^{13}C NMR Chemical Shift Calculations for Some Substituted Pyridines: A Comparative Consideration†

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For three series of mono-, di-, and trisubstituted pyridines, respectively, available incremental methods and calculation programs for estimating the corresponding ^{13}C NMR chemical shifts were employed and compared with the results obtained. The following methods and programs were used for testing them for their accuracy: simple pyridine increments, a simplified increment calculation on the base of benzene increments (program AROSIM[1,2]), the calculation method of Fürst and Pretsch[3−6] (Carbon-13 module for ChemWindows), SPECAL from Specinfo[7] (a database founded calculation program), CSPEC2,[8,9] gNMR,[10] CNMR,[11] and HyperNMR,[12] respectively.

INTRODUCTION

In the last few years a number of computer programs for ^{13}C chemical shift calculation were developed.[1−15] These programs have been used both in education and also in chemical research. It is the major objective of this paper to employ these kinds of computer programs for calculating the ^{13}C NMR spectra of three series of differently substituted pyridines **1**−**34** in order to test the corresponding applicability.

In detail the following questions will be answered: (1) What are the basic principles of the corresponding program? (2) What kind of algorithm is used to calculate the ^{13}C NMR chemical shifts? (3) How accurate are the calculations?

To answer these questions, two series of di- (**1**−**16**) and trisubstituted pyridines (**17**−**25**) were studied experimentally by employing the whole arsenal of 1D and 2D NMR spectroscopic methods (semiselective INEPT,[16] HMBC,[17] and HMQC,[18] respectively); hereby, the ^{13}C NMR chemical shifts of these compounds could be assigned unequivocally. The ^{13}C chemical shifts are given in Tables 1 and 2.

The ^{13}C NMR spectra of these compounds are not yet published in the literature; a good supposition to test available computer programs unbiased. This procedure has a number of further advantages:

(1) The application of substituent chemical shifts (SCS), estimated for substituted benzenes, was studied in detail previously;[2,19−24] for substituted pyridines only a few data are available.[20]

(2) For compounds not yet published, their ^{13}C chemical shifts are not yet available in data bases.

(3) The substituted pyridines are small molecules and the programs can show their power of prediction. Programs which have problems with these small molecules are expected to be even less suitable for larger molecules.

For these reasons, the programs (incremental systems, data bases, chemical shift calculation programs) tested in this paper are of about the same supposition to predict the ^{13}C chemical shifts of the compounds studied. The ^{13}C chemical shifts, calculated in this manner, will be compared with the experimental values; the standard deviation will be calculated and discussed adequately.

Table 1. ^{13}C Chemical Shifts of Experimentally Investigated Disubstituted Pyridines (δ/ppm in $CDCl_3$/TMS-Internal) **1**−**16**

no.	substituents	C-2	C-3	C-4	C-5	C-6
1	2,3-Cl	149.4	130.8	138.9	123.5	147.4
2	2-NH_2, 3-NO_2	153.6	128.3	135.3	113.6	155.8
3	2-Cl, 3-NO_2	143.5	144.9	134.4	123.3	152.6
4	2-NH_2, 4-CH_3	158.9	109.1	148.9	115.6	147.8
5	2-NH_2, 5-Cl	157.0	109.6	137.7	121.1	146.6
6	2-NH_2, 5-I	157.5	111.0	145.5	78.0	153.9
7	2-NH_2, 5-CH_3	157.0	108.5	138.7	122.5	147.5
8	2-NH_2, 5-NO_2	157.3	125.0	133.8	143.5	145.6
9	2-Br, 5-Cl	139.7	129.1	138.4	131.8	149.1
10	2-Br, 5-CH_3	139.1	127.6	139.5	132.6	150.6
11	2,5-Br	140.5	129.6	141.2	120.1	151.3
12	2-OH, 5-Cl	164.3	121.1	132.9	114.3	142.8
13	2-NH_2, 6-CH_3	158.2	105.2	138.2	113.2	156.9
14	2,6-Cl	150.7	123.0	140.9	123.0	150.7
15	2,6-NH_2	157.8	97.9	139.8	97.9	157.8
16	3,5-Br	149.2	120.5	141.0	120.5	149.5

