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LOW RESOLUTION MICROWAVE SPECTROSCOPY AND THE CONFORMATIONAL ANALYSIS OF 4,4-DIFLUOROPIPERIDINE

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Abstract—The low resolution and high resolution microwave spectra of 4,4-difluoropiperidine and the *N*-deutero analog have been recorded. Based on a low resolution microwave adaptation of Kraitchman's equations, the species giving rise to the single observed low resolution band series is seen to be the N–H equatorial conformer. This result is verified by obtaining the principal axis coordinates of the amine hydrogen atom via an assignment of the high resolution microwave spectra of the normal and N–D compounds. Consideration of the least intensity of the N–H axial conformer's spectrum that would be necessary for it to be observed, leads to the result: $\Delta G \geq 0.89$ kcal/mole for the equatorial ⇄ axial equilibrium.

The main interactions influencing the conformation of 6-membered cyclic compounds are generally accepted to be 1,3 diaxial and gauche-vicinal. Because these interactions are small in the case of piperidine, efforts that would have been more than ample in most cases were required to determine its conformation. With the wealth of inconclusive and sometimes conflicting data, it is not surprising that the preference for N–H equatorial in piperidine itself took almost twenty years to gain acceptance.[1]

The piperidine situation was the subject of intensive investigation because it is a simple case wherein, it was hoped, some differentiation might be made between the relative sizes of the hydrogen atom and the lone pair on nitrogen. Now, it is believed that such a concept has only limited validity and that, in any event, the interpretation is dependent on the compound in question.[2]

A number of compounds closely related to piperidine have been examined with the intent of shedding more light on the preferred conformation of the parent compound. Among these, 4,4-difluoropiperidine was studied by Yousif and Roberts by ^{19}F NMR.[3] They were unable to ascertain the identity of the major conformer but did conclude, from variable temperature studies, that the magnitude of the conformational free energy in acetone solution is 0.42 kcal/mole. We have concluded in the present study that the N–H equatorial conformer is predominant in the gas phase at 25°C.

It has been verified previously that piperidine itself prefers the N–H equatorial chair conformation in the gas phase.[4] Further evidence bearing on the problem at hand includes the observation that morpholine exhibits a chair, N–H equatorial preference in the gas phase[5] and tetrahydropyran[6] and 1,1-difluorocyclohexane[7] exist exclusively in a chair conformation.

Stowlow *et al.*[8] have observed that the substitution of fluorine atoms in a polar flexible molecule may significantly alter the conformational preference relative to the unsubstituted compound. Thus, it is not entirely obvious that the conformational preference of 4,4-difluoropiperidine should be the same as that of piperidine.

Low resolution microwave spectroscopy is often able to furnish useful approximate structural information for large, nearly prolate gas phase molecules.[9] It is known that most such molecules exhibit rotational spectra consisting predominately of a-type, R-branch ($\Delta J = +1$) transitions that occur in clusters or bands of nearly the same frequency. The frequencies of these low resolution absorption bands, whose widths at half height are typically 50 to 150 MHz, occur at integral multiples of B + C.

$$\nu = (J+1)(B+C); \quad A = \frac{\hbar}{4\pi I_a}, \; B = \frac{\hbar}{4\pi I_b}, \; C = \frac{\hbar}{4\pi I_c} \qquad (1)$$

A, B and C are the rotational constants related as shown to the inverses of the three principal moments of inertia and hence to the molecular structure.[10]

We had expected to observe two series of a-type, R-branch low resolution absorption bands arising from the N–H axial and N–H equatorial conformers of 4,4-difluoropiperidine, based on model structural and dipole moment calculations. In fact, the low resolution microwave spectrum of 4,4-difluoropiperidine, recorded under standard low resolution conditions, exhibits only a single series of absorption bands attributable to only one conformer. Assignment of the observed low resolution band series to the chair N–H equatorial or axial conformer is by no means clear cut. Rotational constants calculated for energy-minimized chair structures of the N–H equatorial and axial conformers are presented for comparison to the observed value in Table 1.

The standard microwave spectroscopic technique for the determination of molecular structure is isotopic substitution. When the rotational constants are obtained by the assignment of high resolution microwave spectra of several isotopically enriched derivatives, Kraitchman's equations[11] permit the determination of the principal axis coordinates a, b and c of the atoms in question.

