Conformational Preference of 2-(Halomethyl)- and 2-(Oxymethyl)pyridines: Microwave Spectrum, Ab Initio, and MM3 Studies of 2-(Fluoromethyl)pyridine

Christina Moberg,* Hans Adolfsson, Kenneth Wärnmark, Per-Ola Norrby, Karl-Magnus Marstokk, and Harald Møllendal*

Abstract: One single conformer was assigned from the microwave spectrum of 2-(fluoromethyl)pyridine, investigated in the gas phase in the 26.0–39.0 GHz spectral region at about −10 °C. Its Cα–F bond was found to be coplanar with the ring and *anti* to the N–C2 bond (*syn* to the C2–C3 bond). There was no indication in the microwave spectrum of the presence of other rotameric forms of the molecule.

The results of the spectroscopic study were backed up by ab initio calculations at the MP2/6-31G** (frozen core) level. These calculations predict that the assigned conformer is the only stable form of the molecule. The transition state was calculated to have the CH_2F group 180° from the stable *anti* conformation. The energy of the transition state was computed to be 20.2 kJ mol^{-1} higher than the energy of the *anti* rotamer.

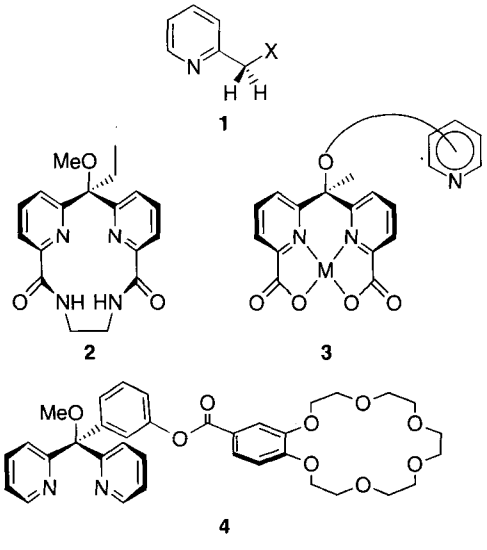
The results are interpreted in terms of a stereoelectronic effect, and the orbital overlaps responsible for the observed effect are discussed. It is shown that 2-(fluoromethyl)pyridine serves as a good model for 2-(alkoxymethyl)pyridines, previously found to show the same conformational preference.

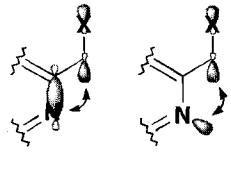
Keywords
ab initio calculations · conformation · microwave spectroscopy · pyridines · stereoelectronic effect

Introduction

A variety of 2-(alkoxymethyl)pyridines (**1**) have been shown by X-ray crystallography to prefer an *anti*-periplanar conformation, with a N-C-C-O torsional angle close to 180°.[1] The tendency to adopt this conformation turned out to be quite pronounced, and it has important consequences for the structure, and thereby the properties, of a number of compounds containing this structural element. This is observed, for example, in 1,1-bis(6-carboxy-2-pyridyl)-1-methoxyalkyl derivatives. The conformational preference results in a bowl-like shape for macrocyclic amides **2**;[1c] it determines whether donating groups present in pendant arm-substituted derivatives, such as **3**, will take part in apical coordination to the metal ion or not,[1f] and it permits bimetallic complexes of crown ether-substituted derivatives such as **4** to adopt an appropriate conformation for simultaneous coordination of the two metal ions to the two functional groups in suitable ω-carboxyolefins.[2]

Ab initio calculations on 2-, 3-, and 4-(hydroxymethyl)-pyridine gave results in accordance with the observed conformations,[3] and suggested that the effect originates from orbital overlap between the antibonding carbon–oxygen σ-bond and the carbon–nitrogen σ-bond (**A**, or carbon–carbon σ-bond in 3- and 4-substituted isomers) and, in the 2-substituted isomer, between the antibonding carbon–oxygen σ-bond and the nitrogen lone pair (**B**).[4, 5] The conformational effect was shown to be quite strong, with a rotational barrier of 20–25 kJ mol^{-1}. It is interesting to note that for (hydroxymethyl)benzene, a conformation with the oxymethyl





[*] Prof. C. Moberg, Dr. H. Adolfsson, Dr. K. Wärnmark
Department of Chemistry, Organic Chemistry
Royal Institute of Technology
S-100 44 Stockholm (Sweden)
Fax: Int. code +(8)791-2333
e-mail: kimo@kth.se

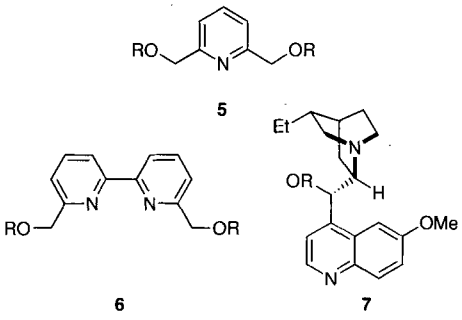
Prof. H. Møllendal, Dr. K.-M. Marstokk
Department of Chemistry, The University of Oslo
P. O. Box 1033, Blindern, N-0315 Oslo (Norway)
e-mail: haraldm@waage.uio.no

Dr P.-O. Norrby
Royal Danish School of Pharmacy, Medicinal Chemistry
Universitetsparken 2, DK-2100 Copenhagen (Denmark)
e-mail: peon@medchem.dfh.dk

0947-6539/96/0205-0516 $ 15.00+.25/0

group situated perpendicular to the plane of the phenyl ring was instead found to be the most stable one.[4]

The observed effect is expected to have consequences also in other situations, since **1** is a common structural element in various types of compounds. Examples are provided by 2-(oxymethyl)-substituted calixarenes,[6] by 2,6-disubstituted pyridine moieties (**5**) in pyridine containing crown-ether-type compounds,[7] and by 2,2′-disubstituted bipyridines (**6**) present



in double-helical complexes made up from oligobipyridine strands[8] and in bipyridine containing crown ethers.[9] The same tendency to prefer a planar conformation was found experimentally also in a 3-substituted oxymethylpyridine group,[1f] a structural element present in, for example, crown ethers incorporating 3,3′-disubstituted bipyridine residues.[10]