Table 2. ^{13}C NMR Chemical Shifts of Experimentally Investigated Trisubstituted Pyridines (δ/ppm in $CDCl_3$/TMS-Internal) **17**−**25**

no.	substituents	C-2	C-3	C-4	C-5	C-6
17	2-NH_2, 3-Br, 5-Cl	154.2	104.2	139.7	120.5	145.5
18	2-NH_2, 3-Cl, 5-Br	153.8	115.5	138.9	107.1	146.9
19	2-NH_2, 3-CH_3, 5-Br	156.1	118.7	139.9	108.3	146.1
20	2-NH_2, 3-Cl, 5-CH_3	152.8	114.9	137.8	124.4	146.1
21	2-Br, 3-Cl, 5-CH_3	138.4	132.7	138.9	134.2	148.1
22	2-Br, 3-CH_3, 5-Cl	142.2	136.6	138.4	131.3	146.0
23	2,3-Br, 5-Cl	141.5	124.1	141.1	131.9	147.0
24	2-Br, 3-NO_2, 6-Cl	133.5	146.0	136.3	124.2	153.4
25	2-NH_2, 4,6-CH_3	158.5	106.0	149.1	114.6	156.4

THEORY

(A) Substituent-Induced Chemical Shifts (SCS). The calculation of the ^{13}C chemical shifts of substituted benzenes (and other aromatic compounds) without any correction for mutual steric and/or electronic interactions of nearby substituents is usually carried out by means of eq 1.

† Dedicated to Prof. Dr. rer. nat. habil. Reiner Radeglia on the occasion of his 60th birthday.

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$$\delta_C^i = A_i + \sum_j B_{ij} \quad (1)$$

The index *i* in this equation means the number of the carbon atom for which the ^{13}C chemical shift calculation is made; the index *j* runs over all positions of the aromatic ring system. The accuracy of this procedure is low and has been examined previously.[19]

It is possible to introduce as many as possible correction terms into this equation. We use the following equation in our program AROSIM for the steric correction of *ortho* substituents:

$$\delta_C^i = A_i + \sum_j B_{ij} + \sum_{i,l,l+1} K_{i,l,l+1} \quad (2)$$

The last term in eq 2 describes the correction for 2-*ortho* substituents in positions *l* and *l*+1 for position *i*. The correction term was determined as the difference between the experimental and calculated ^{13}C NMR chemical shifts for the corresponding 1,2-disubstituted compound.[21,22] For example, eq 3 gives the incremental calculation of the C-1 ^{13}C chemical shift of 1-hydroxy-2,3-dichlorbenzene with ortho correction:

$$\delta_C^1[\text{ppm}] = A_1 + B_{11} + B_{12} + B_{13} + K_{112} + K_{123} \quad (3)$$

A_1 is the ^{13}C chemical shift of C-1 in benzene, B_{11} is the increment for the substituent in position 1 (hydroxy) for position 1 (ipso increment), B_{12} is the increment for the chlorine substituent in position 2 for position 1 (ortho increment), and B_{13} is the increment for the substituent in position 3 (second chlorine) for position 1 (meta increment). The term K_{112} is the correction value for the substituents in positions 1 and 2 for position 1, and K_{123} is the correction term for the substituents in positions 2 and 3 for position 1.

For the ^{13}C chemical shift calculation of the substituted pyridines, AROSIM uses eq 2 with benzene increments and the chemical shifts of pure pyridine in $CDCl_3$ solution for the terms A_i.

The ^{13}C NMR module of the ChemWindows program[24] works analogously to eq 1 for aromatic compounds after a substructure determination using a linear code for describing the molecule as it is. This linear code can describe both axial and equatorial positions in rigid ring systems and *E*- and *Z*-isomerism at C=C double bonds.[3−6] For substituted pyridines the module works in the following way:

The first step is a substructure determination. Next, the program uses pyridine increments if present in this program. In case of nonexisting pyridine increments, the program uses benzene increments (in combination with the chemical shifts for the unsubstituted pyridine as the corresponding base values *A*).[3−6]

The CSPEC2 program is also based on eq 1 for the ^{13}C chemical shift calculation, but it is also possible to use parent structures from a data base for more accurate calculations.[8,9] In the latter modus, the ^{13}C chemical shifts of the parent structure will be used as the values A_i in eq 1. Figure 1 shows the results of the CSPEC2 calculation (a discussion of the results will be presented later in this paper). For the present test we used the pyridine values from the data base included in the latter program.

