October 2007 Volume 2 Issue 3

Physical CHEMISTRY
An Indian Journal

Trade Science Inc.

Full Paper

PCAIJ, 2(3), 2007 [176-186]

# A New Approach For The Calculation Of N-15 Chemical Shifts Of Cyclic Compounds

**Emad A.S.Al-Hyali**
**Chemistry Department, College of Education, University of Mosul (IRAQ)**
*Received: 25th May, 2007 ; Accepted: 30th May, 2007*

## ABSTRACT

Two sets of additive parameters used previously for the calculation of C-13 chemical shifts of mono and poly six member cycloalkanes are applied for the prediction of N-15 chemical shifts of some methyl piperidine derivatives. These sets are based on two principles; The p-character (substituents electronic effect) of the atom under consideration and the steric effect that reflect the spatial arrangement of the molecule. Additional parameter, namely the ring angle at the studied atom, is added to the other parameters to define the structural distortion that due to large steric interactions. The p-character in set (1) is represented by the number of carbon atoms of primary, secondary, tertiary, and quaternary types at α-position to the nitrogen, while in set (2) is introduced as the partial electronic charge. The steric effect is expressed in terms of the actual number of the interacting proton- proton and/or proton-loan pair in both sets. Quantum mechanical and regression analysis methods are employed for this treatment. The results showed that, both sets are good for prediction of N-15 chemical shifts. The parameters of set (2) are found to be more consistent with the theory of nuclear magnetic resonance(NMR) spectroscopy, therefore, they are considered for further studies. The Study also included derivation of a common set of parameters for the calculation of C-13 and N-15 chemical shifts of cyclic systems. The derived parameters are tested by the estimation of the chemical shifts of other systems. Deviations are noticed only in positions that involved in large steric interactions.


## KEYWORDS

N-15 Chemical shift;
Additive parameters;
Regression analysis.

## INTRODUCTION

The chemical shifts behavior of N-15 NMR is often very closely parallels to that of C-13 NMR in which the main factors that affect the chemical shifts are structural and electronic phenomena of the atom under consideration[1-4]. Thus for common organic molecules, the range of N-15 chemical shifts is slightly larger than that of C-13 and reaches to about 500ppm. The feature that distinguishes the nitrogen from carbon is the presence of unshared electron pair which makes the resonance positions very sensitive to solvent changes due to intermolecular interactions. In this case comparison of chemical shift data, obtained from different sources, for structural elucidation purposes become very difficult. Accordingly correlations should be based, as much as possible, on data obtained under comparable conditions.

Treatment of N-15 NMR chemical shifts data, when eliminating the solvent effect by using non polar solvent, could be based(like the C-13 chemical shifts) on two factors[5-7], the paramagnetic term(p-character) and steric effect. The p-character represents the weight of p-electrons in the total bonding electrons of nitrogen, which means it is electronic in nature and consider the effects that come through bond(inductive). The steric effect is represented by proton-proton(H-H) and proton-loan pair(H-Lp) interactions which result from the spatial arrangement of the molecule. Its influence is most probably caused by distortion of the normal tetrahedral geometry[8,9] of the considered atom. Depending on these two factors, several sets of additive parameters have been suggested in order to treat the N-15 chemical shifts by statistical and semi empirical methods.

Duthaler and Robert[3] treated the N-15 chemical shifts data for some primary, secondary and tertiary amines and their hydrochlorides in a similar manner to that employed by Grant and Paul[6] when treated the C-13 chemical shifts of analogous compounds. The p-character is introduced in terms of the type of primary, secondary and tertiary amines. Substituents parameters for carbon atoms, two and three bonds away from the nitrogen atom are introduced. Correction terms are also added in cases where large deviation between the observed and calculated chemical sifts are noticed. This suggests the presence of the influence of proton interactions.

The effect of methylation on the N-15 chemical shifts of piperidines and their hydrochlorides is studied[7]. This investigation showed that, in such compounds both ring and nitrogen inversion allow a large number of conformational possibilities than are present in the corresponding hydrocarbons. The axial-equatorial loan pair orientation is found to have a great effect on the value of the chemical shift; which is likely arising from the interactions between the loan pair and anti-periplanar C-C or C-H orbitals. The experimental results indicated that, the trend displayed by alicyclic amines are quite analogous to those of acyclic compound

Khalil[10] refined the contributed parameters by Shahab and Al-Wahab[11] to the calculation of the C-13 chemical shifts of normal and branched alkanes and used them for calculating the N-15 chemical shifts of analogous compounds. In this contribution, Shahab and Al-Wahab directed the attention towards the role of proton interactions by introducing parameters representing these interactions in terms of the number of protons present on the carbon atoms at $\alpha$, $\beta$, $\gamma$, $\delta$, and $\varepsilon$-positions. The p-character is described as the number of carbon atoms at $\alpha$-position of primary, secondary, tertiary and quaternary types.

Despite the great efforts that undertaken by the authors mentioned in the literature so far, non of the employed methods could treat the N-15 chemical shifts satisfactorily. So we think that, there is a lack in the information regarding this field of investigations and more studies are required in order to give a clear picture of the causative factors those affecting the N-15 chemical shifts.

In a recent study[12], the author succeeded in developing a new set of parameters for the calculation of C-13 chemical shifts of mono and poly six member rings cycloalkanes. The p-character is presented as the number of carbon atoms at $\alpha$-position of primary, secondary, tertiary and quaternary type where as the steric effect is introduced in terms of the exact number of proton-proton interactions relying on the fact that protons located in opposite planes don't affect each others.

