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Structural Assignment of 2,6- and 2,7-Disubstituted Naphthalenes and Prediction of ^{13}C Nuclear Magnetic Resonance Chemical Shifts: Applications of Topology and Two-Dimensional NMR Spectroscopy

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Abstract—Unambiguous assignments of monocarboxymethylnapthalenes isolated as oxidation products of dimethylnaphthalenes by *Pseudomonas putida*, a bacterial strain, were made using two-dimensional nuclear Overhauser enhancement correlation spectroscopy (NOESEY). The two-dimensional long-range heteronuclear correlation NMR technique was also utilized for the assignment of quaternary carbons in the naphthalene system. In addition, we describe methods for prediction of ^{13}C NMR chemical shifts of 2,6- and 2,7-disubstituted naphthalenes using topological approach. The method involves computation of molecular descriptors from topological representation of molecule, namely Wiener (W) and Szeged (Sz) indices. The results have shown that W and Sz indices can be successfully used for predicting ^{13}C NMR chemical shifts and that $\Sigma^{13}Cn$ can be used as a molecular property which in turn can be modeled by both W and Sz indices successfully.

Introduction

Pseudomonas putida, a bacterial strain that carries a naphthalene-degradative plasmid, NAH[1] has been evaluated for oxidation of dimethylnaphthalenes (DMN). Two derivatives were isolated from the cell cultures of *Pseudomonas putida* 2,6- and 2,7-dimethylnaphthalenes. These derivatives were readily identified as monocarboxymethylnapthalenes (MCN) by Gas Chromatography—Mass spectroscopy (GC–MS). Since no reference standards were available, the substitution position could not be determined by the latter. Although the bacteria is not known to isomerizes the DMN used, it was necessary to demonstrate that no isomerization had occurred in the formation of MCN. Therefore, unequivocal assignments of substitution of the isolated MCNs were necessary.

The assignment of the substitution position in disubstituted naphthalene is commonly made by proton and/or carbon-13 NMR. However, such determination is not always trivial when no reference compounds or spectra are available. For instance, the monocarboxymethylnaphthalenes (**1** and **2**) isolated from the cell cultures in very small amounts (>80 μg) could not be distinguished from each other by their normal 1-D ^1H NMR spectra. Both yielded identical proton multiplets. The ^1H or ^{13}C NMR spectra of these derivatives have not been reported. ^1H and ^{13}C chemical shifts of several other disubstituted naphthalene's have been reported,[1] but those would be of little use for unambiguous assignment of **1** and **2**. The limited sample (<80 μg) availability also precluded the use of chemical degradation or techniques involving ^{13}C NMR. In this communication we describe an application of two-dimensional nuclear Overhauser enhancement correlation spectroscopy[5] (NOESY) for unambiguous assignment of the monocarboxylated methylnaphthalenes. In addition, we also describe topological modelling of ^{13}C chemical shift using Wiener (W) and Szeged (Sz) indices. Such a modelling of chemical shifts using

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topological indices may help in prediction of chemical shifts directly from the structure (molecular graph) and confirm experimental assignement. Furthermore, the results, as discussed below, show the possibility of predicting of these compounds and application of these methods, which seem to be helpful for many organic chemists, thus establishing that the methods are of timeliness.

During the course of this work, several dimethylnaphthalenes were analyzed by NMR for unambiguous characterization of the microbial conversion products. Assignment of ^{13}C NMR spectra of 10 dimethylnaphthalenes have been reported by Wilson and Stothers and summarized by Hansen.[1] Most of the assignments were made by the use of selective proton decoupling; however, it is not amnable to distinguish carbons when the long-range coupled protons have near equivalent chemical shifts. In some instances quaternary and methine carbons of these naphthalenes have to be reassigned. Our assignment in most cases were in agreement with those reported except in some cases where chemical shifts are too close to be able to assign using selective proton decoupling. Two-dimensional homo (COSY)[2] and heteronuclear chemical shift correlation spectroscopy (HETCOR)[2] provided unequivocal assignment of those aromatic methines. The long-range hetronuclear 2D chemical shift correlation technique[2,3] was particularly found to be valuable for assignment of the quaternary carbons.

As is well known, ^{13}C Nuclear Magnetic Resonance (NMR) chemical shifts offer a powerful probe in the study of the immediate atomic environment in a molecule. ^{13}C NMR spectroscopy is thus increasingly gaining importance for organic chemists. It was realized that the ^{13}C NMR chemical shift and the bonding between carbons and other nuclei are strongly dependent on even minor change of the geometrical and atomic environment of the organic molecules. Therefore, topology of the organic molecule plays a dominant role in the exhibition of ^{13}C NMR chemical shifts.[4] This is true even for the series of dimethylnaphthalenes used in the present study. Consequently, we can use topological indices for modeling, monitoring, estimating, and predicting ^{13}C NMR chemical shifts in organic molecules.

