

Computer Application of an Incremental System for Calculating the ^{13}C NMR Spectra of Aromatic Compounds

St. Thomas, D. Ströhl, and E. Kleinpeter*

Institut für Analytische Chemie im Fachbereich Chemie der Martin-Luther-Universität Halle-Wittenberg,
Weinbergweg 16, D-06120 Halle/Saale, Germany

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A computer program with many useful functions for the prediction and assignment of the ^{13}C NMR spectra of substituted benzenes, naphthalenes, and biphenyls is described. Additionally, for benzenes and naphthalenes, the program proved useful in searching for the types of substituents and their positions on the rings of the studied aromatic compound.

INTRODUCTION

The use of substituent induced chemical shifts for the prediction of ^{13}C chemical shifts of different classes of compounds is well-known.^{1,2} Aromatic compounds, substituted benzenes especially, were intensively investigated.^{1,3-5} For these kinds of compounds, the calculation of the ^{13}C chemical shifts for derivatives with substituents sterically hindering each other is a serious problem.^{4,5} Previously, only a very simple procedure for the correction of the incrementally calculated ^{13}C chemical shifts proved useful.⁴⁻⁶ In order to simplify and accelerate the application, the computer program AROSIM was written and tested for successful application in assigning the ^{13}C NMR spectra of some selected model compounds.⁶ It is the objective of this paper to report on some further functions (especially the search for unknown substituents) now included in AROSIM in order to succeed in assigning a much larger number of different aromatic compounds at a higher level of confidence.

R. A. Hearmon et al.⁷ recently published a PC program for calculation of the ^{13}C chemical shifts of aromatic compounds, employing the ^{13}C NMR substituent chemical shifts (SCS) values of benzenes. In the presence of serious steric and electronic substituent interactions, these⁷ but also other authors⁸ found large deviations from additivity (up to 15 ppm). Thus the method of simple additivity of SCS values could not always predict the true molecular constitution. For this reason, the application of adequate *ortho* correction terms for the incremental calculation of aromatic chemical shifts had been strongly recommended.⁶ Another solution, now included in our computer program, is a new search routine for unknown substituents.

In comparison to other developed and, more or less, comprehensive spectroscopic data bases⁸⁻¹⁰ for the prediction of ^{13}C chemical shifts, we do not need such a large quantity of spectral data for the estimation. Our program is easy to handle (e.g., compared to the program in ref 11) and readily able to apply the ^{13}C chemical shifts in the database for the estimation of certain ^{13}C chemical shifts of different classes of aromatic compounds.

THEORY

The calculation of the ^{13}C chemical shifts for substituted benzenes and naphthalenes without any correction for mutual steric and/or electronic interaction of nearby substituents is carried out by means of eq 1. The accuracy of this procedure

$$\delta_{\text{C}}^i = A_i + \sum B_{ij} \quad (1)$$

is low and has been examined previously.¹ The increments in the database for the substituents on benzene in our computer program AROSIM originate from ref 1; the increments for substituents on naphthalene, classified into increments for substituents in α (1, 4, 5, and 8) and β positions (2, 3, 6, and 7), were taken from ref 11. Only ^{13}C NMR spectra obtained in CDCl_3 as the solvent were included into the database of AROSIM.

In cases of *ortho*, *ortho'*-disubstitution of biphenyl, *ortho*-disubstitution of benzenes, and *ortho*-di- and *peri*-substitution of naphthalenes, the calculation of the corresponding ^{13}C chemical shifts, applying AROSIM, is carried out by means of eq 2 (K_{iln} = correction term for position i caused by two

$$\delta_{\text{C}}^i = A_i + \sum B_{ij} + \sum K_{iln} \quad (2)$$

sterically hindered substituents in positions l and n); the precision of the calculated ^{13}C chemical shifts dependent on the steric hindrance of the various substituents could be improved remarkably by this procedure.⁶ For example, eq 3

$$\delta_{\text{C}}^1 = A_1 + B_{11} + B_{12} + B_{13} \quad (3)$$

gives the incremental calculation of the C-1 ^{13}C chemical shift of 1-hydroxy-2,3-dichlorobenzene (without *ortho* correction). A_1 is the ^{13}C chemical shift of C-1 in benzene ($\delta = 128.5$ ppm), B_{11} is the ipso increment for the hydroxy substituent in position 1, B_{12} is the *ortho* increment of chlorine in position 2, and B_{13} is the *meta* increment for the second chlorine in position 3. By employing the corresponding values in Table 1, the following ^{13}C chemical shift of C-1 was obtained:

$$\delta_{\text{C}}^1 [\text{ppm}] = 128.5 + 26.9 + 0.3 + 1.4 = 157.1 [\text{ppm}] \quad (4)$$

