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NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME 2,6-DISUBSTITUTED SPIRO[3.3]HEPTANE DERIVATIVES

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Abstract—Analysis of the full splitting pattern of the 100 MHz ^{1}H-NMR spectra of diethyl - 2,6 - dibromospiro[3.3]heptane - 2,6 - dicarboxylate (3) in chloroform and benzene and the 220 MHz ^{1}H-NMR spectrum of dimethylspiro[3.3]heptane - 2,6 - dicarboxylate (2) in naphthalene has been carried out. Puckering of the cyclobutane rings is revealed. Reasonable agreement with an X-ray study on Fecht acid (1) and with the data from the ^{13}C-NMR spectra of compounds 2 and 3 has been obtained. The temperature dependency of the ^{1}H-NMR spectra of 2, 3 and the symmetrically substituted tetraethylspiro[3.3]heptane - 2,2,6,6 - tetracarboxylate (4) has been investigated and is discussed in terms of conformational interconversion.

INTRODUCTION

Recent years have seen the accumulation of considerable data on the NMR spectra of cyclobutane derivatives.[1–8, 16] However, until now no attention has been focused on compounds containing two cyclobutane rings in a spiro[3.3]heptane arrangement such as found in Fecht acid (1). Our interest in Fecht acid and related compounds led us to attack this formidable problem.

Recently, an X-ray study of Fecht acid (1)[9] revealed that in the solid state the two cyclobutane moieties are not planar, but puckered. The presence of similar conformations in the solid and liquid phase would make the current explanations of the chiroptical properties[10–13] of this class of compounds more reliable. The non-planarity of the spiro compounds under investigation cannot be *a priori* assumed, however, since a wide variety of compounds containing planar cyclobutane rings are presently available.[21–28] Therefore, in this study special attention is paid to the conformational behaviour of Fecht acid (1) and related compounds in solution, as investigated by NMR spectroscopy. Two initial approaches for establishing the conformation of this class of compounds, *viz.* dipole moment measurements on Fecht acid and its dimethyl ester (2)† and a recent analysis of the dissociation constants of 6-substituted spiro[3.3]heptane - 2 - carboxylic acids,[14] failed to give unambiguous conformational evidence.

^{13}C-NMR spectroscopy. The ^{13}C spectra at 25·1 MHz of the symmetrically tetrasubstituted spirane 4 and of the chiral spiranes 2 and 3 with C_2 symmetry were recorded. The ^{13}C spectrum of 2 at room temperature was taken in carbon disulfide shown in Fig 1. The ^{13}C spectral data of the compounds 3 and 4 are also tabulated in Table 1‡. A ^{13}C spectrum by itself does not give such decisive evidence for a folded conformation of the cyclobutane rings as the X-ray study on 1 does. The fact that all four C atoms of the 4-membered ring had a different chemical shift indicates that the two methylene groups in one ring are not equivalent in compounds 2 and 3. This phenomenon corresponds with the structural data for 1 in the solid state and is based upon symmetry arguments following from consideration of the asymmetric substitution in the other ring.

On the other hand, from symmetry reasons (extra two-fold axes at room temperature) it was derived that the signals of all methylene groups in compound 4 should be identical at this temperature and this was confirmed by experiment.

^{1}H NMR. The 100 MHz spectra of 2 and 3 and the 220 MHz spectrum of 2 were analysed by means of the computer program LAME. More information about the conformation of the spiro[3.3]heptane skeleton could be obtained by analysis of the ^{1}H NMR spectra of the dimethyl ester of Fecht acid (2). Spectra of this compound were taken at 100, 220 and 300 MHz in benzene and at 100 and 220 MHz in naphthalene solution. Because of the complexity of the other spectra, only the 220 MHz spectrum of 2 in naphthalene at 95° could be analysed. The observed

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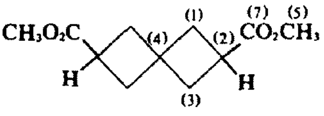
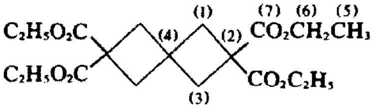
†The values of the dipole moments of compound 1 and 2 (μ = 2·07 D, measured in dioxane at 20° and μ = 2·13 D measured in carbon tetrachloride at 20°, respectively; both determined using Guggenheim's method) did not agree with the calculated dipole moments of the three possible conformers of 2, *viz.* 2a, 2b and 2c, and the analogous structures of 1.