More recently[13] the later parameters are more refined. The p-character of the carbon under consideration is treated in terms of the electronic charge(EG), which is the average substituents effect that, a certain carbon experience. The(H-H) interactions are calculated manually by means of building a model compounds. These parameters are also applied on the mono and poly six member rings hydrocarbons. The mentioned parameters are proved to be conformational dependent and could be used successfully to predict unknown chemical shifts with accepted TABLE errors.

The success in applying these parameters on the calculation of C-13 chemical shifts of cyclic compounds, and since the p-character (EG) doesn't discriminate the type of the studied atoms except in their values, we think that, these parameters could be applied on the calculations of N-15 chemical shifts of compound of analogous structure. Only additional parameters regarding (H-Lp) interactions have to be included.

In this research work, the last two sets of parameters mentioned above are applied to calculate the N-15 chemical shifts of methyl derivatives of piperidines and N-methyl piperidines compounds. Comparison between the results of applying the two sets will be carried out. The study also included an attempt to develop a general set of parameters that can be employed to calculate the C-13 and N-15 chemical shifts for cyclic hydrocarbons.

## EXPERIMENTAL

Two sets of additive parameters are applied in this investigation for the prediction of the N-15 chemical shifts. Those parameters are based on two factors; the p-character of the nitrogen atom under consideration, which reflect the electronic effect of the neighboring substituents, and the steric effect indicated by the (H-H) and/or (H-Lp) interactions. Such interactions are repulsion and/or attraction forces, and depend on the structural geometries of the studied molecules.

In the first set(1) of the applied parameters, the p-character is introduced in terms of the number of α-carbon of primary(α-ptri), secondary(α-sec), tertiary(α-ter) and quaternary(α-quat) types. The(H-H) and (H-Lp) interactions are represented by the actual numbers of the interactions in the α, β, and γ-positions. The β- interactions are divided into two type depending on the distance and angle[14] between the interacting protons or proton-loan pair. The first type is assigned as $\beta^a$ and refers to the interactions between two protons or proton-loan pair located in the same plane, either axial or equatorial. The other is given the symbol $\beta^{ae}$ and explain the interaction between(H-H) or (H-Lp), one of them in the axial position and the other is equatorial figure 1.

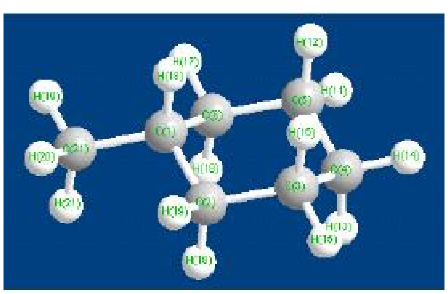


**Figure (1): Methyl cyclohexane, Example of α-(H-H) interactions on C(2) are (H(19)-H(16), H(19)-H(15)), Example of $\beta^a$ –(H-H) interaction on C(2) is (H(19)-H(20)), Example of $\alpha^{ae}$ – (H-H) interaction on C(2) is (H(19)-H(21))**

In the second set(2) of the suggested additive parameters, the p-character is represented as the electronic charge(EG) of the nitrogen atom under consideration, while the(H-H) and(H-Lp) interactions are treated in a similar to that of set(1). Additional structural parameters such as ring angle(<C-N-C) of the studied molecule in some cases of this treatment is added. The number of interacting (H-H) and (H-Lp) are calculated as follow:

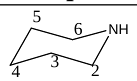
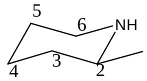
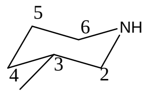
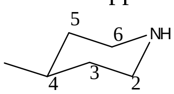
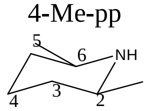
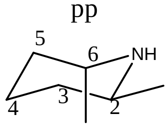
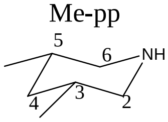
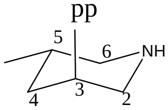
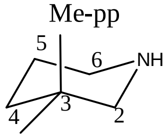
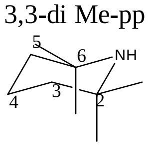
1. A model is constructed for each compound, according to its most stable conformation(less energy) that determined by employing the chem. Office program of cambridge university(version 2000) by energy minimization, and used for the calculation.
2. The compounds of definite conformations(exist in one energically favored conformation), a single model is used for the calculation. This is determined from the molecular energy measurement as will be illustrated later.
3. Compounds, those exist in two interconvertable conformations of equal energies, the number of interacting(H-H) and(H-Lp) are weight average of the two conformations.

The values of the EG(<C-N-C) and TE are calculated by employing the chem. Office program as follow; The structure of the studied molecule is plotted by the CS chem draw program. The molecule is transferred into the CS chem.3D program in order to convert it to a three dimension molecule. This process is followed by molecular dynamic using the MM2 program and then energy minimization is carried out. The TE and(<C-N-C) of the investigated molecule are recorded, and the charge is determined by the extended Hückel method. Their values as well as the other parameters are used for the formulation of the matrix which is employed for the multi-parametric linear regression analysis to calculate the N-15 chemical shifts. The well known statistical program of SPSS is used for this purpose.