One advantage of low resolution microwave spectroscopy is the ease of interpretation of the spectra in terms of various conformers or geometric isomers. But in certain cases, where a conformational interconversion does not lead to a significant change in B + C or when only one conformer can be observed, a low resolution version of Kraitchman's equations may be useful.

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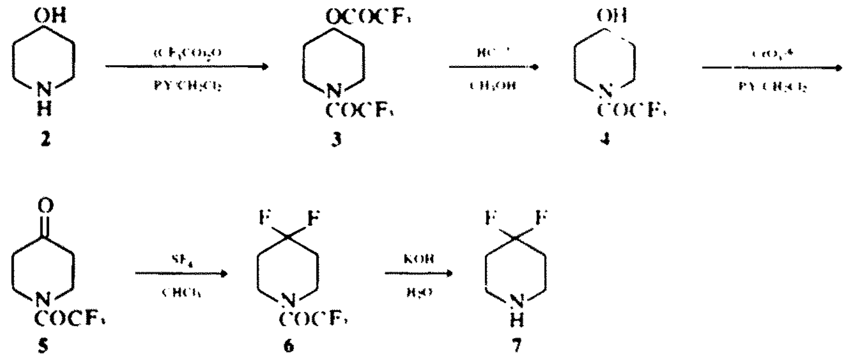
†Based on E. M. Bellott, Jr., Ph.D. Dissertation, Harvard University (1976).



Scheme 1. A scheme for the preparation of 4,4-difluoropiperidine.

Table 1. Calculated rotational constants for 4,4-difluoropiperidine and comparison of calculated and observed B + C

Calculated rotational constants from a postulated structure	
N–H Equatorial	N–H Axial
A = 3313 MHz	A = 3227 MHz
B = 1735	B = 1744
C = 1525	C = 1540
B + C = 3261	B + C = 3284
Observed	
B + C = 3304 ± 5	

Table 2. Determination of the prefered conformation of 4,4-difluoro-piperidine from low resolution microwave spectra by isotopic substitution

$(B+C)_H$	3304 ± 5 MHz
$(B+C)_D$	3210 ± 5
Coordinates of Amine Hydrogen $(2a^2+b^2+c^2)$	
observed	18.1 ± 2 Å^2
calculated EQ.	18.00
calculated AX.	11.14

Given the values of B + C for two isotopic species, it follows from Kraitchman's equations (see Appendix) that

$$\frac{4k}{\mu}\frac{(B+C)-(B'+C')}{(B+C)\quad(B'+C')} \cong 2a^2+b^2+c^2 \qquad (2)$$

Where μ is the reduced mass of the isotopic substitution

$$\mu = \frac{\Delta m M}{\Delta m + M} \qquad (3)$$

Δm is the mass change on isotopic substitution, in AMU, M is the molecular weight of the normal compound in AMU, and k = 505379.1 AMU Å^2 MHz.

N-Deutero 4,4-difluoropiperidine is conveniently prepared in the waveguide cell of the microwave spectrometer by exchanging the amine hydrogen atom for deuterium on the D_2O saturated waveguide walls. A value of the principal axis coordinate ellipsoid may be determined for the amine hydrogen atoms by substituting the values of $(B+C)_H$ and $(B+C)_D$ in eqn (2). Table 2 shows how effectively eqn (2) is employed in this case.

On the basis of the isotopic substitution experiment we conclude that it is the N–H equatorial conformer which is giving rise to the observed low resolution microwave spectrum. The N–H axial conformer, which must be the minor one, is not evident due to its low concentration.

The conformational free energy of 4,4-difluoropiperidine

Examination of Fig. 1 shows that the strongest observed feature of the microwave spectrum is a single low resolution type-I band series. The spectrum of the N–H axial conformer, were it to be seen, would be quite similar. Careful consideration shows that the weakest band of the N–H axial species that could be seen would be about 0.07 times the intensity of the N–H equatorial. Taking into account the a-dipole moments of 1.33 D and 2.42 D, respectively, calculated from bond moments, a practical lower limit is 0.89 kcal/mole for the conformational free energy[12] of 4,4-difluoropiperidine at 25°C.