‡The signal of C(4) in di-ester 2 is observed more upfield than expected. In addition, CNDO/2 calculations[9] indicated a smaller charge on C(4) than on the other C atoms in the spiro skeleton. Thus, apparently other effects influence the chemical shift.[15]

Table 1. ^{13}C parameters of some spiranes



2



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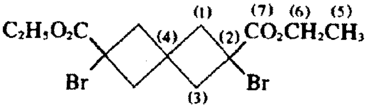

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Compound	Solvent	Chemical shift in ppm with respect to internal TMS						
		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)
2	CS_2	38·6	33·9	39·1	38·0	52·8	—	—
3	$CDCl_3$	48·3	48·6	49·1	34·0	13·6	61·7	170·0
4	$CDCl_3$	40·7	47·6	40·7	32·5	13·4	60·5	170·0

and calculated splitting patterns of this spectrum are shown in Fig 2. The analysis of the ABCDE pattern was carried out with the aid of the LAME program. The results are shown in Table 2. In accord with the ^{13}C spectra, the proton spectrum of this di-ester **2** shows that the two methylene groups in one cyclobutane ring are non-equivalent. Different chemical shifts were observed for both methylene groupings in one ring due to asymmetric substitution in the adjacent ring.

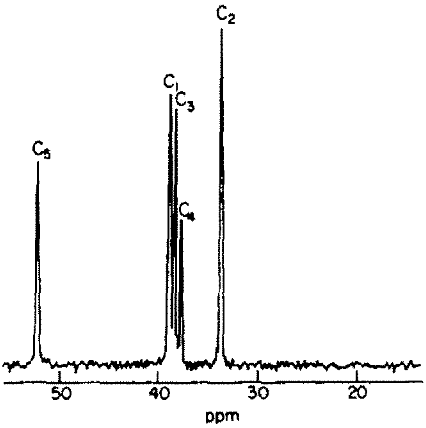
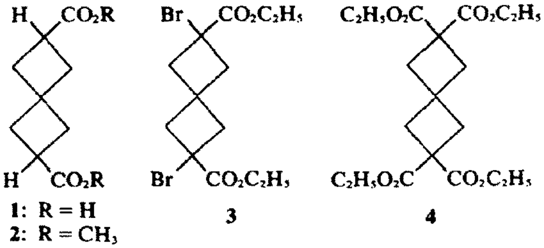


Fig 1. ^{13}C spectrum of **2** in CS_2.



SKETCH 1.

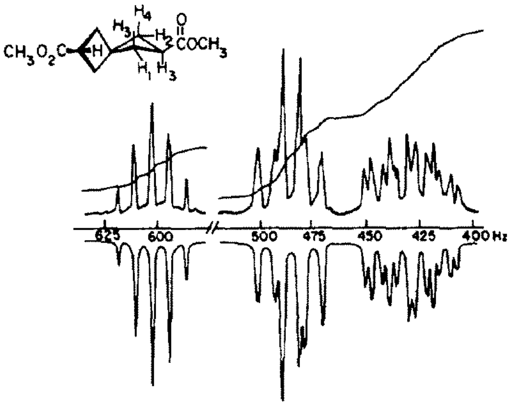


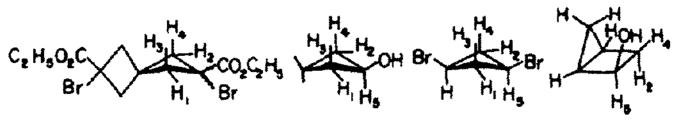
Fig 2. Numbering convention of **2** and 220 MHz spectrum (observed and computed) of **2** in naphthalene at 95°.