A topological index is a graph-theoretical invariant which codes quantitative information regarding the size, shape, bonding type, heteroatom, and branching associated with the molecular structure.[5–7] The Wiener index (W)[8] is the first, the oldest, and even today the most widely used topological index. However, it is applicable to acyclic (trees) graphs only and not to cyclic graphs. Consequent to this, Gutman[9,10] has introduced a new index called Szeged index and abbreviated it as S_z. This new index is considered as the modification of W to cyclic graphs. For acyclic graph (trees), W and S_z coincide. Compared to the Wiener (W) index, little is known about the applicability of S_z in predicting properties as well as physiological activity of organic compounds.[11–17] Hence, as stated earlier, another objective of the present study is to investigate the potential of S_z in predicting ^{13}C NMR chemical shifts of dimethylsubstituted naphthalenes (Table 1) and to compare the results with those obtained by using W. The results as discussed below show that both these indices (W and S_z) have equal predicting potential in that ^{13}C NMR shifts (C_n), sum of ^{13}C NMR chemical shifts (ΣC_n), and mean ^{13}C NMR chemical shifts are predicted successfully using W and S_z.

Results and Discussion.

Monocarboxylated methylnaphthalenes

These derivatives were isolated as their methyl esters (**1** and **2**). Proton NMR spectra of these esters show six well separated aromatic protons, two pairs of *ortho* protons and two isolated protons (the *meta* coupling is not resolved).This pattern would be consistent for 2,6- and 2,7-disubstituted naphthalenes. One of the isolated protons in these spectra is observed significantly downfield near δ 8.5. This proton must be assigned to a *peri* (α) proton *ortho* to the carboxy substituent. Therefore, the carboxy substituent must be assigned to the β position in both derivatives. The position of the other substituent, $-CH_3$ cannot be distinguished by chemical shifts.

Since these *peri* protons are in close proximity to each other, they can be correlated by nuclear Overhauser enhancement (NOE) effects. Indeed NOESY spectra (Figs. 1 and 2) of **1** and **2**, clearly show the NOE connectivities. In **1** the *peri* proton at δ 8.5 shows NOE correlation to the 8 Hz doublet; therefore, it must be 2,6-disubstituted. The *peri* proton at δ 8.5 in **2**, however, shows connectivity with the broad singlet at δ 7.7, as one would expect for the 2,7-disustituted naphthalene.

Table 1. ^{13}C Chemical shifts of dimethylnaphthalenes

Compd	Dimethyl naphthalene	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	$\Sigma^{13}C_n$
1	1,2-	131.0	133.0	128.9	125.5	128.3	124.3	125.6	123.6	132.7	132.1	1285.0
2	1,3-	133.9	128.8	134.9	125.1	127.7	125.5	124.7	132.8	130.8	133.0	1297.2
3	1,4-	132.2	126.1	126.1	132.2	124.5	125.2	125.2	124.5	132.6	132.6	1281.2
4	1,5-	135.0	126.6	125.6	122.7	135.0	126.6	125.6	122.7	132.9	132.9	1285.6
5	1,6-	131.1	124.9	124.8	125.0	126.7	134.1	127.1	123.1	130.1	133.0	1279.9
6	2,6-	126.5	134.3	128.0	126.9	126.5	134.3	128.0	126.9	131.8	131.8	1295.0
7	2,7-	126.1	135.3	127.1	127.3	127.3	127.1	135.3	126.1	133.8	129.8	1295.2

$\Sigma^{13}C_n$, summation of $^{13}C_n$ where *n* varies from 1 to 10.