Molecular mechanics calculations using Allinger's molecular mechanics program[13] indicate that the N–H axial conformer of 4,4-difluoropiperidine experiences a

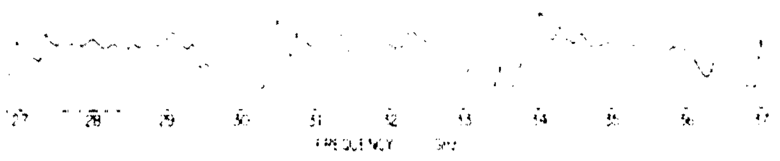


Fig. 1. The low resolution microwave spectrum of 4,4-difluoropiperidine.

Table 3. 4,4-Difluoropiperidine microwave spectral assignments

Transition	Obs. frequency	Calc. frequency	Difference
	Normal compound		
$5_{05} \rightarrow 6_{06}$	19160.3 MHz	19160.230 MHz	0.070 MHz
$5_{15} \rightarrow 6_{16}$	18968.3	18968.167	0.133
$5_{14} \rightarrow 6_{15}$	20291.8	20291.539	0.261
$5_{24} \rightarrow 6_{25}$	19720.3	19721.133	-0.833
$6_{06} \rightarrow 7_{07}$	22208.4	22208.372	0.028
$6_{16} \rightarrow 7_{17}$	22075.6	22075.540	0.060
$6_{15} \rightarrow 7_{16}$	23533.2	23533.233	-0.033
$6_{24} \rightarrow 7_{25}$	23866.7	23866.490	0.210
$6_{25} \rightarrow 7_{26}$	22947.5	22947.446	0.054
$7_{07} \rightarrow 8_{08}$	25255.5	25255.464	0.036
$7_{17} \rightarrow 8_{18}$	25170.7	25170.640	0.060
$7_{26} \rightarrow 8_{27}$	26148.8	26148.897	0.097

A = 3308.072 ± 0.923
B = 1770.409 ± 0.022
C = 1535.052 ± 0.018

Coordinates of N–H Equatorial, calculated	Coordinates of N–H Axial, calculated	Experimental coordinates
a = 3.001 Å	a = 2.191 Å	a = 3.003 ± 0.006 Å
b = 0	b = 0	b = 0
c = -0.064	c = 1.238	c = -0.052 ± 0.35

Transition	Obs. frequency	Calc. frequency	Difference
	N-Deutero compound		
$5_{05} \rightarrow 6_{06}$	18663.2 MHz	18663.162 MHz	0.038 MHz
$5_{15} \rightarrow 6_{16}$	18458.8	18458.644	0.156
$6_{06} \rightarrow 7_{07}$	21633.6	21633.646	0.046
$6_{15} \rightarrow 7_{16}$	22886.7	22886.773	0.073
$6_{16} \rightarrow 7_{17}$	21486.3	21486.171	0.129
$6_{24} \rightarrow 7_{25}$	23143.0	23142.644	0.356
$6_{33} \rightarrow 7_{34}$	22733.3	22734.964	-1.644
$7_{07} \rightarrow 8_{08}$	24599.9	24599.922	-0.022
$7_{16} \rightarrow 8_{17}$	25991.2	25991.355	-0.155
$7_{17} \rightarrow 8_{18}$	24501.9	24501.804	0.096
$7_{25} \rightarrow 8_{26}$	26493.9	26493.527	0.373
$7_{26} \rightarrow 8_{27}$	25429.1	25429.221	0.121
$7_{34} \rightarrow 8_{35}$	26093.7	26093.115	0.585
$7_{35} \rightarrow 8_{36}$	25808.1	25807.865	0.235

A = 3308.979 ± 1.156
B = 1716.309 ± 0.031
C = 1494.376 ± 0.029

steric energy destabilization of 0.29 kcal/mole relative to the N–H equatorial one. Furthermore, a dipole–dipole interaction term, calculated by classical interaction of dipoles in a medium of dielectric constant 1, adds a further 1.61 kcal/mole to the relative instability of the N–H axial species. Professor Allinger considers the dipole portion of the conformational energy to be exaggerated and suggests that the actual conformational energy difference is on the order of 0.5–1.0 kcal/mole.[14]

High resolution microwave spectral assignments

It was possible, furthermore, to make an assignment of the spectrum of 4,4-difluoropiperidine under high resolution conditions. Only a-type, R-branch transitions could be observed. Table 3 presents a least squares fit of the observed transitions to three rotational constants without centrifugal distortion terms, for both the N–H and N–D species. Determination of the rotational constants of both isotopic species leads to the principal axis coordinates of the amine hydrogen atom, from which it is seen that the low resolution microwave spectral results are vindicated.