Pyridine compounds carrying chiral substituents are currently attracting much attention in asymmetric synthesis.[11] The conformation of the chiral ligand has important implications for the selectivity in the reactions. Since **1** is an important structural element present in many asymmetric ligands, the conformational preference discussed here may be important, at least in the free ligand and in cases where the oxygen does not take part in complexation to the metal ion. A preference for coplanarity of the oxymethylquinoline system was thus observed in ligands used in the osmium-catalyzed dihydroxylation (**7**).[12]

That the planar *anti* conformation is also preferred in solution is indicated by the coordination behavior of pendant arm ligands[1f] as well as by ^{1}H NMR spectroscopic coupling constants.[1e] However, to gain further experimental evidence that the observed effect is not due to crystal packing forces, we wanted to acquire gas-phase data for compounds containing the structural element of interest. We therefore decided to undertake a study using microwave spectroscopy, the appropriate technique for studying the C–C bond rotation. Alkoxymethylpyridines were found not to be suitable for this purpose, owing to their high number of degrees of freedom and their low vapor pressure. The compound 2-fluoromethylpyridine, however, was found to be a good model, since ab initio calculations indicated the same conformational preference as for oxymethylpyridines. The results of the calculations and spectroscopic studies are presented here.

Results and Discussion

Ab initio calculations: The ab initio computations were performed with the Gaussian 92 program package.[13] The standard 6-31 G** basis set, as implemented with the program, was employed. Electron correlation was treated by the MP2 (Møller–Plesset) procedure,[14] which is also included in the Gaussian 92 program. The atom numbering of the title compound is given in Figure 1, which shows the *anti* rotamer. Dihedral angles are 0° when the four atoms N-C2-Cα-F are coplanar and *syn*, and 180° when they are *anti*. A positive dihedral angle corresponds to clockwise rotation.

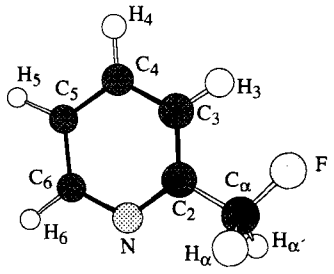


Fig. 1. Atom numbering of 2-(fluoromethyl)pyridine.

The geometry of the conformer with the chain of atoms in the *anti* position (the N-C2-Cα-F dihedral angle is 180°) was fully optimized. It was not initially assumed that this conformer has a symmetry plane (C_s symmetry), but the calculations refined to this geometry within the computational accuracy. No imaginary vibrational frequencies were computed for this rotamer, which indicates that this conformer represents a minimum on the conformational energy surface.[15] The geometry of this rotamer and some other parameters of interest are given in Table 1.

The potential function for rotation around the C2–Cα bond was then calculated. These computations, which were also performed at the MP2/6-31 G** level, were carried out at intervals

Table 1. Structure (bond lengths in Å, angles in °), rotational constants (MHz), dipole moment components (Debye), and energy differences (kJ mol^{-1}) of two selected rotamers of 2-(fluoromethyl)pyridine obtained in ab initio computations at the MP2/6-31 G** (frozen core) level.

Rotamer	*anti*	*syn*		*anti*	*syn*
N–C2	1.345	1.341			
C2–C3	1.395	1.400			
C3–C4	1.394	1.391			
C4–C5	1.394	1.395			
C4–C5	1.395	1.393			
C3–H3	1.080	1.084			
C4–H4	1.083	1.082			
C5–H5	1.082	1.082			
C6–H6	1.084	1.084			
C2–Cα	1.505	1.512			
Cα–F	1.396	1.382			
Cα–Hα	1.091	1.093			
Cα–Hα′	1.091	1.093			
N-C2-C3	123.8	123.3	N-C2-C3-C4	0.0	0.0
C2-C3-C4	118.3	118.9	C2-C3-C4-C5	0.0	0.0
C3-C4-C5	118.8	118.5	C3-C4-C5-C6	0.0	0.0
C4-C5-C6	118.5	118.4	N-C2-C3-H3	180.0	180.0
C2-C3-H3	119.9	120.4	C2-C3-C4-H4	180.0	180.0
C3-C4-H4	120.5	120.6	C3-C4-C5-H5	180.0	180.0
C4-C5-H5	121.3	121.3	C4-C5-C6-H6	180.0	180.0
C5-C6-H6	120.6	120.5	N-C2-Cα-F	180.0	0.0
N-C2-Cα	114.3	117.5	N-C2-Cα-Hα	−60.0	120.5
C2-Cα-F	110.6	111.6	N-C2-Cα-Hα′	+60.0	−120.5
C2-Cα-Hα	110.2	110.0			
C2-Cα-Hα′	110.2	110.0			
A	5 023.3	5 105.2			
B	1 512.8	1 503.9			
C	1 171.2	1 170.2			
$I_a + I_b - I_c$ [a]	3.165	3.158			
μ_a	1.89	2.72			
μ_b	0.65	3.02			
μ_c	0.00	0.00			
ΔE [b]	0.0	20.2			

[a] In uÅ^2. I_a, I_b, and I_c are the principal moments of inertia. Conversion factor: 505379.05 MHz uÅ^2. [b] Energy difference; total energy of *anti*: −385.715945 hartree.

of 30° for the N-C2-Cα-F dihedral angle with full geometry optimization for the remaining structural parameters in each case. The potential function obtained in this manner is drawn in Figure 2. Note that this potential function has only *one* minimum, which corresponds to the *anti* conformer as mentioned above. No other minimum was located at this level of theory, which indicates that one stable rotamer, the *anti*, exists for 2-(fluoromethyl)pyridine. The shape of this curve is very similar to the one for 2-(alkoxymethyl)pyridine.[4]