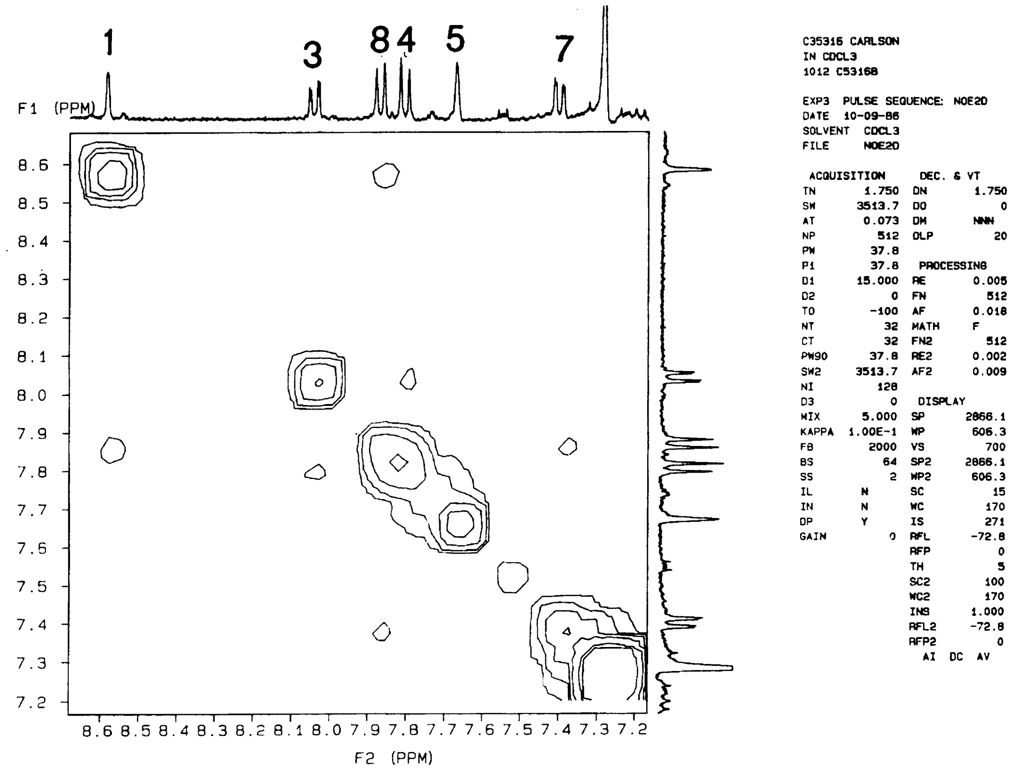

Figure 1.

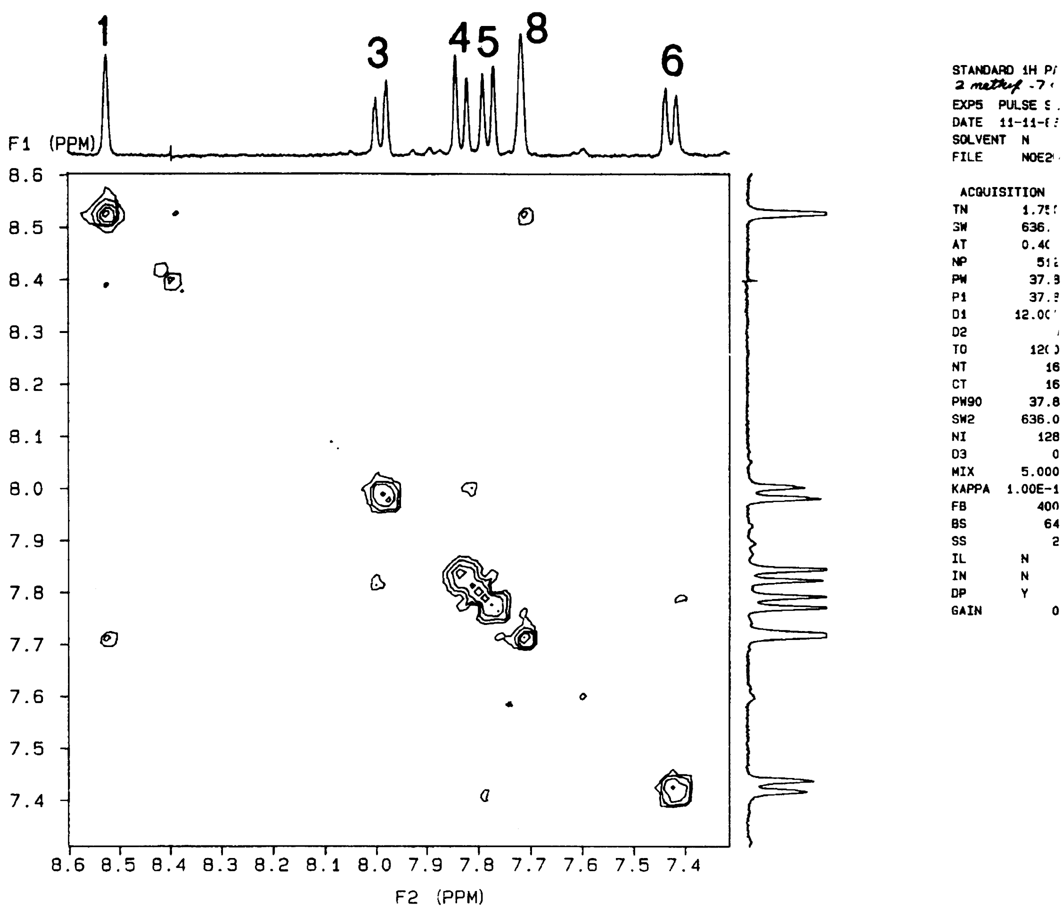

Figure 2.

