A stirred soln of 500 mg (2.54 mmol) of **1** and 470 mg (2.93 mmol) Br_2 in 3 ml CCl_4 was irradiated with a UV lamp for 24 hr. The mixture was diluted with CH_2Cl_2, washed successively with 5% $NaHSO_3$ aq and $NaHCO_3$ aq and with water and dried (Na_2SO_4). Column chromatography on silica gel (CCl_4) yielded 650 mg (95%) of **8** as an oil: ^1H NMR ($CDCl_3$): δ 7.4–7.6 (m, 5H); MS: *m/e* 272 (M^+), 195, 158. (Found: C, 35.23; H, 1.80. Calc. for $C_8H_5BrClF_3$: C, 35.13; H, 1.84%).

1,2 - *Dichloro* - 1,1 - *difluoro* - 2 - *phenylethane* (**2**). A mixture of 1.5 g (8 mmol) of **16** and 1.5 g (13 mmol) $SOCl_2$ was heated on a steam bath for 1 hr. Standard workup yielded 0.9 g (55%) of **2**: b.p. 64–66°/8 mm (lit.[16] b.p. 200°/760 mm); ^1H NMR (CCl_4: δ 514 (dd, J = 7.4 and 10.3 Hz, 1H), 7.40 (s, 5H).

1 - *Chloro* - 1,1 - *difluoro* - 2 - *iodo* - 2 - *phenylethane* (**18**). A slurry of 9 g (46.7 mmol) of **16**, 0.45 g of red P and 6.3 g I_2 was heated to 90° for 3 hr. The cold mixture was digested with ether, the decanted ether phase filtered, treated with 5% $Na_2S_2O_3$ aq and water and dried (Na_2SO_4). After evaporating the solvent a small sample of the crude product was purified by glc: ^1H NMR ($CDCl_3$): δ 5.26 (dd, J = 5.1 and 17.5 Hz, 1H), 7.2 (m, 5H); MS: *m/e* 302 (M^+), 175, 140. (Found: C, 31.54; H, 2.12. Calc. for $C_8H_6ClF_2I$: C, 31.76; H, 1.99%).

1 - *Chloro* - 1,1 - *difluoro* - 2 - *methoxy* - 2 - *phenylethane* (**17**). A soln of 5.12 g (26.6 mmol) of **16** in 7 ml dry THF was added dropwise to a stirred suspension of 5.66 g (39.8 mmol) MeI and 1.46 g NaH in 15 ml dry THF and the mixture was then heated under reflux for 1 hr. The cold mixture was quenched with sat NH_4Claq and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4) and the solvents evaporated. Column chromatography on alumina (neutral, activity I; $CHCl_3$) yielded 4.7 g (86%) of **17** after workup: ^1H NMR ($CDCl_3$): δ 3.25 (s, 3H), 4.31 (dd, J = 7.2 and 8.0 Hz, 1H), 7.22 (s, 5H); MS: *m/e* 206 (M^+), 171, 140, 121, 77. (Found: C, 52.63; H, 4.59. Calc. for $C_9H_9ClF_2O$: C, 52.31; H, 4.39%).

1 - *Bromo* - 2 - *chloro* - 2,2 - *difluoro* - 1 - *methoxy* - 1 - *phenyl* - *ethane* (**22**). A stirred soln of 17 (2 g, 8 mmol) and 1.6 g (10 mmol) Br_2 in 10 ml CCl_4 was irradiated with a UV lamp for 24 hr. The mixture was diluted with ether, washed with 5% $NaHSO_3$ aq and water and dried (Na_2SO_4). After evaporation of the solvents the residue was column chromatographed on alumina (neutral, activity I; CCl_4) to yield 2.2 g (78%) of **22**: ^1H NMR ($CDCl_3$): δ 3.41 (s, 3H), 7.6 (m, 5H); MS: *m/e* 205, 190, 113, 105. (Found: C, 37.98; H, 3.06. Calc. for $C_9H_8BrClF_2O$: C, 37.85; H, 2.82%).