In the regression analysis the observed chemical shifts($\delta_{N\text{-}15\ obs}$) are considered as the dependent variable(Y in eq.1) while the parameters are applied as independent variables ($X_1$, $X_2$, …, Xn). The matrix (TABLE 1 and 2) is generated on the basis of a linear model according to the following equation.

$$Y=B+a_1X_1+a_2X_2+\text{—}+a_nXn \quad (1)$$

TABLE 1:The parameters of sets (1) and (2) applied on the piperdine compounds

| *Compound | Charge on N | No. of carbon | | | No. of interacting | | | | No. of interacting | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -α sec | -α ter | -α quat | -αH-H | -β^a H-H | -β^ae H-H | -γH-H | -αH-Lp | -β^a H-Lp | -β^ae H-Lp | -γ H-Lp |
|  piperidine (pp) | -0.210 | 2 | 0 | 0 | 3 | 1 | 0 | 0 | 3 | 1 | 0 | 0 |
|  2-Me-pp | -0.215 | 1 | 1 | 0 | 1 | 3 | 1 | 0 | 3 | 1 | 1 | 0 |
|  3-Me-pp | -0.211 | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 4 | 0 | 0 | 0 |
|  4-Me-pp | -0.210 | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 4 | 0 | 0 | 0 |
|  cis-2,6-di Me-pp | -0.221 | 0 | 2 | 0 | 1 | 3 | 2 | 0 | 1 | 3 | 2 | 0 |
|  trans-2,6-di Me-pp | -0.222 | 0 | 2 | 0 | 1.5 | 2.5 | 1.5 | 0 | 1.5 | 2.5 | 1.5 | 0 |
|  cis-3,5-di Me-pp | -0.212 | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 4 | 0 | 0 | 0 |
|  trans-3,5-di Me-pp | -0.212 | 2 | 0 | 0 | 3 | 0.5 | 0 | 0.5 | 3 | 0.5 | 0 | 0.5 |
|  3,3-di Me-pp | -0.212 | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 4 | 0 | 0 | 0 |
|  2,2,4,4- Tetra Me-pp | -0.232 | 0 | 0 | 2 | 0 | 4 | 2 | 0 | 0 | 4 | 4 | 0 |

*N-15 chemical shifts are considered as the dependent variable

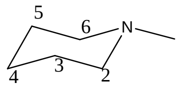
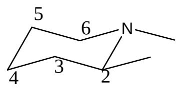
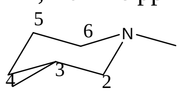
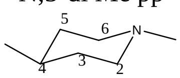
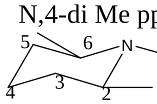
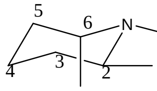
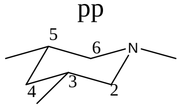
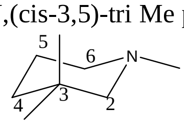
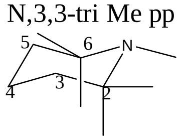
The coefficients of the parameters ($a_1$, $a_2$,…, $a_n$) and the constant (B) are obtained as a results of the regression analysis. The success of the selected parameters is estimated in terms of the correlation coefficient (R) and standard deviation (SD).

## RESULTS AND DISCUSSION

Additive parameters of N-15 NMR chemical shifts have been reported by several authors[5,8]. Most of these parameters were merely empirical and bear no signifi-

Full Paper

TABLE 2 : The parameters of sets (1) and (2) applied on the N-methyl piperdines

| *Compound | Charge on N | Angle <C-N-C | **No. of carbon -$\alpha$-sec | -$\alpha$-ter | -$\alpha$-quat | No. of interacting -$\alpha$H-Lp | -$\beta^{a}$H-Lp | -$\beta^{ae}$H-Lp | -$\gamma$H-Lp |
|---|---|---|---|---|---|---|---|---|---|
|  N-Me-pp | -0.119 | 111.157 | 2 | 0 | 0 | 4 | 2 | 0 | 0 |
|  N,2-di Me pp | -0.127 | 111.280 | 1 | 1 | 0 | 3 | 3 | 1 | 0 |
|  N,3-di Me pp | -0.120 | 111.303 | 2 | 0 | 0 | 4 | 2 | 0 | 0 |
|  N,4-di Me pp | -0.119 | 111.058 | 2 | 0 | 0 | 4 | 2 | 0 | 0 |
|  N,(cis-2,6)-tri Me pp | -0.134 | 111.684 | 0 | 2 | 0 | 2 | 4 | 2 | 0 |
|  N,(trans-2,6)-tri Me pp | -0.128 | 113.000 | 0 | 2 | 0 | 3 | 3 | 1 | 0 |
|  N,(cis-3,5)-tri Me pp | -0.121 | 111.119 | 2 | 0 | 0 | 4 | 2 | 0 | 0 |
|  N,3,3-tri Me pp | -0.121 | 111.033 | 2 | 0 | 0 | 4 | 1 | 0 | 1 |
|  N,2,2,6,6-penta Me pp | -0.131 | 117.053 | 0 | 0 | 2 | 2 | 4 | 2 | 0 |

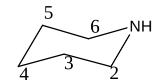
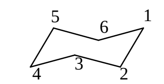
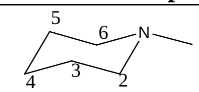
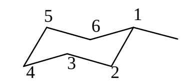
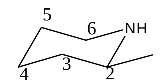
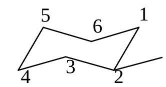
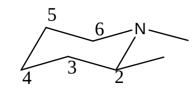
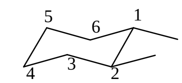
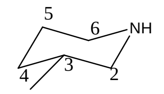
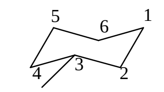
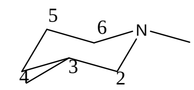
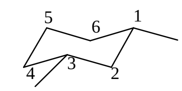
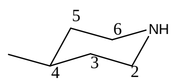
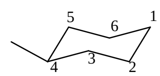
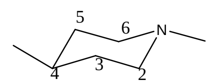
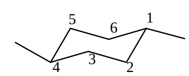
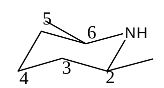
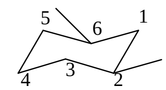
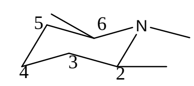
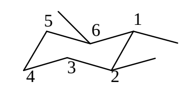
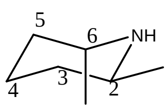
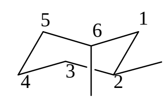
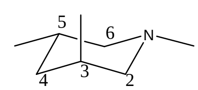
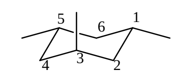
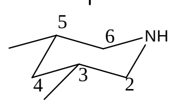
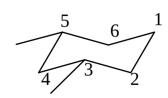
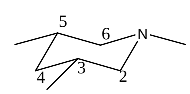
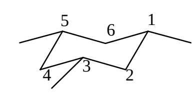
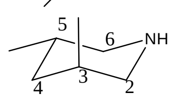
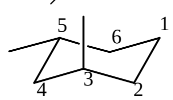
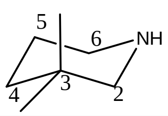
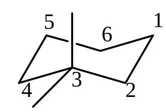
*N-15 chemical shifts are considered as the dependent variable; **The number of carbon atoms ($\alpha$-pri)=1 for all the compounds.