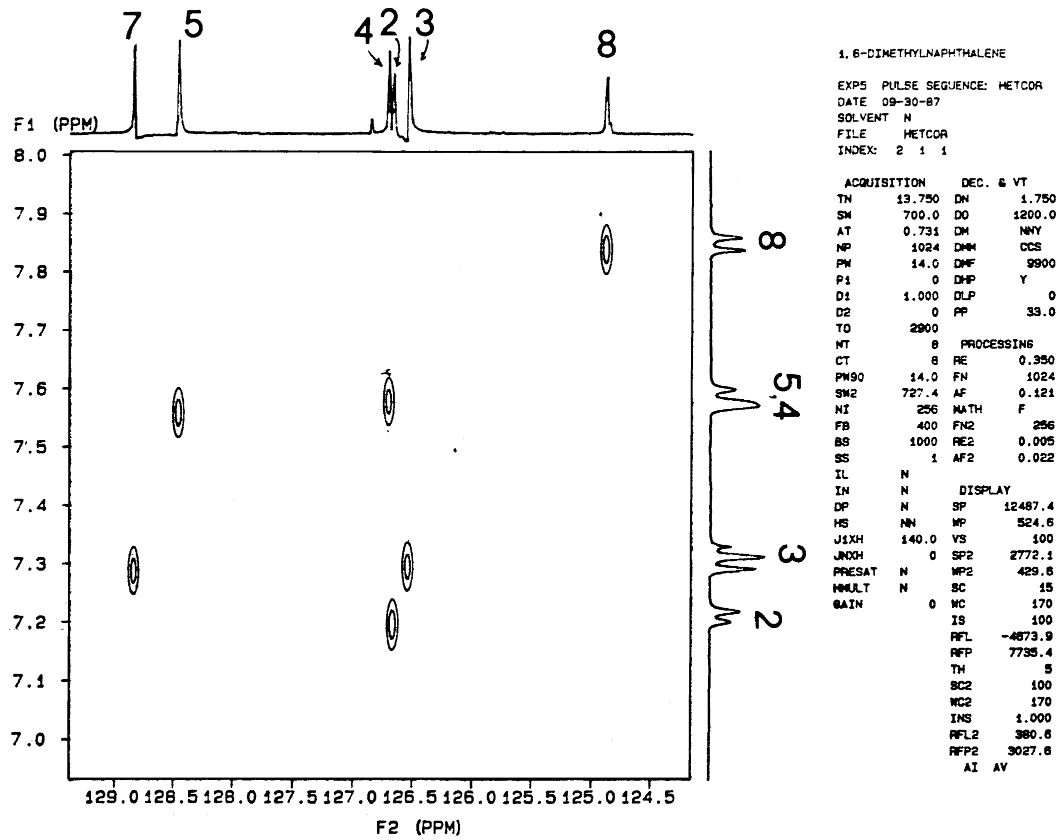

Figure 3.