For estimating the correction terms of *ortho*-disubstitution, simply the differences between the experimental and calculated ^{13}C chemical shifts of the *ortho*-disubstituted compounds were calculated. This means for C-1 and 1-hydroxy-2,3-dichlorobenzene:

$$\delta_{\text{C}}^1 = A_1 + B_{11} + B_{12} + B_{13} + K_{112} + K_{123} \quad (5)$$

K_{112} is the correction term for the ^{13}C chemical shift of C-1

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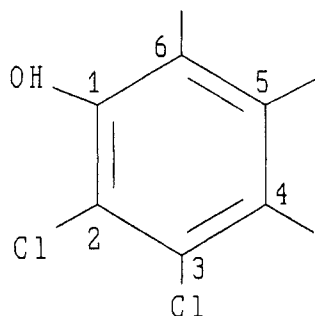


Figure 1. 1-Hydroxy-2,3-dichlorobenzene with the used numbers.

Table 1. Increments for the Substituents Cl and OH

substituent	B_1	$B_2 = B_6$	$B_3 = B_5$	B_4
OH	26.9	-12.8	1.35	-7.4
Cl	5.9	0.3	1.4	-1.9

Table 2. Correction Terms for Use with the Given Example

subst. 1, position 1	subst. 2, position 2	K_1	K_2	K_3	K_4	K_5	K_6
OH	Cl	-2.7	-1.6	-0.3	-2.5	-0.4	-0.2
Cl	Cl	-2.2	-4.2	0.4	-0.1	-0.1	0.4

Table 3. Experimental and Calculated ^{13}C Chemical Shifts [ppm] of 1-Hydroxy-2,3-dichlorobenzene

	C-1	C-2	C-3	C-4	C-5	C-6
exptl	152.9	119.2	132.8	122.3	128.2	114.6
without ^a						
value	157.1	121.9	136.05	122.8	129.35	115.2
diff ^b	-4.20	-2.70	-3.25	-0.50	-1.15	-0.60
with ^c						
value	154.8	118.1	133.55	120.7	128.85	114.9
diff ^b	-1.90	1.10	-0.74	1.60	-0.65	-0.30

^a Calculated without *ortho* correction. ^b Difference between experimental and calculated ^{13}C chemical shifts. ^c With *ortho* correction calculated ^{13}C chemical shifts.

caused by the *ortho* substituents in positions 1 and 2 (determined as the difference between the experimental and calculated ^{13}C chemical shifts of C-1 and 1-hydroxy-2-chlorobenzene), and K_{123} is the correction term for the substituents in positions 2 and 3 for $\delta_{\text{C-1}}$. The other terms are the same as described previously. The numerical values (see Table 2) are as follows:

$$\delta_{\text{C}}^1 [\text{ppm}] = 128.5 + 26.9 + 0.3 + 1.4 - 2.7 + 0.4 = 154.8 [\text{ppm}] \quad (6)$$

The ^{13}C chemical shifts of 1-hydroxy-2,3-dichlorobenzene, estimated with and without *ortho* correction, are given in Table 3.

PROGRAM DESCRIPTION AND RESULTS

By including possibilities of the older version of AROSIM, the computer program can now be employed for the following purposes: (1) The calculation of the ^{13}C chemical shift of substituted benzenes, naphthalenes, and biphenyls with or without *ortho* correction for steric hindrance of *ortho* substituents (display and printout are available). (2) The assignment of experimental ^{13}C NMR spectra of benzenes, naphthalenes, and biphenyls. This assignment procedure can be employed also for compounds with more than one aromatic fragment in the same molecule. (3) Searching for the types of possible substituents and their positions on the aromatic rings, for benzenes with one to six substituents and for naphthalenes with one to three substituents. (4) Manipulation

and extension of the database for the increments and the correction terms. The program uses a SAA menu shell with a context sensitive online help system.

The Increment Calculation. After having been started by activation of the menu point *structure input*, the program asks in the corresponding simulation menu for the input of all substituents (including all hydrogens as substituents). A help menu with the names of substituents (350 for benzene and 30 for naphthalene) available in AROSIM is prepared and can be activated. With a simple text editor, it is possible to manipulate this menu, e.g. in cases of correction or expansion of the database.