cance relating to the theory of N-15 NMR spectroscopy. In addition, none of these investigations were entirely successful since they were not able to introduce a clear picture of the factors those affecting the N-15 chemical shifts. So more detailed studies may be required to clue the ambiguity in this field.

The compounds selected for this study (listed in TABLES 1 and 2) are methyl derivatives of piperidine and N-methyl piperidine. The reason of choosing these compounds is their conformation analogy to cyclohexanes, so comparison could be carried out between the two systems. The effect of axial-equatorial loan pair inversion which may create various conformational that affect the N-15 chemical shifts[3] of the studied compounds could be investigated. The experimental N-15 chemical shifts of the studied compound[7] are obtained under the same medium conditions and measured in an inert solvent (cyclohexane) in order to reduce or eliminate the solvent effect, so the suggested parameters could be applied without any restriction and used for structural correlation.

The idea of this study emerged from the point of similarity of the behavior of N-15 and C-13 chemical shifts of analogous compounds. TABLE 3 shows the results of the correlation between selected piperidines and N-methyl piperidines with their corresponding methyl cyclo-

**TABLE 3: Correlation results of selected piperidines and N-methyl piperidines with their analogous methyl cyclohexanes**

| PP compds. | $\delta_{N-15}$ | Cyclo-hexanes | $\delta_{C-13}$ of $C_1$ | N-Me-PP compds | $\delta_{N-15}$ | Methyl cyclohexanes | $\delta_{C-13}$ of $C_1$ |
|---|---|---|---|---|---|---|---|
|  | 37.7 |  | 27.06 |  | 37.4 |  | 33.06 |
|  | 54.9 |  | 35.77 |  | 48.9 |  | 39.55 |
|  | 37.0 |  | 26.55 |  | 36.4 |  | 32.82 |
|  | 36.5 |  | 26.4 |  | 37.0 |  | 32.61 |
|  | 73.7 |  | 44.7 |  | 62.1 |  | 46.22 |
|  | 63.8 |  | 41.42 |  | 28.9 |  | 26.44 |
|  | 37.5 |  | 26.45 |  | 36.8 |  | 32.68 |
|  | 26.7 |  | 20.75 | | | | |
|  | 30.4 |  | 22.58 | | | | |

Correlation coefficient=0.9998, Standard deviation=1.078, $\delta_{N-15}$=-13.274 +1.905 $\delta_{C-13}$, Correlation coefficient =0.9993,Standard deviation=1.373, $\delta_{N-15}$=-18.940+1.726 $\delta_{C-13}$

**TABLE 4 : Values of the total energies (in Kcal/mole) of piperidines with the loan pair in the axial and equatorial positions**

| Compound | TE with axial loan pair | TE with equatorial loan pair | Difference |
|---|---|---|---|
| piperidine (pp) | 6.065 | 6.371 | 0.306 |
| 2-Me-pp | 6.399 | 6.710 | 0.311 |
| 3-Me-pp | 6.367 | 6.670 | 0.303 |
| 4-Me-pp | 6.358 | 6.662 | 0.304 |
| Cis-2,6-di Me-pp | 6.698 | 7.020 | 0.322 |
| trans-2,6-di Me-pp | 8.825 | 9.056 | 0.231 |
| Cis-3,5-di Me-pp | 6.643 | 9.942 | 0.299 |
| trans-3,5-di Me-pp | 8.301 | 8.627 | 0.326 |
| 3,3-di Me-pp | 8.797 | 8.440 | 0.357 |
| 2,2,4,4- Tetra Me-pp | 14.619 | 14.670 | 0.051 |

hexanes. The values of the correlation coefficients obtained proved the good relation between these compounds. The relatively high values of standard deviations may due to the difference in some geometrical aspects.

The piperidines and N-methyl piperidines are treated separately by applying the set (1) and set (2) parameters mentioned previously. Since the application of the

**TABLE 5 : Values of the total energies (in Kcal/mole) of N-methyl piperidines with the loan pair in the axial and equatorial positions**

| Compound | TE with axial loan pair | TE with equatorial loan pair | Difference |
|---|---|---|---|
| N-Me-pp | 9.749 | 12.283 | 2.534 |
| N,2-di Me pp | 12.015 | 14.159 | 2.144 |
| N,3-di Me pp | 10.025 | 12.532 | 2.509 |
| N,4-di Me pp | 10.018 | 12.515 | 2.497 |
| N,(cis-2,6)-tri Me pp | 14.931 | 16.361 | 1.430 |
| N,(trans-2,6)-tri Me pp | 15.916 | 17.372 | 1.456 |
| N,(cis-3,5)-tri Me pp | 11.906 | 12.944 | 1.038 |
| N,(trans-3,5)-tri Me pp | 11.920 | 17.084 | 5.163 |
| N,3,3-tri Me pp | 12.052 | 17.846 | 5.794 |
| N,2,2,6,6-penta Me pp | 26.598 | 30.445 | 3.847 |

suggested parameters especially the number of (H-H) and (H-Lp) interactions require (according to this method) building model compounds in order to count them manually and formulate the matrix for the regression analysis and since the loan pair could occupy the axial and equatorial positions, knowledge about the con-