(B) Structural Descriptors and Linear Codes. The program SPECAL, included in the SpecInfo Database,[7] uses a linear code (the HOSE code) for each carbon atom of interest and takes up to four spheres into account in order to effectively describe the carbon framework. The result of the calculation is a ^{13}C chemical shift value averaged over all equal fragments in the data base. If the fragment is not existing in the data base, the average of the two most similar fragments, based on the HOSE code, will be employed; the result thus obtained will be marked as interpolated.

Example: The HOSE (hierachically ordered spherical description of environment) code for C-2 in 2,3-dichloropyridine is ***C*NX(*CX,*C„/*C„*&/*&)** (a detailed description of the rules for the HOSE code can be found in ref 20). For this code the program finds two entries in the data base, 149.3 and 147.5 ppm, respectively. The average, being the program output, is 148.4 ppm, in good coincidence with the experimental value of 149.4 ppm (*cf.* **1** in Table 1 and Figure 2).

The CNMR program by ACD[11] works with a large set of substructures and equations for incremental estimations. The program is based on 15 000 compounds with more than 170 000 chemical shifts. This program is able to learn chemical shifts from a user data base for more accurate calculations. A detailed description of the calculation mechanism, however, is not given by the authors.[11] Obviously, this program is also based on a set of structural descriptors.

(C) Semiempirical Calculations. The HyperNMR program from Hypercube[26−48] uses the TNDO (typed neglect of differential overlap) method (version 1 and version 2) for quantum-chemically computing the various chemical shifts (^{13}C included). The semiempirical parameters for the TNDO/1 and TNDO/2 quantum mechanical approach were reparametrized by the authors in order to give more acceptable chemical shifts and also coupling constants. We will not give a detailed description of the TNDO approach here. A detailed description can be found in refs 26−48.

EXPERIMENTAL SECTION

For the ^{13}C chemical calculation, 16 disubstituted pyridines (**1**−**16**, *cf.* Table 1), 9 trisubstituted pyridines (**17**−**25**, *cf.* Table 2), and 9 monosubstituted pyridines (**26**−**34**, *cf.* Table 3) from the literature[20,49−53] were tested. The results of coincidence between calculated and experimental^{13} C chemical shifts are given in Table 4. Calculations employing the following programs were carried out:

(1) The application of pure pyridine increments (not for monosubstituted compounds).

(2) AROSIM without ortho correction.

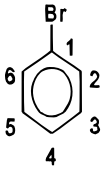
(3) AROSIM with ortho correction; the results for compounds with no substituent in the ortho position are the same as calculated with method 2.

(4) ChemWindows.

(5) SPECAL from Specinfo; the structures were designed with the structure editor from STN-Express (Version 3.2), then uploaded and the calculation performed.

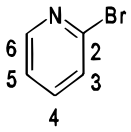
(6) CSpec2 without parent structure.

(7) CSpec2 with parent structure; the parent structure pyridine was taken from the data base of the program.



C-Atom	shift [ppm]
1	122.7
2	131.7
3	130.1
4	126.9
5	130.1
6	131.7

A) 1- bromobenzene



C-Atom	calc shift [ppm]	pcalc shift [ppm]
2	122.7	144.0
3	131.7	126.8
4	130.1	137.3
5	126.9	122.0
6	130.1	151.4

B) 2- bromopyridine

Figure 1. ^{13}C chemical shifts as calculated with the program CSPEC2 for 1-bromobenzene (a) and 2-bromopyridine (b). For part a only the normal calculation module was used, and for part b the parent calculation (with pyridine as parent structure) was used additionally (values of the right column).

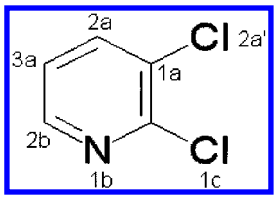


Figure 2. Application of the HOSE code for the ^{13}C chemical shift calculation of 2,3-dichloropyridine (the numbers stand for the spheres, and the letters for the priority within one sphere).