Table 2. ^{1}H-NMR parameters of **2**[a] in naphthalene at 95°

Chemical shifts[b]:	H_1	419·9;	H_2	440·2;	H_3	480·5;	H_4	491·0;	H_5	600·6
Coupling constants[b]:	J_{12}	2·9	J_{23}	0·8	J_{34}	0·0	J_{45}	8·2		
	J_{13}	11·3	J_{24}	12·0	J_{35}	8·1				
	J_{14}	0·9	J_{25}	7·9						
	J_{15}	8·0								

[a] See Fig 2 for the numbering convention.

[b] Data are given in Hz (downfield from internal TMS).



3 5 6 7

Fig 3. Numbering convention of compounds.

Coupling constant data. Application of the equations of Karplus (Table 3) for the calculation of dihedral angles between vicinal protons from coupling constants gave a reasonable agreement with the X-ray data of 1. When a correction was applied for the fact that generally the involved constants are larger if substituents are attached to the bonds under consideration,[18] the agreement between experiment and theory was even better. Moreover, from a study of Wiberg on cyclobutanols[5] it was deduced that the coupling constants in a planar cyclobutane ring (e.g. in 7) between the vicinal protons are about 9 and 3·5 Hz in the *cis* and *trans* configuration, respectively, whereas in a puckered 4-membered ring the mean values are about 7 and 8·0 Hz, respectively. Consequently, the data of di-ester 2 (in solution) suggest that the cyclobutane rings are in any case not flat. Furthermore, from the magnitude of the long-range coupling constants J_{12} and J_{34} the non-planarity of this particular spiro system could also be derived. Support for this conclusion was found in the literature.[5,20] In Table 4 the data of the coupling constants for *endo*-bicyclo[2.1.0]pentan - 2 - ol (7) (as a representative of planar cyclobutanes), for cyclobutanol (5) and *cis* - 1,3 - dibromocyclobutane (6) (both representatives for puckered cyclobutanes) are summarized and compared with spiranes 2 and 3.

The 100 MHz NMR spectra of bis-α-bromoester 3 were also analysed and computer-simulated. The observed and calculated splitting patterns of the ABCD spectra of 3 in benzene and chloroform are shown in Fig 4 and the NMR parameters are compiled in Table 5. The tabulated values show an interesting feature: the long-range coupling constants J_{12} and J_{34} have a comparable magnitude in 3, contrary to the situation in 2. This characteristic

Table 3. Comparison of X-ray structure parameters of 1 and calculated dihedral angles (α) of 2

	α, exp.[a]	J(Hz)	α, calc.[b]	α, calc.[c]
H_{15}	27·7°	8·0 ± 0·2	11·0 ± 3·7°	15·3 ± 2·9°
H_{25}	25·9°	7·9 ± 0·2	9·1 ± 4·4°	14·0 ± 2·7°
H_{35}	156·6°	8·1 ± 0·2	160·6 ± 2·0°	159·2 ± 1·8°
H_{45}	152·8°	8·2 ± 0·2	159·7 ± 1·9°	158·3 ± 1·8°

[a] X-ray structure parameters of 1.
[b] Calculation according to Karplus equations in ref 18.
[c] Calculation according to Karplus equation in ref 19, without use of number 0·28.

Table 4. Comparison of coupling constants in cyclobutanes (in Hz)[a]

	2[b]	3[b,c]	5[d]	6[d]	7[d]
J_{12}	2·9	2·4(3·2)	5·2	5·6	0·1
J_{13}	11·3	13·2	10·9	12·4	—
J_{14}	0·9	1·0	0·9	1·1	1·0
J_{15}	8·0	—	7·0	7·1	4·2
J_{23}	0·8	1·0	0·9	1·1	—
J_{24}	12·0	13·2	10·9	12·4	11·5
J_{25}	7·9	—	7·0	7·1	9·0
J_{34}	0·0	3·2(2·4)	0·01	0·3	—
J_{35}	8·1	—	8·1	8·8	—
J_{45}	8·2	—	8·1	8·8	3·5

[a] See Fig 2 and 3 for numbering convention.
[b] This work.
[c] In deuterochloroform.
[d] Ref 5*b*.