**TABLE 6 : Regression analysis results of piperdines when applying sets (1 and 2) parameters**

| Column A (Set (1)) | | Column B (Set (2)) | |
|---|---|---|---|
| **Parameter** | **Coefficients values** | **Parameter** | **Coefficients values** |
| **P-character** | | **P-character** | |
| -α-ter | -1.773 | Charge | 85.886 |
| -α-quat | -7.632 | No.of (H-H) interaction | |
| No.of (H-H) interaction | | -α | -4.324 |
| -α | -9.500 | $-\beta^{ae}$ | 9.106 |
| -γ | -6.582 | -γ | -6.488 |
| No.of (H-Lp) interaction | | No.of (H-Lp) interaction | |
| -α | -10.245 | - α | -4.917 |
| -γ | -15.473 | - γ | -15.074 |
| Constant | | Constant | |
| Correlation | 96.964 | Correlation | 83.414 |
| Coefficient | 1.0±0.41 | Coefficient | 1.0± 0.54 |
| Standard deviation | | Standard deviation | |

*Res. $=\delta_{N\text{-}15\ calc}-\delta_{N\text{-}15\ obs.}$

**TABLE 7 : Comparison between the experimental[3,7] and calculated values of N-15 chemical shifts of piperidines calculated from the results of sets (1 and 2) in TABLE 6**

| Compounds | $\delta_{N\text{-}15\ obs}$ | $\delta_{N\text{-}15\ calc}$ (set1) | *Res. | $\delta_{N\text{-}15\ cal}$ (set2) | *Res. |
|---|---|---|---|---|---|
| piperidine (pp) | 37.70 | 37.73 | 0.03 | 38.51 | 0.81 |
| 2-Me-pp | 54.90 | 54.96 | 0.06 | 54.97 | 0.07 |
| 3-Me-pp | 37.00 | 36.98 | -0.02 | 36.97 | -0.03 |
| 4-Me-pp | 36.50 | 36.98 | 0.48 | 37.06 | 0.56 |
| Cis-2,6-di Me-pp | 73.70 | 73.67 | -0.03 | 73.40 | -0.30 |
| trans-2,6-di Me-pp | 63.80 | 63.80 | 0.0 | 64.14 | 0.34 |
| Cis-3,5-di Me-pp | 37.50 | 36.98 | -0.52 | 36.89 | -0.61 |
| trans-3,5-di Me-pp | 26.70 | 26.70 | 0.0 | 26.70 | 0.0 |
| 3,3-di Me-pp | 30.40 | 30.40 | 0.0 | 30.40 | 0.0 |
| 2,2,4,4- Tetra Me-pp | 81.70 | 81.70 | 0.0 | 81.70 | 0.0 |

formations must be available to do this job.

The total energy of each compound is estimated with the loan pair being in the axial and equatorial positions. TABLES 4 and 5 show the values obtained for piperidines and N-methyl piperidines respectively.

The results of TABLES 4 and 5 indicate that, the piperidines exist in two conformations of nearly equal energies, so the number of interacting (H-H) and (H-Lp) are weight average over the two conformations. The great (H-Lp) interactions of the γ-gauche type[6] in the N-methyl piperidine compounds when the methyl group located in the axial position create a relatively high difference in the total energy of the molecule compared to the same molecule in the equatorial position. This suggest that, the studied N-methyl piperidines exist in one favorable conformation. For this reason the (H-Lp) interactions are calculated by considering the conformation of the lower energy(more stable one).

## Piperidines

The two sets of additive parameters(sets 1 and 2) stated in the experimental part are applied for the estimation of N-15 NMR chemical shifts of the piperidine compounds considered for this study. The results obtained from the multiple regression analysis when employing sets (1 and 2) parameters are listed in TABLE 6, column A and B, respectively.

Comparison between the observed and calculated N-15 chemical shifts of those obtained by using the results of TABLE 6 are portrayed in TABLE 7.

The application of sets (1) and (2) parameters on the piperidine (TABLES 6 and 7) compounds gave comparable results. They suggest that, both sets could be used successfully for the prediction of N-15 chemical shifts of such compounds. A close look at the coefficient values of the parameters obtained from the regression analysis (TABLE 6) indicate the following:

**(1)** The negative values of the coefficients of the parameters of set (1) belonging to the paramagnetic term (p-character)(α-pri, α-sec, α-ter, and α-quat) refer to shielding effect which is inconsistent with the nmr theory. The replacement of these parameter by the electronic charge(in set 2) gave a better physical meaning in terms of the theory of the NMR spectroscopy, in which, the increase in electronic charge increases the non spherical distribution of electrons(in the p-orbital) around the nucleus and leading to a more de-shielding effect. The replacement of several parameters by a single one is an additional advantage that makes set 2 more preferable for such calculations.