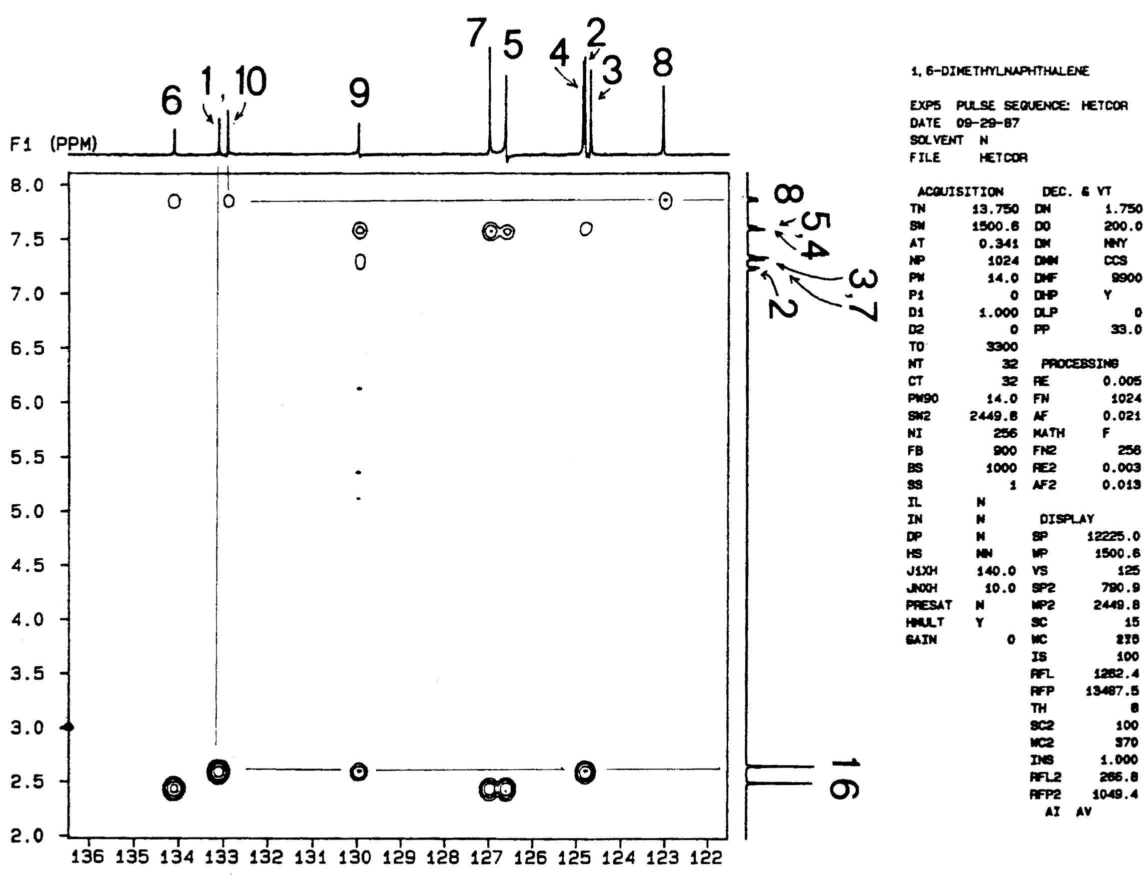

Figure 4.

Hence, **1** and **2** are 2,6- and 2,7-carboxy-methylnaphthalene, respectively.

Dimethylnaphthalenes

The normal high-resolution heteronuclear and long-range heteronuclear 2D chemical shift correlation spectra provided ^{13}C NMR assignment (Table 1). The technique is elucidated for 1,6-dimethylnaphthalene. The proton spectrum of 1,6-dimethylnaphthalene is assigned from a COSY experiment. The assignment of carbons C-2, C-3, and C-4 was made from the HETCOR spectrum. These carbons and C-1 and C-10 have not been assigned earlier[2] due to resolution problem. The quaternary carbons C-1 and C-10 can be unambiguously distinguished by along range heteronuclear correlation spectrum (Figs. 3 and 4).The H-8 proton shows the correlation with the quaternary carbon at δ 133.0 and C-1 carbon is correlated with the methyl protons at C-1. The assignment of 2,7-dimethylnaphthalene ^{13}C spectrum was similarly made.

The proton spectrum of 1,3-dimethylnaphthalene can be assigned on the basis of chemical shifts.[1,2] The singlets of the isolated protons H-2 and H-4 and doublet of H-8 and H-5 are distinguished because the *peri* protons are more desheilded. The assignment was confirmed by a NOESY spectrum which showed NOE between H-5 and H-4. The long-range heteronuclear correlation spectrum in agreement with the earlier assignments[1,2] of carbons except for C-1 and C-10, which should be reversed. Although the peaks due to C-4 and C-7 of 1,2-dimethylnaphthalene are separated by less than 0.4 ppm, resolution was sufficient to make the unequivocal assignment also indicated long-range C-H coupling of C-2 with H-4 and C_2-CH_3, and of C-9 with H-5 and C_1-CH_3 to confirm the assignment of those carbons.

Prediction of ^{13}C NMR chemical shifts

The data presented in Tables 1–3 show that ^{13}C NMR chemical shifts (C_n, $n=1, 2, 3...0$) and their sums ($\Sigma^{13}C_n$) are linearly correlated with W and S_z indices. Hence, if TI stands for one of the topological indices W and S_z, then the following approximation can be used for $^{13}C_n$ ($n=1, 2, 3,...10$) NMR chemical shifts:

$$^{13}C_n = A_1TI + B_1 \quad (1)$$

and

$$\Sigma^{13}C_n = A_2TI + B_2 \quad (2)$$

for sum of the $^{13}C_n$ NMR chemical shifts of the dimethylnaphthalenes used in the present study. The calculated values for the coefficients A_i ($i=1$, 2) and B_i ($i=1$,2) of the aforementioned equations as well as the data showing the quality of the respective correlations are given in Table 3.