1 - *Bromo* - 2 - *chloro* - 1,2,2 - *trifluoroethane* (**5**). The literature procedure[15] for preparing this compound could not be reproduced, but **5** could easily be made by heating 22 g (0.13 mol) bromotrifluoroethylene, 20 g (0.55 mol) dry HCl and 4 g anhyd $AlCl_3$ in an autoclave to 90° for 15 hr. Standard workup by fractional distillation yielded 12.9 g (48%) of **5**: b.p. 50–54°/760 mm (lit.[15] b.p. 52.3–52.6°/760 mm); ^1H NMR ($CFCl_3$): δ 6.16 (ddd, J = 4.2, 6.5 and 47.2 Hz, ^1H); MS: *m/e* 196 (M^+), 161, 117.

1 - *Bromo* - 1,2 - *dichloro* - 2,2 - *difluoroethane* (**6**). The starting material 1,2 - dibromo - 1,1 - difluoroethane was prepared in 95% yield according to literature directions,[16] but without using a light source; 45 g (0.2 mol) of it was placed in a 3-necked flask whose reflux condenser was connected to a trap cooled to −78°. A cold soln of 18 g (0.32 mol) KOH in 50 ml water was added dropwise under stirring and the mixture was then heated to 85° for 3 hr, after which time 10 g (35%, 0.07 mol) 1 - bromo - 2,2 - difluoroethylene had been collected in the trap. The crude olefin was heated with 20 g (0.28 mol) Cl_2 and 3 g $SnCl_4$ in 50 ml CH_2Cl_2 to 60° in an autoclave for 16 hr. The cooled mixture was washed with 5% $NaHCO_3$aq and water and dried (Na_2SO_4). Distillation yielded 10.5 g of **6**: b.p. 76–78°/760 mm; ^1H NMR ($CFCl_3$): δ 5.90 (dd, J = 5.7 and 6.5 Hz, 1H); MS: *m/e* 214 (M^+), 195, 179, 133, 129, 98. (Found: C, 10.96; H, 0.42. Calc. for $C_2HBrCl_2F_2$: C, 11.23; H, 0.47%).

1 - *Bromo* - 1,2 - *dichloro* - 2,2 - *difluoro* - 1 - *phenylethane* (**9**). The starting material α - bromo - β,β - difluorostyrene, previously obtained[8] in poor yield from 1 - bromo - 2 - chloro - 2,2 - difluoro - 1 - phenylethane, was prepared in 55% yield by HBr elimination from 1,2 - dibromo - 2,2 - difluoro - 1 - phenylethane,[16] using a procedure analogous to that described.[8] A slow stream of Cl_2 was passed through a soln of 2 g (9.1 mmol) of α - bromo - β,β - difluorostyrene in 20 ml CCl_4 for 5 hr. Standard workup yielded 2.5 g (94%) crude **9**, of which a small sample was purified by glc: ^1H NMR ($CDCl_3$): δ 7.4 (m, 5H); MS: *m/e* 290 (M^+), 255, 236, 205, 77. (Found: C, 33.32; H, 1.87. Calc. for $C_8H_5BrCl_2F_2$: C, 33.14; H, 1.73%).

α,α-Difluoroacetophenone (**28**). An ether soln of 7.5 g (78 mmol) difluoroacetic acid was added dropwise to a cold (0°) soln of PhMgBr in ether, prepared in standard fashion from 5 g Mg turnings and 31.5 g (200 mmol) bromobenzene, and the mixture was then heated under reflux for 1 hr. The cooled soln was poured onto ice, thrice extracted with 50 ml portions of ether, the combined ether extracts were washed with water and dried (Na_2SO_4). Workup by distillation yielded 7.3 g (70%) of **28**: b.p. 67–70°/11 mm; ^1H NMR ($CDCl_3$): δ 6.25 (t, J = 53.1 Hz, 1H), 7.6 (m, 5H); IR (CCl_4): cm^{-1} 1700 (C=O); MS: *m/e* 156 (M^+), 105, 77, 51. (Found: C, 61.38; H, 3.63. Calc. for $C_8H_6F_2O$: C, 61.54; H, 3.87%).