**(2)** The (H-H) interaction parameters α and γ have negative values referring to shielding effect. This effect can be explained in terms of the repulsion among protons of nitrogen and carbon atoms which depend on their spatial arrangements. Such repulsions may push further the valence electrons of N-H towards the nitrogen nucleus, and therefore, this would extend the shielding around it. The β-interactions are found to exhibit de-shielding effect, this could be related to the difference in direction of the interacting protons present on the β-positions. These observations are in good agreement with the reported re-

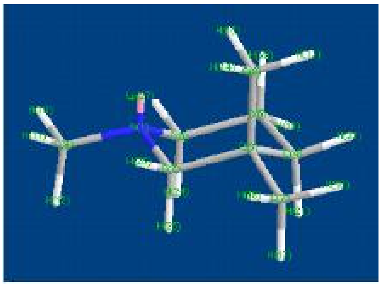


**Figure 2: This model shows example of the γ-interaction in which the H(16) and loan pair Lp(17)) are directed toward each other, while the α-interacting H(10) and Lp(17) are not**

**TABLE 8 : Regression analysis results of applying set (1) on the N-methyl piperidines**

| Parameters | Coefficient value |
|---|---|
| p-character | |
| No. of carbons -α-ter | -4.957 |
| -α-quat | -10.543 |
| No. of interacting H-Lp | |
| $-\beta^{ae}$ | 17.471 |
| -γ | -4.243 |
| Constant | 36.843 |
| Correlation coefficient | 0.9999 |
| Standard deviation | ± 0.44 |
| No. of observation | 9 |

**TABLE 9 : Regression analysis results of applying set (2) on the N-methyl piperidines and then adding the ring angle (<C-N-C)parameter to the regression**

| Column A | | Column B | |
|---|---|---|---|
| **Parameter** | **Coefficient** | **Parameter** | **Coefficient** |
| **p-character** | | **p-character** | |
| Charge | -1347.619 | Charge | 545.169 |
| No of interacting H-Lp | | No of interacting H-Lp | |
| -α | 0.990 | $-\beta^{ae}$ | 16.966 |
| -γ | -5.648 | -γ | -3.785 |
| | | Angle (<C-N-C) | -2.372 |
| Constant | -124.814 | Constant | 365.743 |
| Correlation coefficient | 0.9960 | Correlation coefficient | 0.9999 |
| Standard deviation | ± 3.36 | Standard deviation | ± 0.58 |
| No. of observation | 9 | No. of observation | 9 |

sults of the literature[6,11,14] of C-13 NMR studies.

**(3)** The coefficient values of α-(H-H) and (H-Lp) interaction parameters are close to each other which are(-4.324) and (-4.917) respectively, while the value of the coefficient of the γ-(H-Lp ) interactions parameter(-15.074) is nearly double the value of γ-(H-H) interactions (-4.324). This can be related to the spatial distance and the difference in the direction of the interaction. The molecular structure models show that, in the γ-gauche interactions, the two protons or proton and loan pair of electrons are directed toward each other, while the α-protons are not(Figure 2). Since the space occupied by the free loan pair is relatively larger than that of the valence electrons of the C-H bond, The γ-(H-Lp) interactions will be greater than that of γ-(H-H) interactions.

**(4)** The values of the correlation coefficients and standard deviations are good indication of the correct choice of parameters that selected for this study.

## N-methyl piperidines

The methyl piperidines are treated in a similar way as the piperidine compounds. The main difference between them is that, the proton in the later is replaced by a methyl group, so only(H-Lp ) interactions are noticed in these compounds.

The results of the regression analysis when applying(set1) and (set 2) parameters on N-methyl piperidines are listed in TABLES 8 and 9 respectively.

The results of TABLES 8 and 9 column B show the same trend as that noticed in the results of regression analysis of TABLE 6 columns A and B of piperidine compounds respectively, which could be interpreted in the same way. The difference in the values of proton interaction coefficients of the two types may refer to the structural dimensions which reflect the dependence of such interactions on the size and distance between the interacting atoms or loan pairs. The angle(<C-N-C) values (calculated by the chem. Office program and listed in

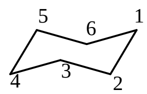
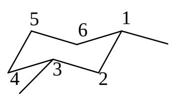
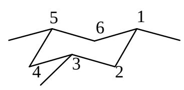
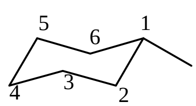
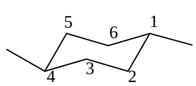
**TABLE 10 : Comparison between the observed and calculated chemical shifts obtained from employing the results of TABLES 8 and 9 column B respectively**

| Compound | $\delta_{N\text{-}15\ obs}$ | $\delta_{N\text{-}15\ calc}$ TABLE 8 | *Res. | $\delta_{N\text{-}15cal}$ TABLE 9B | *Res. |
|---|---|---|---|---|---|
| N-Me-pp | 37.4 | 36.84 | -0.56 | 37.20 | -0.20 |
| N,2-di Me pp | 48.9 | 49.36 | 0.46 | 49.52 | 0.62 |
| N,3-di Me pp | 36.4 | 36.84 | 0.44 | 36.31 | -0.09 |
| N,4-di Me pp | 37.0 | 36.84 | -0.16 | 37.44 | 0.44 |
| N,(cis-2,6)-tri Me pp | 62.1 | 61.87 | -0.23 | 61.71 | -0.39 |
| N,(cis-3,5)-tri Me pp | 44.4 | 44.40 | 0.00 | 44.89 | 0.49 |
| N,(trans-3,5)-tri Me pp | 36.8 | 36.84 | 0.04 | 36.20 | -0.60 |
| N,3,3-tri Me pp | 32.6 | 32.60 | 0.00 | 32.62 | 0.02 |
| N,2,2,6,6-penta Me pp | 50.7 | 50.70 | 0.00 | 50.61 | -0.09 |