As seen from Tables 1 and 3, by means of eq 1 it is possible to quite accurately estimate the ^{13}C NMR chemical shifts of the dimethylnaphthalenes, however, poor results are obtained in case of C_3, C_5 and C_6. It is interesting to record that although individual chemical shifts for different atoms have received wide attention, it is somewhat surprising that there is hardly any study devoted to the collection of chemical shifts in a molecule. However, the present study shows that sum of the ^{13}C NMR chemical shifts $\Sigma^{13}C_n$ display regularity in variations. The statistics presented in Table 3 show that $\Sigma^{13}C_n$ NMR chemical shifts of the dimethylnaphthalenes act as a very good molecular property which can be estimated successfully employing the above mentioned eq 2. The corresponding regression models are found as under:

$$\Sigma^{13}C_n = 1100.6465 + 1.0425\ W \quad (3)$$

$$\Sigma^{13}C_n = 1091.9475 + 0.5254\ S_z \quad (4)$$

In order to confirm our findings, we have estimated $\Sigma^{13}C_n$ from eqs 3 and 4 and compared them with the experimental values of $\Sigma^{13}C_n$. Such a comparison is shown in Table 2. The results show that using distance-based topological indices W and S_z it is possible to infer about the $\Sigma^{13}C_n$ and that it ($\Sigma^{13}C_n$) can be used as a molecular property. The data also show that W and S_z indices have practically the same predictive ability, W being slightly better than S_z. This is obvious because S_z index is a modification of the W index for cyclic

Table 2. Wiener (W) and Szeged (Sz) indices of dimethylnaphthalenes used in the present investigation and estimated $\Sigma^{13}C_n$ using W and Sz indices

Compd	W	Sz	Sz/W	$\Sigma^{13}C_n$	$\Sigma^{13}C_n$ W		Estimated from Sz	
					Est.	Res.	Est.	Res.
1	178	369	2.0730	1285.0	1286.22	−1.22	1285.82	−0.82
2	179	372	2.0782	1297.2	1287.25	9.95	1287.40	9.80
3	176	366	2.0796	1281.2	1284.13	−2.93	1283.77	−2.57
4	176	366	2.0796	1285.6	1284.13	1.47	1283.77	1.83
5	181	376	2.0774	1279.9	1289.34	−9.44	1289.50	−9.60
6	186	386	2.0753	1295.0	1294.15	0.45	1294.75	0.25
7	185	383	2.0703	1295.2	1293.51	1.69	1293.18	2.02
			$\gamma=2.0757$					

Res, residue, that is difference between experimental and estimated $\Sigma^{13}C_n$ of dimethylnaphthalenes.

Table 3. Regression parameters and quality correlation for estimated[13] chemical shift and $\Sigma^{13}C_n$ of dimethylnaphthalenes used in the present investigation

Correlation	$A_i(i=1,2)$	$B_i(i=1,2)$	Sx	Sy	R
C_1–W	242.5728	−0.6202	4.4615	3.5220	0.7856
C_1–Sz	−2330.6753	6.6968	8.9149	6.0901	0.6213
C_2–W	40.1933	0.4997	4.1173	4.2751	0.4813
C_2–Sz	39.9921	0.2408	8.9149	4.2751	0.5022
C_3–W	163.2337	−0.1965	4.4615	3.3860	−0.2530
C_3–Sz	164.7814	−0.0988	8.9149	3.3860	−0.0988
C_4–W	77.8242	0.2702	4.4615	2.9678	0.4062
C_4–Sz	75.9030	0.1353	8.9149	2.9678	0.4064
C_5–W	155.2366	−0.1516	4.4615	3.3131	−0.2041
C_5–Sz	156.0137	−0.0751	8.9149	3.3131	−0.2020
C_6–W	73.5120	0.3041	4.4615	4.228	0.3208
C_6–Sz	67.4795	0.1626	8.9149	4.2284	0.3428
C_7–W	31.6313	0.5327	4.4615	3.6846	0.6450
C_7–Sz	31.8326	0.2560	8.9149	3.6927	0.6179
C_8–W	68.9022	0.3087	4.4615	1.5668	0.8791
C_8–Sz	67.4082	0.1527	8.9149	1.5668	0.8688
C_9–W	107.1206	0.1390	4.4615	1.2858	0.4824
C_9–Sz	107.9206	0.0648	8.9149	1.2858	0.4493
C_{10}–W	167.8446	−0.1978	4.4615	1.2734	−0.6932
C_{10}–Sz	167.1742	−0.6546	8.9149	1.2734	−0.6546
$\Sigma^{13}C_n$–W	1088.6842	1.1026	4.4615	6.3989	0.7818[a]
$\Sigma^{13}C_n$–Sz	1081.9385	0.5491	8.9149	6.3989	0.7685[a]
Mean ^{13}C–W	91.0414	0.0901	4.4615	0.5155	0.7749[a]
Mean ^{13}C–Sz	90.5053	0.0448	8.9149	0.5155	0.7755[a]