EXPERIMENTAL

Low resolution microwave spectra were recorded in the K- and R-bands (18–26.5 and 26.5–40 GHZ, respectively) on a Hewlett-Packard 8460 A microwave spectrometer at room temperature (24–25°C). The spectra were recorded at a scan rate of 10 MHz per sec with a 1 sec recorder time constant. 1600 V base-to-base Stark voltage was found to modulate the transitions sufficiently for a strong spectrum to be recorded at −50 dB gain with total gas pressures of 50–100 mTorr pressure in the cell. High resolution spectra were recorded on the same instrument at slow scan rates with 10–20 mTorr total gas pressure.

NMR spectra were obtained using Varian Associates A-60 and XL-100 instruments. All spectra were obtained as $CDCl_3$ solutions. Proton chemical shifts are reported in ppm downfield from internal TMS (δ scale). ^{19}F chemical shifts are reported in ppm from external trifluoroacetic acid.

IR spectra were recorded on a Perkin-Elmer 137 instrument. IR frequencies are reported in wavenumbers (cm^{-1}).

4,4-difluoropiperidine, **1**, was prepared via a sequence of reactions outlined in Scheme 1. All chemicals and solvents are reagent grade, used as received.

N-Trifluoroacetyl-4,4-difluoropiperidine **6**

In chloroform (10 ml) at 20°C, 550 mg (2.82 mmole) of the ketone, **5**, were treated with a stream of SF_4, bubbled vigorously through the reaction mixture via a stainless steel hypodermic needle. Sufficient SF_4 was bubbled into the reaction flask in this manner to inflate a rubber balloon to approximately 8 inches in diameter. Stirring was continued for 3 days under the SF_4 atmosphere. The SF_4 was replenished occasionally when the balloon became limp.[17]

Solvent was removed and the residue was chromatographed (0.25 × 200 × 200 mm silica plate, ethyl acetate eluent) to give *ca.* 400 mg of the amide **6**. $R_f = 0.65$ (65% yield).

IR (NaCl): amide, 1700 cm^{-1}; gem difluoro, 1100–1200; CF_3, 754, 758. NMR ($DCCl_3$): 3,5-CH_2, 2.11 (4H, m); 2,6-CH_2, 3.80 (4H, m); CF_3, 6.64 ppm downfield from external TFA (3F, S); CF_2, 22.85 ppm upfield (2F, quintet, JHF = 12 Hz). Mass Spectrum: *m/e* 217, 48%, Parent; *m/e* 148, 50%, P–CF_3; *m/e* 120, 16%, P–CF_3CO.

4,4-*Difluoropiperidine* 1

The volatile amine, obtained by ether extraction of the basic aqueous hydrolysate and gas chromatographic purification has the following spectral properties:

IR (NaCl): Amine, 3240 cm^{-1}, 780; CF_2, 1120, 1147. NMR ($DCCl_3$): 3.5 CH_2, 1.93 (4H, m); 2.6 CH_2, 2.98 (4H, m, broad); N-H, 1.61 (1H, S); CF_2, 19.84 ppm upfield from external TFA, (2F, m, broad). Mass spectrum: *m/e* 121, 67%, P; *m/e* 120, 100%, P-H; *m/e* 100, 38%, 120 − HF; *m/e* 80, 35%, 100 − HF.

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REFERENCES

[1] An excellent review on this subject is I. D. Blackburne, A. R. Katritzky and Y. Tukeuchi, *Acts. Chem. Res.* **8**, 300 (1975).

[2a] N. L. Allinger *et al.*; *Tetrahedron Letters* 3729 (1967); [b] F. G. Riddell, *Quart. Rev.* 21, 364 (1967).

[3] G. A. Yousif and J. D. Roberts, *J. Am. Chem. Soc.* **90**, 6428 (1968).

[4] P. J. Buckley, C. C. Costain and J. E. Parkin, *Chem. Comm.* 668 (1968).

[5] J. J. Sloan and R. Kewley, *Can. J. Chem.* 47, 3453 (1969).