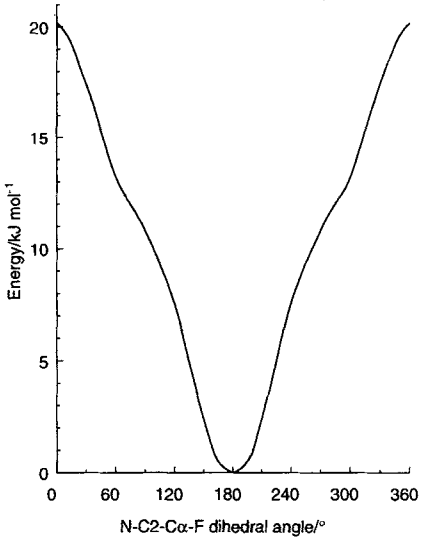


Fig. 2. Potential function for torsion around the C2–Cα bond calculated at the MP2/6-31G** level. The shape of this curve is very similar to that calculated for 2-(hydroxymethyl)pyridine.

The transition state was located at the *syn* (N-C2-Cα-F dihedral angle is 0°) conformation with an energy of 20.2 kJ mol^{-1} above the energy of the stable *anti* form, quite similar to the transition state for (alkoxymethyl)pyridines,[4] which further supports the choice of 2-(fluoromethyl)pyridine as a model compound. This represents the maximum of the potential function drawn in Figure 2. The geometry of the *syn* transition state is given in Table 1. The vibrational frequencies of this conformer were computed and one of them, corresponding to torsion around the C2–Cα bond, was calculated to have an imaginary value. This corresponds to a first-order saddle point, that is, in this case a transition state.[15]

MW spectrum and assignment: The ab initio calculations predict that the conformation having the Cα–F bond *anti* to the N–C2 bond of the ring is the most stable form of the molecule. The rotational constants calculated (Table 1) for this conformer were $A = 5.02$, $B = 1.51$, and $C = 1.17$ GHz, respectively. The asymmetry parameter κ calculated from these constants is -0.82. The components of the dipole moments along the principal inertial axes were calculated by ab initio methods to be $\mu_a = 1.9$, $\mu_b = 0.7$, and (for symmetry reasons) $\mu_c = 0$ Debye. This prolate conformer was then predicted to possess the strong and characteristic *a*-type *R*-branch pile-ups of high K_{-1} lines separated by approximately $B + C = 2.68$ GHz. Such pile-up transitions are modulated at low Stark voltages and generally easy to assign. The microwave spectra taken in the 26–39 GHz spectral region at low field strengths (about 100 Vcm^{-1}) revealed such typical pile-ups very close to their predicted frequencies. The assignments of the *a*-type ground vibrational state transitions were then straightforward with these pile-up transitions as the starting point.

The strongest lines of the *b*-type are the *Q*-branch transitions, and they were searched for next and found with ease. These transitions were much weaker than the ^aR transitions. This is consistent with the ab initio prediction that μ_a is much larger than μ_b (see Table 1). The ^bR transitions were then searched for, but no unambiguous assignments could be made, presumably because these transitions were too weak to be identified with certainty. A total of 124 transitions were measured for the ground state. A portion of this spectrum is listed in Table 2.

Table 2. Selected transitions of the microwave spectrum of the ground vibrational state of 2-(fluoromethyl)pyridine (frequencies in MHz).

Transition $J''_{K''-1,K''+1} \leftarrow J'_{K'-1,K'+1}$			$\tilde{\nu}_{obs}$ [a]	$\tilde{\nu}_{obs} - \tilde{\nu}_{calcd}$
$10_{1,9}$	←	$9_{1,8}$	27238.31	−0.09
$10_{3,7}$	←	$9_{3,6}$	27658.69	−0.08
$10_{7,3}$	←	$9_{7,2}$	26925.65	−0.06
$10_{7,4}$	←	$9_{7,3}$	26925.65	−0.06
$11_{0,11}$	←	$10_{0,10}$	26973.43	−0.14
$11_{2,10}$	←	$10_{2,9}$	28741.39	0.02
$11_{5,6}$	←	$10_{5,5}$	29747.92	−0.12
$11_{9,2}$	←	$10_{9,1}$	29594.00	0.10
$11_{9,3}$	←	$10_{9,2}$	29594.00	0.10
$12_{1,11}$	←	$11_{1,10}$	31958.63	−0.02
$12_{5,8}$	←	$11_{5,7}$	32488.95	−0.01
$12_{8,4}$	←	$11_{8,3}$	32319.92	−0.10
$12_{8,5}$	←	$11_{8,4}$	32319.92	−0.10
$13_{1,12}$	←	$12_{1,11}$	34248.65	0.08
$13_{2,11}$	←	$12_{2,10}$	36532.34	0.00
$13_{4,10}$	←	$12_{4,9}$	35322.28	0.00
$13_{9,4}$	←	$12_{9,3}$	35004.58	0.08
$13_{9,5}$	←	$12_{9,4}$	35004.58	0.08
$14_{0,14}$	←	$13_{0,13}$	33959.00	0.01
$14_{5,10}$	←	$13_{5,9}$	38009.48	−0.01
$15_{1,14}$	←	$14_{1,13}$	38798.73	0.04
$16_{0,16}$	←	$15_{0,15}$	38633.82	0.02
$16_{4,13}$	←	$16_{3,14}$	28680.65	0.06
$19_{5,15}$	←	$19_{4,16}$	33687.82	0.00
$22_{3,19}$	←	$22_{2,20}$	33360.69	0.05
$25_{6,19}$	←	$25_{5,20}$	30003.62	−0.12
$31_{7,24}$	←	$31_{6,25}$	33435.74	0.08
$34_{7,27}$	←	$34_{6,28}$	31190.97	0.04
$37_{8,29}$	←	$37_{7,30}$	36698.13	−0.04
$41_{8,33}$	←	$41_{7,34}$	36413.80	−0.03

[a] $\tilde{\nu}_{obs}$ = observed frequency; $\tilde{\nu}_{calcd}$ = calculated frequency; ±0.10 MHz.