Table 3. ^{13}C Chemical Shifts of Monosubstituted Pyridines **26**−**34** As Obtained from Refs 20, and 49−53 (δ/ppm, TMS-Internal)

no.	substituents	C-2	C-3	C-4	C-5	C-6	ref
26	2-NH_2	158.9	108.5	137.5	113.3	147.7	49
27	2-Br	142.0	128.0	138.5	122.7	150.0	50
28	2-Cl	151.7	124.4	138.8	122.4	149.6	50
29	2-I	118.1	135.0	137.6	122.9	150.8	51
30	3-Br	151.0	120.8	138.5	124.7	147.8	20
31	3-Cl	148.0	131.8	136.7	124.5	148.0	52
32	3-I	155.6	93.6	143.9	125.0	147.8	20
33	3-COOH	150.2	126.7	136.9	123.7	153.2	20
34	4-Cl	150.9	124.2	144.0	124.2	150.9	53

(8) gNMR Version 3.6.5[10] with the ChewWindows structures; only the ^{13}C chemical shifts were calculated. All hydrogens and abundant and rare isotopes were excluded from the calculations, and only shifts (no coupling constants) were estimated.

(9) HyperNMR with TNDO/2, with special slater exponents for shielding and without three-center integrals. All atoms were defined as quantum atoms, and all carbons as NMR atoms and labeled atoms. Default parameters were used for SCF, and the structures came from Mopac6.0 calculations (Keywords: PM3, PREC, DENSITY, XYZ, BONDS).

(10) HyperNMR with TNDO/2, with special slater exponents for shielding and with three-center integrals. All atoms were defined as quantum atoms, and all carbons as NMR atoms and labeled atoms. Default parameters were used for SCF, and the structures came from Mopac6.0 calculations (Keywords: PM3, PREC, DENSITY, XYZ, BONDS).

(11) HyperNMR with TNDO/1, with special slater exponents for shielding and without three-center integrals. All atoms were defined as quantum atoms, and all carbons as NMR atoms and labeled atoms. The use of *d-orbitals on 2nd row elements* was enabled for all compounds without chlorine. Default parameters were used for SCF, and the structures came from Mopac6.0 calculations (Keywords: PM3, PREC, DENSITY, XYZ, BONDS).

(12) HyperNMR with TNDO/1, with special slater exponents for shielding and with three-center integrals. All atoms were defined as quantum atoms, and all carbons as NMR atoms and labeled atoms. The use of *d-orbitals on 2nd row elements* was enabled for all compounds without chlorine. Default parameters were used for SCF, and the structures came from Mopac6.0 calculations (Keywords: PM3, PREC, DENSITY, XYZ, BONDS).

Table 4. Averaged Error (ppm) Calculated as $|\delta^i_{exp} - \delta^i_{calc}|/i$ for All Tested Programs (i Is the Number of Carbon Atoms Studied)

method	monosubst pyridines	disubst pyridines	trisubst pyridines
pyridine increments	no calculations performed	1.217	2.42
AROSIM without ortho correction	1.416	4.071	3.356
AROSIM with ortho correction	no calculations performed	3.665	2.951
ChemWindow	3.913	3.6	4.5
SPECAL	0.696	3.15	4.79
C-Spec2	11.18	9.948	9.551
C-Spec2 with parent structure[a]	1.44	4.421	3.309
gNMR	2.107	3.422	3.29
HyperNMR 1[b]	15.864	21.367	21.9
HyperNMR 2[c]	15.136	17.18	13.79
HyperNMR 3[d]	16.84	22.702	22.55
HyperNMR 4[e]	11.128	15.06	11.61
CNMR	1.204	2.264	2.593

[a] With unsubstituted pyridine as parent structure. [b] TNDO/2 with special slater exponents for shielding and without three-center integrals. [c] TNDO/2 with special slater exponents for shielding and three-center integrals. [d] TNDO/1 with special slater exponents for shielding and without three-center integrals. [e] TNDO/1 with special slater exponents for shielding three-center integrals.

All compounds with bromine and iodine have been excluded from all HyperNMR calculations because of the definition of the program parameters for TNDO/2 (elements > Ar cannot be calculated). Calculations 9−11 were carried out without calculation of the Fermi spin−spin coupling constants.

(13) The CNMR Version 2.0 from ACD-Labs.[11] The structures were drawn with the internal structure editor. A detailed list with results can be ordered from the authors or read on our Web-Site (http://www.chem.uni-potsdam.de/calcnmr.html).