[6] V. M. Rao and R. Kewley, *Ibid.* 47, 1284 (1969).

[7] D. Daminai and L. Ferrentti, *Chem. Phys. Lett.* **24**, 357 (1974).

[8] R. D. Stowlow, T. W. Giants and J. D. Roberts, *Tetrahedron Letters* 5777 (1968).

[9a] L. H. Scharpen, *24th Symposium on Molecular Structure and Spectroscopy*, Paper 09, Ohio State Univ., Columbus Ohio; [b] S. Armstrong, *Appl. Spectrosc.* **23**, 575 (1969); [c] L. H. Scharpen and V. W. Laurie, *Anal Chem.* **44**, 378R (1972); [d] W. Steinmetz, *J. Am. Chem. Soc.* **96**, 685 (1974); [e] E. M. Bellott, Jr., Doctoral Dissertation, Harvard University (1976).

[10] W. Gordy and R. L. Cook, *Microwave Molecular Spectra*, p. 7. New York, Interscience (1970).

[11a] J. Kraitchman, *Am. J. Phys.* 21, 17 (1953); [b] W. Gordy and R. L. Cook, *Microwave Molecular Spectra*, Chap. 13.

[12] E. M. Bellott and E. B. Wilson, *J. Mol. Spectroscopy* in press.

[13] N. L. Allinger *et al.*, *J. Am. Chem. Soc.* **93**, 1637 (1971); **95**, 3893 (1973); **96**, 5100 (1974); *Idem. Tetrahedron* **30**, 1579 (1974).

[14] N. L. Allinger, private communication.

[15] L. F. Fieser and M. Fieser, *Reagents for Organic synthesis*, Vol. 1, p. 668. Wiley, New York (1967).

[16] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.* **35**, 4000 (1970).

[17] This procedure results in a good yield without the difficulties of the preparation outlined in W. R. Hasek, *et al.*, *J. Am. Chem. Soc.* 72, 543 (1960).

Appendix. Derivation of isotope rule

In case the substitution of one nucleus by an isotope has negligible effects due to the rotation of the principal axes, Kraitchman's equations[11] lead immediately to the result:

$$2a^2 + b^2 + c^2 = (k/\mu)(\Delta I_b + \Delta I_c)$$

where a, b, c are the coordinates of the substituted nucleus in the principal axes of the unsubstituted molecule. Here

$$\mu = \frac{\Delta m \cdot M}{M + \Delta m}$$

where M is the total mass of the original molecule and Δm is the change in mass of the isotopically substituted nucleus. $\Delta I_a = I'_a - I_a$, the change in the **a** principal moment of inertia on isotopic substitution at one nucleus.

But $I_a = k/A$ where $k = (h/8\pi^2)$ and A is the A rotational constant in frequency units.

In near prolate molecules $B \sim C$ so if we let $x = (1/2)(B + C)$, $\delta = (1/2)(B - C)$, δ/x will be relatively small. Then

$$\begin{aligned}\frac{1}{B} + \frac{1}{C} &= \frac{1}{x + \delta} + \frac{1}{x - \delta} \cong \frac{1}{x}\left(1 - \frac{\delta}{x} + \frac{\delta^2}{x^2}\cdots\right) \\ &\quad + \frac{1}{x}\left(1 + \frac{\delta}{x} + \frac{\delta^2}{x^2}\cdots\right) \\ &= \frac{2}{x}\left(1 + \frac{\delta^2}{x^2}\cdots\right) \cong \frac{2}{x} \text{ with neglect}\end{aligned}$$

of $(B - C/B + C)^2$ compared with unity.

$$\begin{aligned}\therefore 2a^2 + b^2 + c^2 &= (4k/\mu)\left(\frac{1}{B' + C'} - \frac{1}{B + C}\right) \\ &= (4k/\mu)\frac{B + C - B' - C'}{(B + C)(B' + C')} \qquad (2)\end{aligned}$$

With near prolate rotors, substitution of an isotope may well cause little change in the direction of the **a** axis but, because $B \cong C$, the **b** and **c** axes are very likely to be turned appreciably around the **a** axis. However, with assumption of a fixed **a** axis, the diagonal sum rule makes $I_b + I_c$ independent of the orientation of **b**, **c** around **a**. Therefore, eqn (2) is correct even if substitution causes a large reorientation of **b**, **c** around **a**.