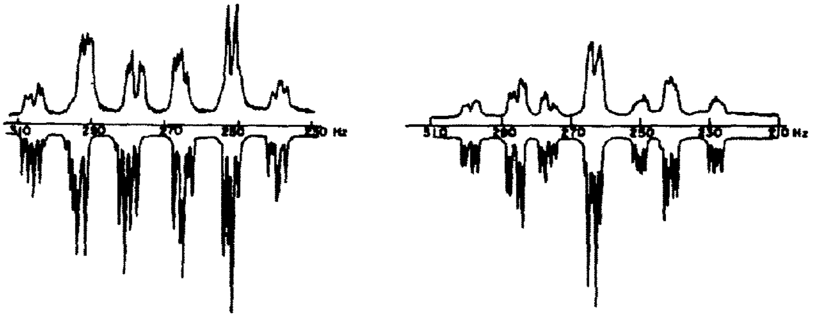


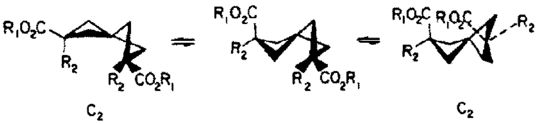
Fig 4. Observed an calculated 100 MHz spectrum of 3 in benzene (on the left) and of 3 in chloroform (on the right).

Table 5. 100 MHz–NMR parameter of 3[a]

Chemical shifts[b]:	H_1	259·8;	H_2	245·8;	H_3	284·7;	H_4	299·0	(C_6D_6)	
	H_1	235·8;	H_2	257·8;	H_3	268·8;	H_4	291·0	$(CDCl_3)$	
Coupling constants[bc]:	J_{12}	2·4	J_{23}	1·5	(C_6D_6)	J_{12}	2·4	J_{23}	1·0	$(CDCl_3)$
	J_{13}	13·4	J_{24}	13·0		J_{13}	13·2	J_{24}	13·2	
	J_{14}	1·5	J_{34}	3·3		J_{14}	1·0	J_{34}	3·2	

[a] See Fig 3 for numbering convention.
[b] Data are given in Hz (downfield from internal TMS).
[c] The values of J_{12} and J_{34} cannot be attributed unambiguously to the corresponding protons.

indicates that in compound **2** one conformer predominates whereas in compound **3** conformers **3a** and **3c** (Fig 5) are about equally populated, because in this situation both proton pairs H_1-H_2 and H_3-H_4 spend comparable lifetimes in the pseudo-diequatorial "zig-zag" conformation, which is favourable for coupling.[19,29]



2a ($R_1 = CH_3$ $R_2 = H$) 2b 2c
3a ($R_1 = C_2H_5$ $R_2 = Br$) 3b 3c

Fig 5. Ring interconversion of 2 and 3.

Variable temperature NMR spectroscopy. Evidence for an equilibrium between different conformers at room temperature can be obtained from variable temperature NMR spectroscopy. With compound **3** peak broadening was observed at a coalescence temperature of about −100° in methylene chloride or in a mixture of this solvent and carbon disulfide (Fig 6). On the other hand, the spectrum of di-ester **2** did not change in the temperature range of −60° to +200° (solvents methylene chloride, benzene and naphthalene). All of the literature data[6,30,31] indicate a relatively low inversion barrier (1–2 kcal/mole) in cyclobutane derivatives. Moreover, a coalescence point is difficult to observe when one of the conformers is present in a very high population. As mentioned above, this might be the case in **2**. It is probable therefore that in compound **2** the rate of interconversion is still relatively high at −60°. The energy difference between a spirane containing substituents in the pseudo-equatorial positions and one having substituents in the pseudo-axial positions might explain for di-ester **2** the large amount of pseudo-diequatorial forms in the equilibrium mixture. In bis-α-bromoester **3**, which has substituents of comparable size in both positions, the pseudo-axial/pseudo-equatorial equilibrium might then lie closer to a situation in which both conformers are equally populated.