A_i,B_i, regression parameters; Sx, standard deviation in W or Sz; Sy, standard deviation in ^{13}C chemical shift or $\Sigma^{13}C_n$; R, correlation coefficient.
[a]When compounds **2** and **5** are deleted being outliers the R values becomes as high as 0.9643 and 0.9622 when W and Sz are respectively used for modelling $\Sigma^{13}C_n$.
Under similar conditions R values for modelling Mean ^{13}C changes to 0.9656 and 0.9641 respectively when W and Sz are used. The other statistics reported herein are for modelling O ^{13}Cn and Mean ^{13}C when either of the two compounds **2** and **5** are deleted.

compounds and that the number of cycles remained the same in all the dimethylnaphthalenes used. Hence, variations in S_z is due to tree-like substituent at different positions for which coincidence of S_z with W is well known.

The data presented in Table 2 show that difference in the experimental and estimated values of $\Sigma^{13}C_n$ NMR chemical shifts are much larger for compounds **2** and **5**. Thus, they can be considered as outliers. When treating either of the two compounds as outliers we observed that the correlation is increased dramatically to the extent that the correlation coefficient increases from 0.5880 to 0.7818 and from 0.5856 to 0.7685 when W and S_z indices are respectively used for predicting $\Sigma^{13}C_n$ NMR chemical shifts. Furthermore, when both these compounds, **2** and **5**, are deleted the correlation in dramatically increased to 0.9643 and 0.9622, respectively, when W and S_z are used for modelling $\Sigma^{13}C_n$.

If the derived chemical shifts sums are normalized by dividing the values with the number of carbon atoms in the molecule one apparently derives an average or mean carbon-13 chemical shifts for individual dimethylnaphthalenes. Because carbon-13 chemical shifts are atomic property, it seems more agreeable to refer to the composition when suitably normalized as a 'mean atomic' property. An additional advantage of this use of 'mean carbon-13 chemical shifts' over 'chemical shifts sums' is that the former facilitates comparison between molecules of different size. In view of this, we have normalized the chemical shifts sum by dividing them by the number of carbon atoms present in the dimethylnaphthalenes and observed that there was no improvement in the quality of correlations discussed above. This is obvious because the normalization factor (number of carbon atoms = 12) remained the same in all the cases. However, the regression expression changed to the following:

$$\text{Mean carbon-13 chemical shifts} = 91.6986 + 0.0870\,\text{W} \tag{5}$$

$$\text{Mean carbon-13 chemical shift} = 90.9663 + 0.0439\,S_z \tag{6}$$

The corresponding statistical parameters are shown in Table 3. Interestingly, S_y (standard deviation in mean carbon-13 chemical shift) values for these expressions are found lower than those for $\Sigma^{13}C_n$ NMR chemical shifts indicating that mean carbon-13 chemical shifts is a better molecular property than $\Sigma^{13}C_n$ NMR shifts.

Conclusions

From the aforementioned results and discussion, we conclude that the two-dimensional long range heteronuclear correlation NMR technique can be utilized for the assignment of quaternary carbon for the naphthalene systems. Also that, the W and Szeged Sz indices provide inside into variation of sum as well as mean carbon-13 chemical shifts and the same can be modeled successfully. To a lesser extent the individual carbon-13 chemical shifts are also modeled by both W and S_z indices. Our results also show that sum of the carbon-13 chemical shifts as well as mean carbon-13 chemical shifts are the excellent molecular properties. The case of ^{13}C NMR shifts in dimethylnaphthalenes well illustrate the difference between the statistical approaches such as graph theoretical approach where one can identify the critical structural parameters from observations rather than from computer read-outs of statistical packages, that at best give answers but cannot anticipate them. The results obtained may be useful for pharmaceutical and medicinal chemistry to better explain physiological activity exhibited by disubstituted naphthalenes.