**$*Res = \delta_{N\text{-}15calc} - \delta_{N\text{-}15obs}$**

Full Paper

TABLE 11 : Cyclohexanes employed for the regression analysis in combination with the compounds of TABLE 2

| *Compound | $C_{No}$ | $\delta_{C\text{-}13\ ob}$ | Charge | <C-N-C | No. of interacting (H-H) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | -α | -$\beta^{a}$ | -$\beta^{ae}$ | -γ |
|  Cyclohexan | 1 | 27.06 | -0.057 | 110.948 | 6 | 2 | 0 | 0 |
| | 2 | 27.06 | -0.057 | 110.948 | 6 | 2 | 0 | 0 |
| | 3 | 27.06 | -0.057 | 110.967 | 6 | 2 | 0 | 0 |
| | 4 | 27.06 | -0.057 | 110.967 | 6 | 2 | 0 | 0 |
| | 5 | 27.06 | -0.057 | 110.969 | 6 | 2 | 0 | 0 |
| | 6 | 27.06 | -0.057 | 110.958 | 6 | 2 | 0 | 0 |
|  Cis-1,3 DMC | 1 | 32.82 | 0.017 | 110.435 | 4 | 2 | 0 | 0 |
| | 2 | 32.82 | 0.017 | 110.358 | 2 | 6 | 4 | 0 |
| | 3 | 44.70 | -0.068 | 112.116 | 4 | 2 | 0 | 0 |
| | 4 | 35.37 | -0.062 | 111.094 | 4 | 4 | 2 | 0 |
| | 5 | 35.37 | -0.062 | 111.147 | 6 | 2 | 0 | 0 |
| | 6 | 26.45 | -0.060 | 110.759 | 4 | 4 | 2 | 0 |
|  1-cis-3-cis-5-TMC | 1 | 32.68 | 0.016 | 110.477 | 4 | 2 | 0 | 0 |
| | 2 | 32.68 | 0.016 | 110.385 | 2 | 6 | 4 | 0 |
| | 3 | 32.68 | 0.016 | 110.306 | 4 | 2 | 0 | 0 |
| | 4 | 44.20 | -0.068 | 111.668 | 2 | 6 | 4 | 0 |
| | 5 | 44.20 | -0.068 | 111.546 | 4 | 2 | 0 | 0 |
| | 6 | 44.20 | -0.068 | 111.727 | 2 | 6 | 4 | 0 |
|  1-MC | 1 | 33.06 | 0.018 | 110.413 | 4 | 2 | 0 | 0 |
| | 2 | 35.77 | -0.063 | 111.304 | 4 | 4 | 2 | 0 |
| | 3 | 35.77 | -0.063 | 111.304 | 6 | 2 | 0 | 0 |
| | 4 | 26.55 | -0.058 | 110.890 | 6 | 2 | 0 | 0 |
| | 5 | 26.55 | -0.058 | 110.871 | 6 | 2 | 0 | 0 |
| | 6 | 26.40 | -0.057 | 110.594 | 4 | 4 | 2 | 0 |
|  Trans-1,4- DMC | 1 | 32.61 | 0.018 | 110.063 | 4 | 2 | 0 | 0 |
| | 2 | 32.61 | 0.018 | 110.052 | 4 | 4 | 2 | 0 |
| | 3 | 35.63 | -0.064 | 111.544 | 4 | 4 | 2 | 0 |
| | 4 | 35.63 | -0.064 | 111.449 | 4 | 2 | 0 | 0 |
| | 5 | 35.63 | -0.064 | 111.063 | 4 | 4 | 2 | 0 |
| | 6 | 35.63 | -0.064 | 111.163 | 4 | 4 | 2 | 0 |

***D=di, M=methyl, T=tri, and C=cyclohexane**

TABLE 2) in addition to its relatively high coefficient support the idea that, the proton interactions affect the N-15 chemical shifts through the distortion of their tetrahedral symmetry. Comparison between the observed and calculated N-15 chemical shifts those obtained from the regression analysis results of TABLES 8 and 9 column B are portrayed in TABLE 10.

The values of TABLE 10 show good agreement between the observed and calculated chemical shifts when applying both of sets (1) and (2) parameters. The parameters of set (2) are considered for further calculations because of their consistency with the theory of N-15 chemical shift and their physical meaning in terms of the nmr spectroscopy.

## Combination of C-13 and N-15 chemical shifts

The success of applying the parameters of set (2) for the prediction of N-15 chemical shifts of six member ring compounds, as well as, the previous success of the application of these parameters on mono and poly six member rings cycloalkanes[12], and according to the assumption that made earlier in which the partial

**TABLE 12 : Results of regression analysis of applying set (2) on a mixture C-13 and N-15 chemical shifts of methyl cyclohexanes and piperidines**

| Parameters | Coefficient value |
|---|---|
| Charge | 14.018 |
| No. of interacting H-H | |
| -α | -1.88 |
| -$\beta^{ae}$ | 2.954 |
| No. of interacting H-Lp | |
| -$\beta^{ae}$ | 12.899 |
| -γ | -4.310 |
| Angle<C-N-C | -1.975 |
| Constant | 257.861 |
| Correlation coefficient | 0.9998 |
| Standard deviation | ±0.56 |
| No. of observation | 39 |

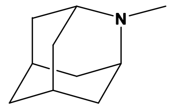
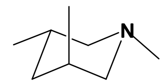
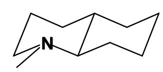
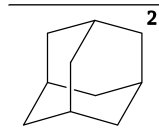
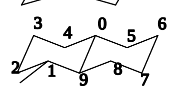
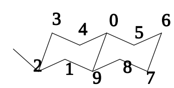
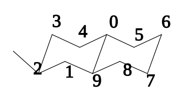
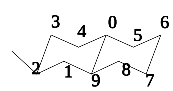
**TABLE 13 : Comparison between the observed and calculated C-13 and N-15 chemical shifts obtained from employing the results of TABLE 12**