After the input of the structure of the compound under study, the ^{13}C chemical shifts of the latter can be calculated with or without steric correction. If any substituent is not available in the database, a message appears and the calculation is aborted. If any correction term is not available, the program announces this with a message and sets the terms equal to zero; in this case, the calculation is not aborted. The results of successful calculations are displayed in a window which is movable. The user can display, save, and print out the obtained ^{13}C NMR spectrum.

The accuracy of the incremental calculations for benzenes and naphthalenes with and without *ortho* correction was reported previously.⁶ For the calculation of the ^{13}C chemical shifts of biphenyls, a new simplified procedure was used; the two benzene rings were treated separately. The mutual influence of the two substituted benzene rings was simulated by adequately substituted phenyl substituents. The accuracy of this simplified procedure has been tested for a set of 13 substituted biphenyls with present *ortho* substituents.¹² Without *ortho* correction, an averaged error of 2.05 ppm was obtained; the number of wrong assignments was 27. With *ortho* correction, the averaged error was still 1.88 ppm but the number of wrong assignments was reduced to only 17.

The Assignment of Experimental ^{13}C NMR Spectra. The program offers two different ways of assigning the experimental ^{13}C NMR spectrum of a compound with known structure. In following the first one (for molecules with only one benzene, naphthalene, and biphenyl system, respectively), the ^{13}C chemical shifts must be calculated, just as described before, and then the menu point *assignment* must be activated. After choice of this point, the program requests the input of the experimental ^{13}C chemical shifts, separated into the values of protonated and quaternary carbon atoms. Now the program assorts the experimental and calculated ^{13}C chemical shifts according to their size (if the ^{13}C chemical shifts were calculated with and without steric correction, the program automatically favors the usually more trustful ^{13}C chemical shifts obtained by including the correction terms) and assigns the assorted calculated ^{13}C chemical shifts accordingly. For example, the position of the methine carbon atom with the ^{13}C chemical shift calculated at lowest field will be assigned to the position of the methine carbon with the largest experimental δ value. The resulting assignment is given in a window and can be displayed and/or printed out. Figure 2 displays a plot of the experimental and the calculated ^{13}C NMR spectra of 2,3,5-trimethylnaphthalene with *ortho* correction. The experimental assignment of the ^{13}C chemical shifts on the basis of the values estimated by AROSIM can be plotted separately.

For compounds with more than one aromatic moiety within the same molecule, a second and different assignment procedure must be used. In the first step, the ^{13}C NMR spectra of the different aromatic systems in the studied molecule must

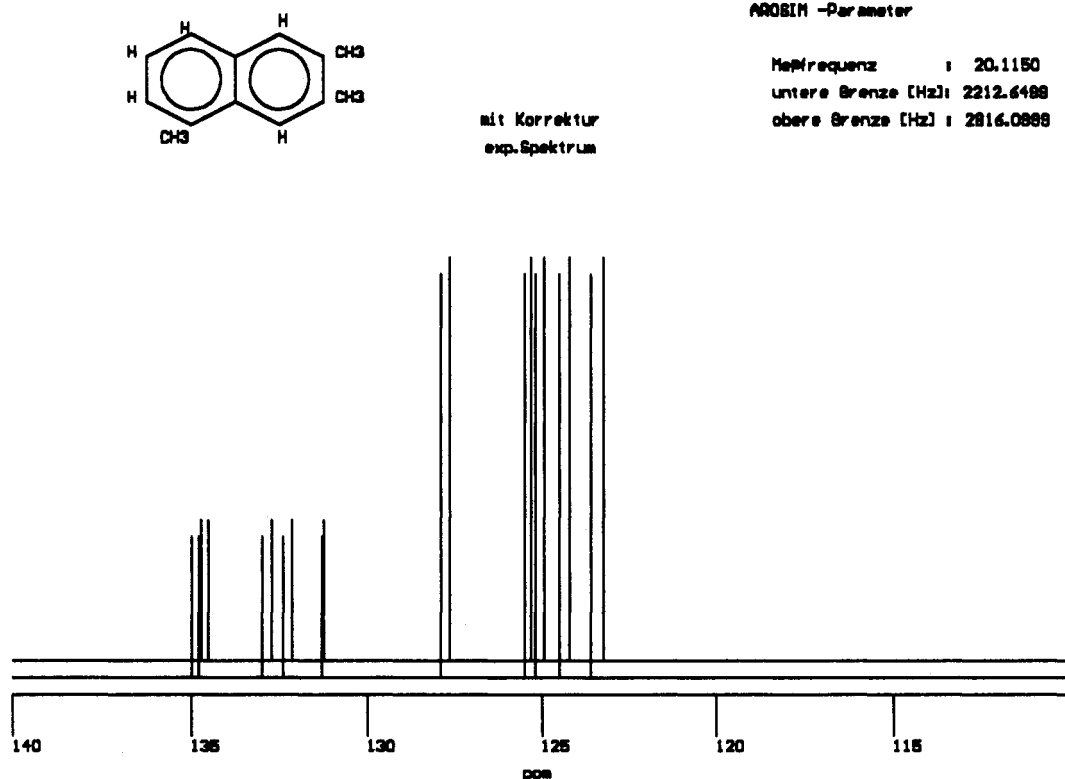


Figure 2. Experimental and calculated ^{13}C NMR spectrum of 2,3,5-trimethylnaphthalene (printed from the german program version).