The maximum value of the *J* quantum number for the ^aR transitions is 16, and the maximum value of *J* for the ^bQ transitions is 41. A least-squares fit involving all the five Watson quartic centrifugal distortion constants in the *A* reduction I^r representation[16] was first made. However, it turned out that the value of Δ_{JK} obtained in this way was very uncertain. This constant was therefore preset to zero in the final fit, which has a root-mean-square deviation comparable to the experimental uncertainty (±0.10 MHz). Inclusion of sextic centrifugal distortion constants[16] yielded no improvement. The spectroscopic constants are listed in Table 3.

As observed in Table 3, $\Delta = I_a + I_b - I_c = 3.46954(36)$ uÅ^2 (I_a, I_b, and I_c are the principal moments of inertia). This value is typical for molecules having a symmetry plane and two out-of-plane methylene hydrogens.[17] Two conformations of 2-(fluoromethyl)pyridine are compatible with this, namely the *syn* and the *anti* forms, as observed in Table 1, where Δ is calculated to be about 3.2 uÅ^2 for both *syn* and *anti* conformers. The rotational constants are generally rather different for different

0947-6539/96/0205-0518 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 5

Table 3. Spectroscopic constants [a,b] of the ground and vibrationally excited states v of 2-(fluoromethyl)pyridine.

Vibrational state	$v_T = 0$	$v_T = 1$	$v_T = 2$	$v_T = 3$	$v_T = 4$	$v_T = 5$	$v_{O.P.} = 1$
no. of transitions	124	108	91	51	46	52	51
r.m.s. dev. [c]/MHz	0.074	0.088	0.091	0.088	0.080	0.082	0.073
A_v/MHz	5047.0583(74)	5035.7138(92)	5024.038(14)	5011.89(10)	4999.685(81)	4986.956(82)	5018.15(11)
B_v/MHz	1509.4357(14)	1508.6457(18)	1507.8334(21)	1506.9883(29)	1506.1151(28)	1505.1961(27)	1509.5352(24)
C_v/MHz	1171.2767(14)	1173.0385(19)	1174.9303(21)	1176.9437(39)	1179.1086(36)	1181.4366(34)	1172.0806(32)
Δ_J/kHz	0.1022(40)	0.0975(53)	0.1031(63)	0.0749(86)	0.0821(87)	0.0866(83)	0.0537(75)
Δ_{JK}/kHz	0.0 [d]	0.0 [d]	0.0 [d]	0.126(16)	0.136(20)	0.118(16)	0.117(17)
Δ_K/kHz	1.49(14)	1.93(19)	1.39(27)	0.0 [d]	0.0 [d]	0.0 [d]	0.0 [d]
δ_J/kHz	0.020072(33)	0.02303(45)	0.02007(61)	0.0 [d]	0.0 [d]	0.0 [d]	0.0 [d]
δ_K/kHz	0.195(12)	0.169(16)	0.198(25)	0.0 [d]	0.0 [d]	0.0 [d]	0.0 [d]
$(I_a + I_b - I_c)$ [e]	3.46954(36)	4.51851(48)	5.62589(58)	6.7936(31)	8.0225(25)	9.3298(25)	4.3202(31)

[a] A reduction, I^r representation. [b] Uncertainties represent one standard deviation. [c] Root-mean-square deviation. [d] Preset at zero. [e] Conversion factor 505379.05 MHz u Å^2.

conformations and can often be used in a straightforward manner to decide which conformer has been assigned. Fortuitously, the rotational constants of *syn* and *anti* obtained by ab initio computations do not differ greatly in this case (Table 1) and some other evidence must be employed in addition to the rotational constants to make an unambiguous conformational assignment. One such piece of evidence is the spectral line intensity, which shows that μ_a is considerably larger than μ_b. This is predicted for *anti*, while the opposite is the case for *syn* (Table 1). In addition, the ab initio predictions (above) indicate that *anti* is the only stable form of the molecule, whereas *syn* represents a transition state.

Several attempts were made to resolve the Stark effects of some of the transitions in order to determine the dipole moment. However, the spectrum was not intense enough to display well-resolved Stark components that could be used for quantitative measurements, and only some semiquantitative measurements could be made yielding dipole moment components of approximately 2.2 Debye for μ_a and 0.7 Debye for μ_b. These values are in good agreement with the ab initio results (Table 1) and give an additional indication that the *anti* conformer has indeed been assigned and not confused with *syn* which would have had a similar value for Δ, but a rather different dipole moment. The final conclusion is that the spectrum in Table 2 undoubtedly belongs to the *anti* conformer.

Vibrationally excited states: The ground-state spectrum was accompanied by several satellite spectra which could readily be ascribed to vibrationally excited states of the C2–Cα torsional fundamental vibration. The rotational transitions of the successively excited states of this mode were shown to be separated by roughly constant frequency intervals with the intensities decreasing by about 25% upon excitation by one vibrational quantum. This behavior is typical for a nearly harmonic vibration.[18]

Five excited states of the torsion were ultimately assigned, as shown in Table 3. *a*- and *b*-type transitions were assigned for the first and second excited states, whereas only *a*-type lines were assigned for the remaining excited states. Four of Watson's quartic centrifugal distortion constants[16] were used in the least-squares fit of the first and second excited states, while only two such constants were used for the remaining excited states. A satisfactory fit was achieved in each case.

In Table 3 it is shown that Δ increases rather smoothly with the vibrational quantum number. Again, this is typical for a near-harmonic out-of-plane mode,[18] which must be the C2–Cα torsional mode. Relative intensity measurements performed largely as described in ref. [19] with carefully selected lines of the ground and first excited state yielded 53(15) cm^{-1} for the torsional fundamental. This is close to the 57 cm^{-1} that was predicted in the MP2/6-31G** computations (not given in Table 1).