Experimental

Chemicals

All dimethylnaphthalenes except **1** and **2** were purchased from Aldrich Chemical Company and used after purification. Proton and carbon NMR spectra of these compounds are consistent with the structural assignment as discussed above. Compounds 1 and 2 were analysed by mass spectra. All NMR spectra were obtained on $CDCl_3$ solution on a Varian XL-400 NMR spectrometer (^1H, 400 MHz; ^{13}C,101 MHz) using a 5-mm broad band probe. Two-dimensional spectra were recorded using standard pulse sequence and software available on the spectrometer system.

Cultural conditions

P. putida 1013, a strain that carries a naphthalene-degradative plasmid, NAH cell were grown in basal medium[18] overnight in a 30 °C shaker with the addition of sodium acetate (0.1%) as the carbon source and 2-aminobenzoate (0.005%) as the inducers. The cells were washed with 0.5 M Tris–HCl buffer. A typical incubation mixture contained: 1.4 mL of 0.05 M Tris–HCl, pH = 7.5, 0.01 mL of 0.1 M naphthalene substrates dissolved in *N*,*N*-dimethylformamide, 0.1 mL of 0.03 M NADH solution, and 0.02 mL of the cell suspension.

Isolation of 1 and 2

After 24 h, the culture supernant was filtered through a 0.22-μ filter. The monocarboxylic acids were precipitated with concentrated HCl. The precipitate was washed once with 70% aq ethanol. Metabolites were separated by HPLC using a reverse-phase C_{18} column; and subsequently derivatized with BF_3-CH_3OH (Pierce Chemical Co. Rockford, IL, USA) to convert carbon metabolites into their methyl esters for analysis by GC–MS. The fractions containing monocarboxymethylesters were then analyzed by NMR.

NMR experiments

NMR spectra were obtained in $CDCl_3$ solutions on a Varian XL-400 NMR spectrometer operating at 400 and 101 MHz for ^1H and ^{13}C, respectively. Using a 5-mm switchable probe. Normal 1-D ^1H and ^{13}C, NMR were obtained using the following acquisition parameters:

	^1H	^{13}C
Spectral width	4000 Hz	20,000 Hz
Pulse width	5 μs (12°)	6 μs (40°)
Acquisition	2.5 s	0.75 s

Two-dimensional spectra COSY and HETCOR were recorded using standard pulse sequences and parameters available on the spectrometer system. The two-dimensional NOE experiment (NOESY) consists of a sequence of three non-selective 90° pulses: $[90°-t_1-90°-t_m-90°-AT]_n$. The mixing time t_m was varied systematically as: mix + $0.1*t_1$ to diphase *J* correlations.[19] The delay 'mix' was chosen to be between 1 T_1 and 1.5 T_1. The longitudinal relaxation time T_1 for the protons of interest were determined by nonselective inversion-recovery experiment. The T_1 of the aromatic protons of 1 and 2 range from 3.5 to 4.6 s. The optimum mix was selected to be 5 s. The pulse sequence was repeated with a delay of 15 s, typically 32 transients were accumulated for each of 128 increments. The chemical shifts are reported in ppm downfield from tetramethylsilane.

Topological indices

Wiener index (W).[8] The Wiener index (W)[8] is the oldest and widely used topological index. It is based on the vertex distance of the respective molecular graph. Let us denote a molecular graph by ***G*** and having v_1, v_2, $v_3 \ldots v_n$. its verices. Let $d(v_i,v_j|G)$ stands for the distance between the vertices v_i and v_j. Then the Wiener index (W) is defined as:

$$W = W(G) = \_\sum_{i=1}^{n}\sum_{j=1}^{n} d(v_i, v_j|G)$$

Szeged index *(Sz)*.[9,10] Let *e* be an edge of the molecular graph ***G***. Let $n_1(e|G)$ be the number of vertices of *G* lying closer to one end of *e*; let $n_2(e|G)$ be the number of vertices of *G* lying closer to the other end of *e*. Then the Szeged index (*Sz*) is defined as:

$$Sz = Sz(G) = \sum_{e} n_1(e|G) n_2(e|G)$$

with the summation going over all edges of *G*.

In cyclic graphs, there are edges equidistant from both the ends of edge *e*; by definition of *Sz,* such edges are not taken into account. These calculations were made using the Software provided by Professor Lukovits.

Regression analysis.[20] All the regression analyses[20] were carried out using the software provided by Professor Lukovits, Hungarian Academy of Sciences, Budapest, Hungary.

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