be assigned as described before. The calculated spectra must be displayed and saved, and the calculated ^{13}C chemical shifts must be noted or printed out. Then, the menu point *graphic display* must be selected and, hereby, the various ^{13}C NMR spectra added simply on the display. The graphic display uses autoscaling, e.g. all resonances are displayed with correct intensities relative to each other and the various spectra can be distinguished by different colors. The assignment can be managed now by means of the noted ^{13}C chemical shifts and the intensities of the corresponding resonances on the condition that displayed and experimental ^{13}C NMR spectra are similar.

The assignment procedure for substituted benzenes, naphthalenes, and biphenyls can be used as a proof for the accuracy of the incremental system by means of determining the number of wrong assignments in cases of compounds where the assignment had been determined by *ab initio* NMR methods. It is our understanding that this is a better way of characterizing the usefulness of any incremental system than the specification of the statistical margin of error. For example, the average error in the assignment of the ^{13}C NMR spectrum of 4-acetoxibiphenyl proved to be 0.256 ppm; however, only seven of a total eight assignments are correct. In the case of 5,5'-diformyl-2,2'-dimethoxybiphenyl, the average uncertainty is 4.55 ppm but all signals were assigned correctly.

The assignment procedure for compounds with more than one aromatic moiety within the molecule was tested for a set of (*E*)-stilbenes (the assignment of the ^{13}C NMR spectra was taken from the ref 13). For compound 1, the ^{13}C chemical shifts of ring A carbon atoms were estimated from substituent 1 is a model compound and those of ring B from the values of substituent 2 (Figure 3).

Both the experimental and calculated ^{13}C chemical shifts estimated this way are given in Table 4. It can be concluded from these results that all experimental ^{13}C resonances could be assigned confidently. Of the 90 ^{13}C resonances of the complete set of investigated (*E*)-stilbenes,¹³ only four signals were assigned incorrectly. Therefore, the assignment pro-

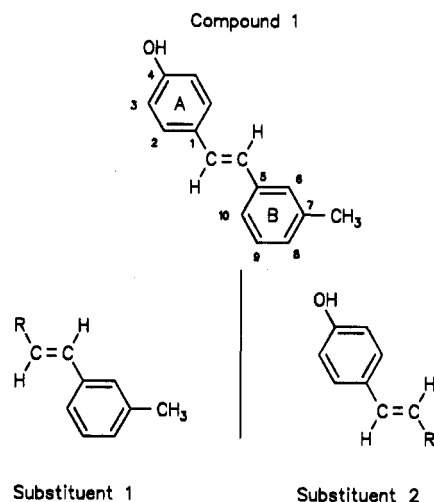


Figure 3. Calculation of ^{13}C chemical shifts of (*E*)-4-hydroxy-7-methylstilbene.

Table 4. Experimental and Calculated ^{13}C Chemical Shifts for (*E*)-4-Hydroxy-7-methylstilbene

C atom	exptl shifts [ppm]	calcd shifts [ppm]
1	130.0	130.0
2	128.7	127.95
3	116.4	115.9
4	158.1	154.5
5	138.8	139.6
6	127.6	127.2
7	138.8	138.5
8	128.6	128.4
9	129.3	129.2
10	124.2	123.5

cedure applied proved useful for the fast and simple assignment of the ^{13}C NMR spectra of aromatic compounds.

Search for Unknown Substituents. Our search function is a new tool for the determination of the types and positions of present substituents. In contrast to the search function

described by R. A. Hearmon et al.,⁷ AROSIM can search at the same time for more than one substituent and for all substitution patterns possible.

Before starting this function of the computer program, it is necessary to generate the search file. If there is no idea about the present substituents, it is possible to use the complete database as a search file. In the case of substituted benzenes, AROSIM opens generally two ways of generating the search file; a combination of these two is possible as well. The first and simplest one is the input of all the elements of the unknown compound; for this purpose 16 characteristics are available which are H, C, O, N, S, P, Si, F, Cl, Br, I, Se + Te + Po, As + Sb + Bi, file 1, file 2, and file 3 (file 1, elements of the 1 and 2 main groups; file 2, elements of the 3 and rest of the 4 main groups; file 3, other elements).