The changes in Δ upon excitation can be used to calculate the torsional vibration frequency, provided it is well separated from other vibrational modes.[20] This criterion is met rather well in the present case, as the second lowest vibration is found experimentally to be 162(20) cm^{-1} (see below). From ref. [20], we know that the torsional frequency ω_T in such cases is approximated by $\omega_T \approx 67.45/\delta\Delta$ u Å^2 cm^{-1} where $\delta\Delta$ is taken as the change in Δ between the first excited and ground state. From the values given in Table 3, the torsional fundamental frequency is found to be $\omega_T \approx 64$ cm^{-1}, close to 53(15) cm^{-1} obtained by relative intensity measurements above. The uncertainty limit of the torsional fundamental obtained in this manner is hard to estimate, but ± 8 cm^{-1} seems plausible. Our best estimate of the torsional frequency ω_T is thus 64(8) cm^{-1}, and this frequency is used below to derive the shape of the potential well for torsion near the well bottom.

It is seen in Table 3 that in addition to the five excited torsional states, the first excited state of what is presumed to be the second lowest out-of-plane vibration has been identified. Our reason for assigning this excited state as an out-of-plane vibration is the fact that Δ increases.[18, 20] Relative intensity measurements[19] yielded 162(20) cm^{-1} for this vibration, compared with 189 cm^{-1} from the MP2/6-31G** computations. The only other vibration with a calculated frequency below 300 cm^{-1} is an in-plane substituent bending (at 220 cm^{-1}, or 214 cm^{-1} from MM3, vide infra), with $\delta\Delta$ expected to be negative.[18]

All the strong lines as well as nearly all transitions of intermediate intensities in this spectrum were assigned to the ground and the six excited states of the *anti* rotamer. This is one indication that the *anti* is much more stable than any other hypothetical rotameric form, because the ab initio calculations reported above predict that such forms will have comparatively large dipole moments and would hence have strong MW spectra provided they were present in significant amounts. In fact, the MP2/6-31G** prediction that *anti* is the only stable conformer is in agreement with the MW observations.

The C_s symmetry of 2-(fluoromethyl)pyridine: The nonzigzagging behavior of the rotational constants described in the previous section rules out a low or intermediate barrier to the planar form,[20, 21] but instead indicates that the torsional mode is nearly harmonic and that *anti* 2-(fluoromethyl)pyridine thus has a *planar* (with the exception of the two methylene hydrogen

atoms) equilibrium conformation. Gwinn and co-workers[21, 22] have given a quantitative treatment of this problem. They have shown that it is possible to define a potential function for the torsion of the form given in Equation (1), where z is a dimensionless coordinate. If B is *positive*, the molecule has a symmetry plane; if B is *negative* a potential hump exists at the planar conformation and the potential function of the *anti* conformer would be of the double-minimum type. The equilibrium conformation would in such a case be nonplanar.

$$V = A\,(\langle z^4\rangle + B\langle z^2\rangle) \qquad (1)$$

The Gwinn theory[21, 22] implies that rotational constants can be expanded in a power series of the expectation values of z^2 and z^4, where b_n is the A_n, B_n or C_n rotational constant in the nth excited state of the torsion. b_0, b_2, and b_4 are empirical parameters adjusted to give the best fit to the data. The values of $\langle z^2\rangle_n$ and $\langle z^4\rangle_n$ depend only on the value of B constant of Equation (1).

The rotational constants of successively excited states of the torsional vibration were least-squares fitted to Equation (2) em-

$$b_n = b_0 + b_2\langle z^2\rangle_n + b_4\langle z^4\rangle_n \qquad (2)$$

ploying the computer programs described in ref. [23] for a series of B values. It was found that the value $B = 2.8$ yielded the best overall fit (Table 4). This positive value of B is further evidence that the *anti* conformer indeed has C_s symmetry with no potential hump at the planar form.

Table 4. Comparison of calculated and observed rotational constants (MHz); B is taken to be 2.8.

v_T	A_v [a]	A_v calcd − obs [b]	B_v [a]	B_v calcd − obs [b]	C_v [a]	C_v calcd − obs [b]
0	5047.102	0.043	1509.430	−0.005	1171.289	0.013
1	5035.665	−0.049	1508.648	0.003	1173.006	−0.032
2	5023.893	−0.145	1507.826	−0.007	1174.939	0.009
3	5012.002	0.112	1506.988	0.000	1176.966	0.022
4	4999.754	0.069	1506.118	0.003	1179.114	0.005
5	4986.866	−0.090	1505.197	0.001	1181.432	−0.004

A_v [a] = 5052.85(19) − 19.66(42) $\langle z^2\rangle_v$ − 5.38(13) $\langle z^4\rangle_v$
B_v [a] = 1509.818(8) − 1.297(18) $\langle z^2\rangle_v$ − 0.404(5) $\langle z^4\rangle_v$
C_v [a] = 2233.29(13) + 24.20(35) $\langle z^2\rangle_v$ + 4.79(11) $\langle z^4\rangle_v$

[a] Calculated rotational constants (MHz) for the $v_T = 0$ through $v_T = 5$ torsional states; see text. [b] Observed values, "obs", refer to the experimental rotational constants listed in Table 3. The values of the calculated rotational constants were obtained from the equations appearing at the bottom of this table.

The A constant [Eq. (1)] was then adjusted to reproduce the torsional fundamental frequency of 64 cm^{-1}. This was achieved with $A = 15.7$ cm^{-1}. The potential function derived in this manner is $V = 15.7(\langle z^4\rangle + 2.8\langle z^2\rangle)$ cm^{-1}. It is sketched in Figure 3 and presumed to give a fairly accurate description of the potential function near the bottom of the potential well (*anti*).