RESULTS

The use of pure pyridine increments (1) was found to be the best method for this kind of estimations; the applicability, however, is strongly limited to relevant cases. The best result gave the CNMR program (13) followed by the incremental

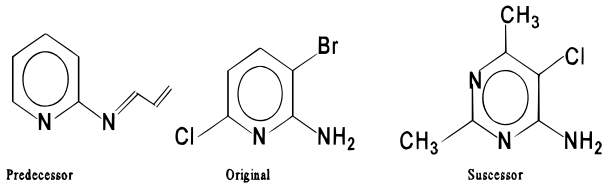


Figure 3. Predecessor and suscessor if calculating the ^{13}C chemical shift of C-2 in 2-amino-3-bromo-5-chloropyridine. The structure which was used for the calculation of C-2 has some deviations from the target structure.

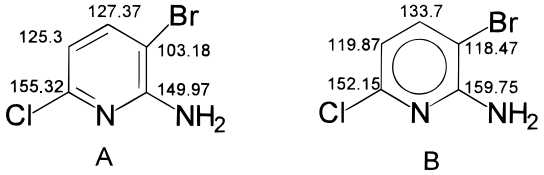


Figure 4. SPECAL differences between the identical structures A and B. Consequently, the calculated ^{13}C chemical shifts (ppm) are also different.

calculation programs (2, 3, 4, 6, 7, and 8) and the database-oriented program SPECAL (5).

In detail:

(1) The results from all the latter programs with the exeption of *C-Spec2 without parent structure* were found in approximately the same range.

(2) The application of correction terms for di- and trisubstituted pyridines results in better ^{13}C chemical shifts, as obtained from calculations without correction. Hönig et al. introduced besides the ortho correction also 1,3- and 1,4-correction terms and obtained even better results than with ortho correction only.[54] We are planning to introduce these terms in our Internet Versions of AROSIM in the near future.

(3) The increase of the averaged error for the datebase-founded calculation program SPECAL shows the disadvantage of the implemented interpolation algorithm. A similar HOSE code must not necessarily represent a similar structure. Figure 3 shows the predecessor and the suscessor used for the interpolation of the ^{13}C chemical shift of C-2 of 2-amino-3-bromo-5-chloropyridine. Both the predecessor and the suscessor show more or less strong deviations from the target structure. These deviations are hard to understand because of being without any structural relevance.

(4) Another disadvantage of SPECAL is the limitation to four spheres. Without this limitation, it should be possible to reduce the errors in the calculation.[55]

(5) The most dangerous disadvantage is the interpretation of structures. Figure 4 will demonstrate this. SPECAL makes differences between the identical structures A and B for 2-amino-3-bromo-5-chloropyridine. A comparison of the HOSE code for C-2 shows these differences:

C-2 (form A):

=CNN(CY,=C,/=C,,X&/&,)

C-2 (form B):

*C*NN(*CY,*C,/*C,,*&X/*&,)

(6) The semiempirical calculation program HyperNMR gives no results comparable to those of the other programs. The parametrization of the TNDO/1 and TNDO/2 methods gives no accurate results for the ^{13}C NMR spectra of the compounds studied. The application of the time-consuming inclusion of the three-center integrals gives better but not yet satisfactory results.

(7) The use of programs with increments or structural fragments with a large amount of data (for example CNMR) gives the best results in short calculation times (only some seconds on a 486/DX2-66 PC).

With the experiences made along with this study, ab-initio calculations are expected to give better results than HyperNMR, but these methods require a set of modern computers and a lot of computation time and the results are probably not better than those which came out from the programs tested in this study.

CONCLUSIONS

Most of the available programs give similar coincidence between calculated and experimental ^{13}C chemical shifts of the pyridines **1**−**36**. The introduction of sterical correction terms gives better results, especially in the case of trisubstituted pyridines (*cf.* Table 4).

The use of the database-oriented program SPECAL has some disadvantages especially for users not detailly educated in structure elucidation. The program CNMR, which has a knowledge base, gives the best results in our work. The greatest advantage of this program is the possibility to train this knowledge base by the user.

The semiempirical program HyperNMR is only useful in cases which require an accuracy not smaller than 20 ppm.

Future developments in this field should be oriented on the results of the CNMR program; the best chances will have programs with a large set of individual equations for as many as possible different classes of compounds in combination with a large data base.

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