2,2-Difluoro-1-phenylethanol (**29**). A soln of 3 g (19.2 mmol) of **28** in 10 ml dry ether was added dropwise to a stirred soln of 0.38 g LAH in 10 ml dry ether and the mixture was heated under reflux for 1 hr. The reaction was quenched by the successive addition of 0.38 ml water, 0.38 ml 15% NaOHaq and 1.2 ml water and filtered. The ether layer was washed with water and dried (Na_2SO_4) and the ether was evaporated to yield 2.4 g (80%) of **29** as a colorless oil, of which a small sample was purified by glc: ^1H NMR ($CDCl_3$): δ 2.92 (d, J = 3.7 Hz, 1H), 4.75 (ddt, J = 3.7, 4.5 and 12.0 Hz, 1H), 5.70 (dt, J = 4.5 and 55.8 Hz, 1H), 7.32 (s, 5H); IR (CCl_4): cm^{-1} 3610 (OH); MS: *m/e* 158 (M^+), 107, 77, 51. (Found: C, 60.51; H, 5.28. Calc. for $C_8H_8F_2O$: C, 60.77; H, 5.10%).

1 - *Chloro* - 2,2 - *difluoro* - 1 - *phenylethane* (**11**). A mixture of 2.3 g (14.5 mmol) of **29**, 2 ml Et_3N, 1.93 g (16.2 mmol) $SOCl_2$ and 10 ml $CHCl_3$ was heated under reflux for 4 hr. The cooled mixture was diluted with 20 ml ether, filtered, washed with water and dried (Na_2SO_4). Distillation yielded 2.1 g (82%) of **11**: b.p. 75–76°/10 mm; ^1H NMR ($CDCl_3$): δ 4.90 (dt, J = 4.1 and 10.6 Hz, 1H), 5.92 (dt, J = 4.1 and 55.1 Hz, 1H), 7.35 (s, 5H); MS: *m/e* 176 (M^+), 125, 77, 51. (Found: C, 54, 24; H, 4.16. Calc. for $C_8H_7ClF_2$: C, 54.40; H, 3.99%).

1 - *Bromo* - 2,2 - *difluoro* - 1 - *phenylethane* (**12**). Compound **29** (0.5 g, 3.2 mmol) was boiled with 5 ml 47% HBr for 2 hr. The

mixture was diluted with 10 ml water and extracted with ether. The ether layer was washed with 5% $NaHCO_3$aq and water, dried (Na_2SO_4) and the ether was evaporated. Column chromatography on silica gel (CCl_4) yielded 0.63 g (90%) of **12**: ^1H NMR ($CDCl_3$): δ 4.92 (dt, J = 4.1 and 11.1 Hz, 1H), 5.96 (dt, J = 4.1 and 55.1 Hz, 1H), 7.35 (s, 5H); MS: *m/e* 220 (M^+), 141, 90, 77, 51. (Found: C, 43.21; H, 3.08. Calc. for $C_8H_7BrF_2$: C, 43.47; H, 3.19%).

1,1,2-Trifluoro-1,2-diphenylethane (**13**). A mixture of 10 g (47.1 mmol) benzoin, 30 g (270 mmol) sulfur tetrafluoride and 80 ml CH_2Cl_2 was shaken in an autoclave for 40 hr at room temp. The excess reagent was removed in an aspirator vacuum, the residue taken up in CH_2Cl_2, filtered, washed with 5% $NaHCO_3$aq and water and dried (Na_2SO_4). The product was column chromatographed on silica gel (CCl_4) and recrystallised from pentane to yield 7.5 g (68%) of **13** as colorless crystals: m.p. 84–85°; ^1H NMR ($CDCl_3$): δ 5.65 (ddd, J = 8.0, 8.4 and 44.5 Hz, 1H), 7.28 (s, 10H); MS: *m/e* 236 (M^+), 127, 109, 77. (Found: C, 71.32; H, 4.73. Calc. for $C_{14}H_{11}F_3$: C, 71.18; H, 4.69%).

1 - Chloro - 2,2 - difluoro - 1,2 - diphenylethane (**14**). Desyl chloride (2 g, 7.9 mmol), 9 g (83.3 mmol) sulfur tetrafluoride and 10 ml CH_2Cl_2 were heated to 110° in an autoclave for 42 hr. Workup as for **13** yielded 1.4 g (62%) of **14**: m.p. 76–78°; ^1H NMR ($CDCl_3$): δ 5.20 (dd, J = 10.0 and 11.1 Hz, 1H), 7.2 (m, 10H); MS: *m/e* 252 (M^+), 217, 127. (Found: C, 66.34; H, 4.31. Calc. for $C_{14}H_{11}ClF_2$: C, 66.53; H, 4.38%).