Structure of *anti*-2-(fluoromethyl)pyridine: The experimental rotational constants shown in Table 3 are quite close (better than 1%) to their theoretical counterparts in Table 1. Some discrepancies are to be expected because the theoretical rotational constants are approximations of the equilibrium structure, while the experimental rotational constants are "contaminated" by zero-point vibrational effects. A "methodological" difference of roughly 1–3% is therefore to be expected. The good

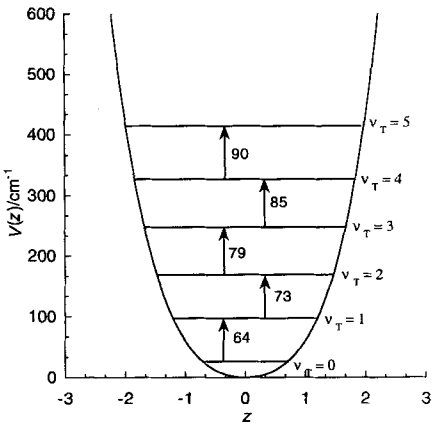


Fig. 3. Potential function $V = 15.7(\langle z^4\rangle + 2.8\langle z^2\rangle)$ cm^{-1} presumed to describe the bottom of the potential well near its *anti* minimum quite accurately. The ground state lies 30 cm^{-1} above the bottom. Eigenstates of the first six torsional states are indicated. Microwave spectra of these states have been assigned.

agreement seen here is one indication that the MP2/6-31G** structure is close to the "real" equilibrium structure.

Further evidence supporting the *anti* structure in Table 1 is the fact that the structural parameters of the pyridine ring are all close to the highly accurate structure of pyridine.[24] The structural parameters of the $-CH_2F$ group are close to their counterparts in CH_3F.[25] It is presumed that the structure of *anti* in Table 1 will prove to be very close to any experimental structure that might be determined in the future.

MM3 calculations: MM3 is a recent molecular mechanics force field developed by Allinger et al.[26] As opposed to the ab initio approach described above, the molecular mechanics method, which is based on a classic treatment of interatomic forces, requires specific parameters for each unique structural unit appearing in the molecule of interest. As was shown previously,[4] the α-substituted 2-methylpyridine motif is not parameterized in MM3.[26] For the alkoxymethylpyridines, it was found that the common practice of "similarity parameterization" (i.e., copying torsional parameters from similar subunits[27]) gave very bad results. New parameters were developed for the specific 2-oxymethylpyridine subunit.[4] With the calculated rotational profile at hand, we decided to perform a similar parameterization of the torsional parameters for the F-C_{sp^3}-C_{sp^2}-N_{sp^2} moiety. It should be noted here that the torsional parameters for the F-C_{sp^3}-C_{sp^2}-C_{sp^2} moiety,[28] which influences the same rotational profile, are tentative. Any future update of the F-C_{sp^3}-C_{sp^2}-C_{sp^2} moiety will require a corresponding change in the F-C_{sp^3}-C_{sp^2}-N_{sp^2} moiety.

A fully optimized rotational profile[29] was determined at the MP2 level. Therefore, it was not necessary to utilize the resource-saving methodology described in our earlier work.[4] Instead, the initial values of the three new torsional parameters were set to zero, and the fully optimized rotational profile was calculated by MM3 with the same resolution as for the ab initio work. A new set of parameters was calculated by fitting the *difference* between the two profiles to the MM3 torsional energy function [Eq. (3)].[26] The procedure was repeated iteratively until no further improvement in the parameters could be ob-

$$E_{tor} = 0.5(v_1\cos\omega - v_2\cos 2\omega + v_3\cos 3\omega) \qquad (3)$$

0947-6539/96/0205-0520 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 5

tained. The final set of optimized parameters was: $v_1 = 2.8260$, $v_2 = -0.4920$, $v_3 = -0.5430$.

MM3 has been parameterized to reproduce microwave data whenever possible.[26] It was therefore expected that calculations with MM3 including the additional parameters determined here would yield results corresponding very well to the experimental observations. In order to verify this assumption, rotational constants and vibrational frequencies were calculated for the *anti* isomer. The obtained rotational constants were $A = 5.09$, $B = 1.50$, and $C = 1.16$ GHz. These values are very close to the experimental results (Table 3), and indeed give an even better agreement than the ab initio calculated values (Table 1). It should be noted here that part of the better correspondence in the MM3 calculations comes from the use of r_z bond lengths in the determination of moments of inertia, not the r_e values generally resulting from ab initio geometry optimizations. The torsional harmonic frequency is calculated to be 57.5 cm^{-1}. This of course corresponds almost exactly to the MP2/6-31G** calculations used in the parameterization of this specific potential. The other experimentally determined vibration, the out-of-plane bending that was observed at 162 cm^{-1}, was calculated at 180 cm^{-1} by MM3, as compared with 189 cm^{-1} from the ab initio calculations.

Stereoelectronic effects: The strong preference for *anti* conformation in 2-oxymethylpyridines (the homoanomeric effect) was interpreted mainly in terms of orbital overlap between the ring nitrogen and the C–O antibonding orbital. Purely electrostatic effects and lone-pair repulsion (disfavoring the *syn* conformation) were found to contribute strongly whereas hyperconjugation (favoring out-of-plane conformations) only had a small influence on the torsional potential. For 2-fluoromethylpyridines, a similar analysis was performed by studying the variation in Mulliken populations along the rotational profile. In addition to the C_s-symmetrical *syn* and *anti* conformations, the *perpendicular* conformation (with a fixed N-C-C-F dihedral angle of 90°) will be discussed.

Compared with the previously studied oxymethylpyridines, the effect of hyperconjugation seems to be more pronounced in fluoromethylpyridine. The Mulliken overlap population increases between C2 and Cα when going from a planar to a *perpendicular* conformation. At the same time, Mulliken electron density is relocated to fluorine from the aromatic ring, especially C3 and C5. However, the *perpendicular* conformation is not a minimum; the effect of hyperconjugation is only to widen the potential well, giving a small negative v_2 parameter in the MM3 torsional energy expression [Eq. (3)].