After the input of the corresponding characteristics for the substituents most likely present, the computer program automatically generates a search file with all the substituents with the denoted elements. For example, the input of H, C, and O as the relevant elements includes substituents like CH₃, OH, and CHO but not COCl or CH₂Cl in the search file.

As a second way of generating the search file, the complete basic file of the database (or the search file generated by use of the first way) is called up substituent by substituent and the operator must decide by dialog with the computer which substituents should remain in the search file and which substituents can be cancelled simply. For the naphthalenes, only the second way is practicable.

Then, after the search file has been created, the search with or without steric correction must be chosen and the following inputs are requested by the program: (1) the name of the search file(s); (2) the number of quaternary carbon atoms; (3) the ¹³C chemical shifts separated into methine and quaternary carbon atoms.

The results of the search (the first 10 compounds of best fit) are displayed in 10 windows which are again movable. The obtained ¹³C NMR spectra with the experimental and calculated ¹³C chemical shifts can be displayed and/or printed out. Also, an overview of the first six compounds of best fit together with the average error can be printed out.

This search function has been tested first for a set of 53 substituted benzenes with the assignments given in ref 14. The search file contained 19 substituents: H, CH₃, F, OH, Cl, NO₂, CHO, N(CH₃)₂, COCH₃, Br, NH₂, COOH, Bu^t, I, CON(CH₃)₂, OCH₃, Si(CH₃)₃, COOCH₃, SO₂Cl. For each of the corresponding compounds, the search with and without steric correction was carried out. The following results were obtained: with steric correction, the program found 26 compounds at the first position; 12 compounds were not found among the first 10 compounds. Without steric correction, the program found only 17 compounds at the first position; 20 compounds were not found.

In a second attempt, 15 disubstituted benzenes were tested using a search file generated from the elementary analysis. With steric correction, the program found eight compounds at the first position; three compounds were not found. Without steric correction, only two compounds were found at the first position but seven compounds were not found (Table 5).

In a third attempt, 40 di- and trisubstituted naphthalenes¹¹ were tested. The search files for substituents in positions 1 and 2 contained the following substituents: H, Cl, F, NO₂, OCOCH₃, Br, OCH₃, CH₃, I, OH, NH₂, CHO, COOH, COCH₃. The results are as follows: with steric correction, the program found 30 compounds at the first position; seven compounds were not found. Without steric correction, the

Table 5. Result of the Use of the Search Function for Substituted Benzenes and Naphthalenes

compounds	first	first 10 ^a	not found
benzenes without correction, search 1 ^b	17	33	20
benzenes with correction, search 1	26	41	12
benzenes without correction, search 2 ^c	2	8	7
benzenes with correction, search 2	8	12	3
naphthalenes without correction	20	27	13
naphthalenes with correction	30	33	7

^a The compound was found within the first 10 compounds but not in position 1. ^b Search 1 means a search with the same 19 substituents in the present search file. ^c Search 2 means a search with a search file as generated by means of the elementary analysis.

program found 20 compounds at the first position; 13 compounds were not found among the first 10.

EXPERIMENTAL SECTION

The program was written with Turbo Pascal (Trademark Borland Int.) and runs on AT 80 × 86 compatible personal computers with a VGA graphic adapter. EMS memory and an arithmetic coprocessor can be used but are not needed. The program was run for all tests on AT 80386 DX and AT 80386 SX PCs with a coprocessor.

For plotting of the figures, the output of graphics in the HPGL language from the file was used. Other possible output devices are EPSON LQ and EPSON FX printers, IBM Proprinter, HP Deskjet, HP Laserjet, PCX graphic files, and a memory resident AUTOCAD driver for printer and plotter.

CONCLUSIONS

(1) The accuracy of incremental calculations was, as had been found already,⁶ remarkably improved by using the *ortho* correction system.

(2) The simplified incremental calculation, applied for biphenyls, was found to be of sufficient accuracy and could be used for the fast estimation of the ¹³C chemical shifts of many biphenyls as well as for the computer-aided assignment of the ¹³C NMR spectra of the latter.

(3) The search system for unknown substituents and their positions in the corresponding aromatic ring system proved very useful, especially when employing the steric correction terms.

(4) For compounds with more than one aromatic system in the molecule, the *graphic display* proved very useful for a first assignment of the ¹³C chemical shifts of the present compounds.

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