2 - Bromo - 1 - chloro - 1,1 - difluoro - 2 - phenylpropane (**21**). 1 - Chloro - 1,1 - difluoro - 2 - phenyl - 2 - propanol[17] (4 g, 19.4 mmol) was boiled with 40 ml 47% HBr for 4 hr. Workup as for **12** yielded 3.2 g (60%) of **21** as an oil, of which a small sample was purified by glc: ^1H NMR ($CDCl_3$): δ 2.35 (s, 3H), 7.4 (m, 5H); MS: *m/e* 268 (M^+), 170, 153, 103, 77. (Found: C, 40.27; H, 3.14. Calc. for $C_9H_8BrClF_2$: C, 40.10; H, 2.99%).

Reaction of 1 - chloro - 1,1 - difluoro - 2 - phenyl - 2 - propanol with thionyl chloride. A mixture of 1.3 g (6.3 mmol) of the starting alcohol, 0.63 g Et_3N and 0.78 g $SOCl_2$ was heated under reflux for 10 hr. The cooled mixture was taken up in ether, filtered, washed with water and dried (Na_2SO_4). The ether was evaporated and the two products separated by preparative glc to yield **29** and **30** in the ratio of 40:60.

Compound **29**: ^1H NMR ($CDCl_3$): δ 2.00 (s, 3H), 7.35 (s, 5H); MS: *m/e* 224 (M^+), 188, 153, 139, 103. (Found: C, 48.26; H, 3.62. Calc. for $C_9H_9Cl_2F_2$: C, 48.02; H, 3.58%).

Compound **30**: ^1H NMR ($CDCl_3$): δ 5.63 (d, J = 1.5 Hz, 1H), 5.96 (d, J = 1.5 Hz, 1H), 7.45 (s, 5H); MS: *m/e* 188 (M^+), 153, 139, 103. (Found: C, 57.12; H, 3.82. Calc. for $C_9H_7ClF_2$: C, 57.31; H, 3.74%).

Hydrogenation of 3 - chloro - 3,3 - difluoro - 2 - phenylpropene. When a soln of 200 mg (1.06 mmol) of **30** in 3 ml EtOH was subjected to catalytic hydrogenation in the presence of Pd–C, 36 ml (1.60 mmol) H_2 were taken up in 20 min. The products were separated by glc to yield **15** and **31** in the ratio of 70:30.

Compound **15**: ^1H NMR ($CDCl_3$): δ 1.36 (d, J = 7.1 Hz, 3H), 3.3 (m, 1H), 7.06 (s, 5H); MS: *m/e* 190 (M^+), 105. (Found: C, 56.82; H, 4.68. Calc. for $C_9H_9ClF_2$: C, 56.71; H, 4.76%).

Compound **31**: ^1H NMR ($CDCl_3$): δ 1.20 (d, J = 7.0 Hz, 3H), 3.1 (m, 1H), 5.53 (dt, J = 4.0 and 57.1 Hz, 1H), 7.00 (s, 5H); MS: *m/e* 156 (M^+), 105. (Found: C, 68.96; H, 6.28. Calc. for $C_9H_{10}F_2$: C, 69.19; H, 6.45%).

1 - Bromo - 1,1 - difluoro - 2 - methoxy - 2 - phenylethane (**26**). A soln of 2 g (8.4 mmol) 2-bromo-2,2-difluoro-1-phenyl-ethanol[9] in 3 ml anhydrous THF was added dropwise, under stirring, to a mixture of 0.25 g NaH, 1.8 g MeI and 5 ml THF. The mixture was then heated under reflux for 1.5 hr, cooled, quenched with NH_4Claq and thrice extracted with 10 ml portions ether. The crude product obtained on standard workup was column chromatographed on alumina (neutral, activity I; $CHCl_3$) to yield 1.8 g (85%) of **26**: ^1H NMR ($CDCl_3$): δ 3.21 (s, 3H), 4.21 (dd, J = 7.3 and 9.2 Hz, 1H), 7.15 (s, 5H); MS: *m/e* 250 (M^+), 117, 121, 77. (Found: C, 40.45; H, 2.94. Calc. for $C_9H_7BrF_2O$: C, 40.54; H, 2.97%).

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