The overlap between Cα and F is at a maximum in the *syn* conformation, and decreases because of hyperconjugation when going to the *perpendicular* conformation. The decrease continues (albeit only slightly) when going to the *anti* conformation, showing that electron donation to the antibonding Cα–F orbital is even more efficient from the nitrogen than from the aromatic ring, explaining the low energy of the *anti* conformation. In addition to this, there is also a strong electrostatic repulsion between F and N, which further destabilizes the *syn* conformation. This repulsion causes a reduction of the electron density on the proximal heteroatoms in the *syn* conformation, in effect depolarizing the C–N and C–F bonds slightly.

Conclusions

2-(Fluoromethyl)pyridine serves as a good model for 2-(alkoxymethyl)pyridines, as shown by the similar theoretical potential curve shapes and similar rotational barriers. The compound has one single stable conformation in which the N-C-C-F dihedral angle is 180° (C_s symmetry), as shown theoretically as well as experimentally in this work. This conformation is similar to that observed experimentally also in 2-(alkoxymethyl)pyridines. The tendency to adopt this conformation is due to stereoelectronic interactions resulting from orbital overlap between the antibonding carbon heteroatom (O, F) bond and both the C2–N σ-bond and nitrogen lone pair in the *anti* conformation, as well as from electrostatic repulsion in the *syn* conformation, thus representing a homoanomeric effect. The observed effect has important consequences for the design of conformationally restricted compounds containing these structural elements.

As expected, MM3 calculations with well-determined parameters give at least as good gas-phase structures and energetics as ab initio calculations at the MP2/6-31G** level.

Experimental Section

General: ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 400 MHz, 100.6 MHz, and 376.5 MHz, respectively. The ab initio computations were run on the Cray Y-MP computer in Trondheim and the IBM-RS6000 cluster in Oslo.

2-(Fluoromethyl)pyridine: To a solution of 18-crown-6 (1.12 g, 4.25 mmol) in 80 mL acetonitrile was added potassium fluoride (9.9 g, 170 mmol) and 2-(chloromethyl)pyridine (10.8 g, 85 mmol) in 20 mL acetonitrile. The reaction mixture was refluxed for 7 d; after cooling, aq. $NaHCO_3$ (150 mL) was added and the mixture was extracted with diethyl ether (3 × 150 mL). The combined ether phases were washed with H_2O (3 × 200 mL) and dried (Na_2SO_4), and the solvent was distilled off under atmospheric pressure. Distillation of the remaining crude product yielded 2-(fluoromethyl)pyridine as a colorless oil (993 mg, 11%); b.p. 80 °C (12 mmHg); ^1H NMR (400 MHz/$CDCl_3$/TMS): $\delta = 5.48$ (d, 2H, $J_{H,F} = 47.7$ Hz, CH_2), 7.24 (dd, 1H, $J = 7.7$ and 4.8 Hz, 5-pyridyl), 7.45 (d, 1H, $J = 7.7$ Hz, 3-pyridyl), 7.74 (td, 1H, $J = 7.7$ and 1.5 Hz, 4-pyridyl), 8.57 (d, 1H, $J = 4.8$ Hz, 6-pyridyl); ^{13}C NMR (100.6 MHz/$CDCl_3$/TMS): $\delta = 84.47$ (d, $J_{\alpha,F} = 169.5$ Hz, C-α), 120.55 (d, $J_{3,F} = 6.0$ Hz, C-3), 123.05 (s, C-5), 136.89 (s, C-4), 149.27 (s, C-6), 156.44 (d, $J_{2,F} = 21.4$ Hz, C-2); ^{19}F NMR (376.5 MHz/$CDCl_3$/$CFCl_3$): $\delta = -203.42$ (t, $J_{F,H_2} = 47.7$ Hz). The compound was stored as its hydrochloride salt and liberated with sodium carbonate prior to use [30].

Microwave spectroscopy: The MW spectrum was studied with the Oslo spectrometer described in ref. [31]. The 26.0–39.0 GHz spectral region was investigated with the microwave absorption cell cooled to about −10 °C. Some measurements were also made in lower frequency regions. Lower temperatures, which would have increased the intensities of the spectral lines, were not employed, owing to the low vapor pressure of the compound. The pressure was about 3–9 Pa when the spectra were recorded and stored electronically by means of the computer programs written by Waal [32]. The accuracy of the spectral measurements is presumed to be better than ±0.10 MHz. The ^{14}N nucleus can display quadrupole interaction with the molecular rotation. However, no transitions were found to be split by this interaction [33].

Acknowledgements: Mrs. Anne Horn is thanked for drawing the figures and for experimental assistance. This work was supported by the Norwegian Supercomputer Committee (TRU) of the Norwegian Research Council through a grant of computer time and by the Swedish Natural Science Research Council.

Received: September 18, 1995 [F215]

[1] a) I. Csöregh, B. Elman, C. Moberg, *Acta Chem. Scand. Ser. B* **1988**, *42*, 339–344; b) I. Csöregh, B. Elman, K. Högberg, C. Moberg, M. Nygren, *Inorg. Chem.* **1988**, *27*, 235–240; c) C. Moberg, K. Wärnmark, I. Csöregh, A. Ertan, *J. Org. Chem.* **1991**, *56*, 3339–3344; d) I. Csöregh, A. Ertan, C. Moberg, K. Wärnmark, *Acta Cryst.* **1991**, *C47*, 2171–2176; e) A. Ertan, I. Csöregh, K. Wärnmark, L. Mäler, C. Moberg, *Inorg. Chim. Acta* **1993**, *203*, 21–27; f) H. Adolfsson, K. Wärnmark, C. Moberg, *J. Org. Chem.* **1994**, *59*, 2004–2009; g) A. Ertan, I. Csöregh, H. Adolfsson, C. Moberg, *Acta Cryst.* **1995**, *C51*, 385–392.

[2] M. Cernerud, K. Wärnmark, C. Moberg, *Tetrahedron Lett.* **1994**, *35*, 5473–5476.

[3] Only conformations without potential for hydrogen bonding were investigated.

[4] P.-O. Norrby, K. Wärnmark, B. Åkermark, C. Moberg, *J. Comput. Chem.* **1995**, *16*, 620–627.