The latter inference was supported by a ring-flip which was demonstrated also in the symmetrically substituted spirane **4** and in the corresponding methyl ester.[34] Peak broadening in the spectrum of **4** was clearly observed at a coalescence temperature of approximately −100° in toluene and carbon disulfide (Fig 7). From these phenomena it is evident that ring inversion at low temperature is indeed sufficiently slow in this type of compounds, which in turn implies the presence of puckered conformations. An interesting feature is provided

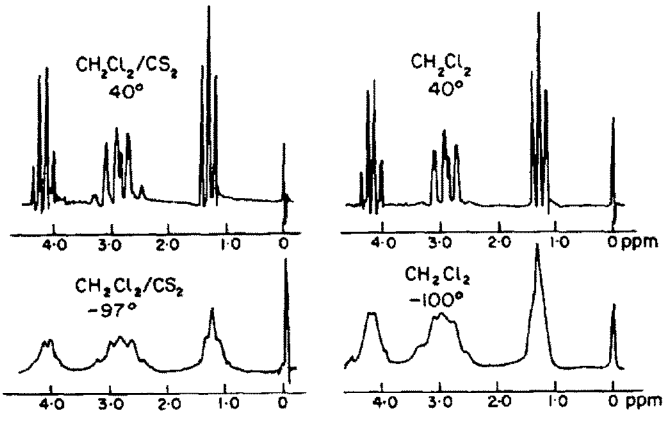


Fig 6. Temperature dependent 60 MHz spectra of 3 in a mixture of methylene chloride and carbon disulfide (on the left) and in methylene chloride (on the right).

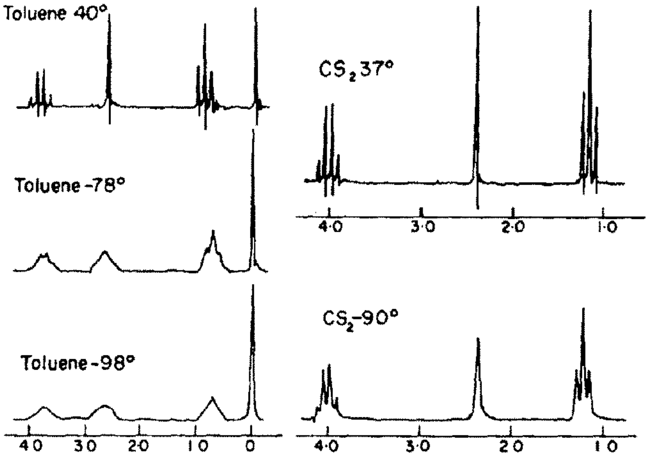


Fig 7. Temperature dependendent 60 MHz spectra of **4** in toluene (on the left) and 100 MHz spectra of **4** in carbon disulfide (on the right).

by tetraester **4**. The two conformational isomers **4a** and **4b** are mirror images and can be interconverted by inversion of one ring (Fig 8). This means that the classical (planar) picture of the stereochemistry of this "symmetrically" tetrasubstituted spirane given in a number of textbooks is incorrect. At low temperature it should be possible to resolve this tetra-ester into its optical antipodes. The situation is related to that obtaining in *cis*-1,2-dimethylcyclohexane[35] and, of course, in principle in numerous other compounds.

4a 4b

R = $-CO_2C_2H_5$

Fig. 8. Ring interconversion of **4**.

CONCLUSION

This study reveals puckering of the 4-membered rings in 2,6 - disubstituted spiro[3.3]heptanes. Moreover, it is clear that consideration of the position of the equilibrium of the possible conformers is required for a detailed conformational analysis of these compounds.

The results were used for interpreting the optical rotatory properties of this class of compounds.[13] This indeed leads to a better agreement between experiment and calculation of the optical activity than neglect of the possible conformers.

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