[5] MM2 and MM3 did not have parameters for the 2-oxymethylpyridine subunit. Simple "analogy parameterization" resulted in low rotation barriers and nonplanar minima (ref. [4]).
[6] S. Pappalardo, L. Giunta, M. Foti, G. Ferguson, J. F. Gallagher, B. Kaitner, *J. Org. Chem.* **1992**, *57*, 2611–2624.
[7] a) C. J. van Staveren, H. J. den Hertog, Jr, D. N. Reinhoudt, J. W. H. M. Uiterwijk, L. Kruise, S. Harkema, *J. Chem. Soc. Chem. Commun.* **1984**, 1409–1411; b) E. Weber, H.-J. Köhler, K. Pannerselvam, K. K. Chacko, *J. Chem. Soc. Perkin Trans. 2* **1990**, 1599–1605; c) E. Weber, R. Pollex, M. Czugler, *J. Org. Chem.* **1992**, *57*, 4068–4070.
[8] a) J.-M. Lehn, A. Rigault, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1095–1097; b) U. Koert, M. M. Harding, J.-M. Lehn, *Nature* **1990**, *346*, 339–342.
[9] a) G. R. Newcome, H. C. R. Taylor, F. R. Fronzek, T. J. Delord, *J. Org. Chem.* **1984**, *49*, 2961; b) G. R. Newkome, D. K. Kohli, F. Fronczek, *J. Chem. Soc. Chem. Commun.* **1980**, 9–11.
[10] a) J. Rebek, Jr, J. E. Trend, R. V. Wattley, S. Chakravorti, *J. Am. Chem. Soc.* **1979**, *101*, 4333–4336; b) J. Rebek, Jr, R. V. Wattley, *J. Am. Chem. Soc.* **1980**, *102*, 4853–4854.
[11] G. Chelucci, *Gazz. Chim. Ital.* **1992**, *122*, 89–98.
[12] a) J. S. Svendsen, I. Markó, E. N. Jacobsen, C. P. Rao, S. Bott, K. B. Sharpless, *J. Org. Chem.* **1989**, *54*, 2263–2264; b) R. M. Pearlstein, B. K. Blackburn, W. M. Davis, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 639–641.
[13] J. M. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, J. A. Pople, *Gaussian 92, Revision C*, Gaussian, Pittsburgh PA, **1992**.
[14] C. Møller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618–622.
[15] W. J. Hehre, L. Radom, P. v. R. Schleyer, J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, **1985**, p. 227.
[16] J. K. G. Watson, in *Vibrational Spectra and Structure, Vol. 6* (Ed.: J. R. Durig) Elsevier, Amsterdam, **1977**, pp. 1–89.
[17] Landolt-Börnstein, *Numerical Data and Functional Relationships in Science and Technology*, New Series, *Vol. II/7* (Ed.: K.-H. Hellwege), Berlin, **1976**; *Vol. II/15*, **1987**; *Vol. II/21*, **1992**.
[18] D. R. Herschbach, V. W. Laurie, *J. Chem. Phys.* **1962**, *37*, 1668–1686.
[19] A. S. Esbitt, E. B. Wilson, *Rev. Sci. Instrum.* **1963**, *34*, 901–907.
[20] Y. Hanyu, C. O. Britt, J. E. Boggs, *J. Chem. Phys.* **1966**, *45*, 4725–4728.
[21] W. D. Gwinn, A. S. Gaylord, *International Review of Science, Physical Chemistry, Series Two*, Vol. 3, Butterworths, London and Boston, **1976**, pp. 205–261.
[22] A. C. Legon, *Chem. Rev.* **1980**, *80*, 231–262.
[23] K.-M. Marstokk, H. Møllendal, S. Samdal, E. Uggerud, *Acta Chem. Scand.* **1989**, *43*, 351–363.
[24] W. Pyckhout, N. Horemans, C. van Alsenoy, H. J. Geise, D. W. H. Rankin, *J. Mol. Struct.* **1987**, *156*, 315–329.
[25] T. Egawa, S. Yamamoto, M. Nakata, K. Kuchitsu, *J. Mol. Struct.* **1987**, *156*, 213–228.
[26] a) N. L. Allinger, Y. H. Yuh, J.-H. Lii, *J. Am. Chem. Soc.* **1989**, *111*, 8551–8566; b) J.-H. Lii, N. L. Allinger, *J. Am. Chem. Soc.* **1989**, *111*, 8566–8575; c) J.-H. Lii, N. L. Allinger, *J. Am. Chem. Soc.* **1989**, *111*, 8575–8582.
[27] N. L. Allinger, X. Zhou, J. Bergsma, *J. Mol. Struct. (THEOCHEM)* **1994**, *312*, 69–83.
[28] Current parameters for the F-C_{sp^3}-C_{sp^2}-C_{sp^2} moiety: $v_1 = 1.243$, $v_2 = 1.445$, $v_3 = -1.243$.
[29] When determining a fully optimized rotational profile, the dihedral angle under study is fixed, whereupon the total energy of the system is minimized with respect to all remaining degrees of freedom. By performing the operation for several different values of the fixed dihedral angle, a potential energy profile for the rotation around one specific bond is obtained.
[30] Attempted preparation from tetrabutylammonium fluoride, following a published procedure, in our hands resulted in considerably lower yield and remaining starting material, which was difficult to separate from the product.
[31] G. A. Guirgis, K.-M. Marstokk, H. Møllendal, *Acta Chem. Scand.* **1991**, *45*, 482–490.
[32] Ø. Waal, *Cand. Scient. Thesis*, University of Oslo, **1995**.
[33] The full ground-state spectrum and the spectra of the vibrationally excited states are available from the authors upon request, or from the Molecular Spectra Data Center, National Institute for Standards and Technology, Molecular Physics Division, Bldg. 221, Room B265, Gaithersburg, Maryland 20899 (USA).

0947-6539/96/0205-0522 $ 15.00+.25/0