| Compound | $C_{No.}$ | $\delta_{C-13\ or\ N-15obs.}$ | $\delta_{C-13\ or\ N-15calc}$ | Res. |
|---|---|---|---|---|
| Cyclohexane | 1 | 27.06 | 26.66 | -0.40 |
| | 2 | 27.06 | 26.66 | -0.40 |
| | 3 | 27.06 | 26.62 | -0.44 |
| | 4 | 27.06 | 26.62 | -0.44 |
| | 5 | 27.06 | 26.62 | -0.44 |
| | 6 | 27.06 | 26.64 | -0.42 |
| Cis-1,3 DMC | 1 | 32.82 | 32.47 | -0.35 |
| | 2 | 32.82 | 32.62 | -0.20 |
| | 3 | 44.70 | 43.53 | -1.17 |
| | 4 | 35.37 | 35.97 | 0.60 |
| | 5 | 35.37 | 35.86 | 0.49 |
| | 6 | 26.45 | 26.99 | 0.54 |
| 1-cis-3-cis-5- | 1 | 32.68 | 32.37 | -0.31 |
| TMC | 2 | 32.68 | 32.55 | -0.13 |
| | 3 | 32.68 | 32.71 | 0.03 |
| | 4 | 44.20 | 44.42 | 0.22 |
| | 5 | 44.20 | 44.66 | 0.46 |
| | 6 | 44.20 | 44.30 | 0.10 |
| | 1 | 33.06 | 32.53 | -0.53 |
| 1-MC | 2 | 35.77 | 35.54 | -0.23 |
| | 3 | 35.77 | 35.54 | -0.23 |
| | 4 | 26.55 | 26.76 | 0.21 |
| | 5 | 26.55 | 26.80 | 0.25 |
| | 6 | 26.40 | 27.36 | 0.96 |
| Trans-1,4- DMC | 1 | 32.61 | 33.22 | 0.61 |
| | 2 | 32.61 | 33.24 | 0.63 |
| | 3 | 35.63 | 35.05 | -0.58 |
| | 4 | 35.63 | 35.24 | -0.39 |
| | 5 | 35.63 | 36.00 | 0.37 |
| | 6 | 35.63 | 35.80 | 0.17 |
| N-Me-pp | N | 37.4 | 36.66 | -0.74 |
| N,2-di Me pp | N | 48.9 | 49.20 | 0.30 |
| N,3-di Me pp | N | 36.4 | 36.36 | -0.04 |
| N,4-di Me pp | N | 37.0 | 36.85 | -0.15 |
| N,(cis-2,6)-tri Me pp | N | 62.1 | 61.20 | -0.90 |
| N,(cis-3,5)-tri Me pp | N | 44.4 | 45.79 | 1.39 |
| N,(trans-3,5)-tri Me pp | N | 36.8 | 36.70 | -0.10 |
| N,3,3-tri Me pp | N | 32.6 | 32.56 | -0.04 |
| N,2,2,6,6-penta Me pp | N | 50.7 | 50.64 | -0.06 |

***Res.**=$\delta_{calc}$-$\delta_{obs}$

atomic charge (representing the p-character of the studied atom) does not discriminate the atoms except in their values, it is suggested that, a general set could be derived for the calculation of the C-13 and N-15 NMR chemical shifts. Relying on the above discussion, regression analysis is carried out (using the parameters of set (2)) on a number of selected cyclohexanes of definite conformation and least strain(listed in TABLE 11 combined with the N-methyl piperidines listed in TABLE 2. The choice of the later compound based on their structural similarities to the methyl cyclohexanes and their presence in one favorite conformation. The results of the regression analysis are given in TABLE 12.

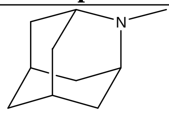
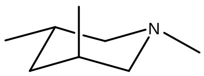
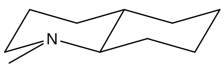
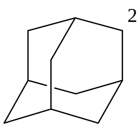
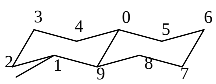
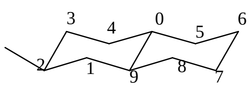
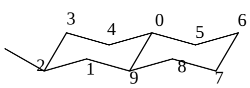
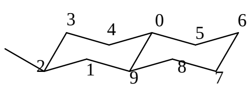
**TABLE 14 : Parameters of some rigid systems used for testing the success of the results of TABLE 12**

| Compd. | $C_{No.}$ | Charge | <C-N-C | No. of interacting (H-Lp) -α | -β[a] | -β[ae] | -γ |
|---|---|---|---|---|---|---|---|
|  | N | -0.125 | 110.635 | 4 | 2 | 0 | 0 |
|  | N | -0.121 | 111.119 | 4 | 1 | 0 | 1 |
|  | N | -0.130 | 111.616 | 3 | 3 | 1 | 0 |
| **Compd.** | **$C_{No.}$** | **Charge** | **<C-C-C** | **No. of interacting (H-H) -α** | **-β[a]** | **-β[ae]** | **-γ** |
|  | 2 | -0.069 | 109.456 | 4 | 4 | 0 | 0 |
|  | 1 | 0.007 | 112.187 | 3 | 3 | 1 | 0 |
|  | 2 | 0.017 | 110.129 | 4 | 2 | 0 | 0 |
|  | 1 | -0.071 | 113.154 | 2 | 6 | 4 | 0 |
|  | 3 | -0.064 | 111.366 | 4 | 4 | 2 | 0 |

The results of TABLE 12 agree in their trend and coefficient values with those obtained earlier (TABLE 9 column B). The high correlation coefficient and relatively low standard deviation give an indication to the agreement between the observed and calculated C-13 and N-15 chemical shifts of the considered compounds TABLE 13. Deviations are noticed only in cases of large steric interactions due to ring flattening[6].

The success of the suggested parameters for such treatment could be further tested by using the results of TABLE 12 for estimation the C-13 and N-15 chemical

**TABLE 15 : Observed chemical shifts of the compounds of TABLE 14 and their calculated values estimated by using the results of TABLE 12**

| Compound | Atom no. | $\delta_{N\text{-}15\text{ or }C\text{-}13\text{ obs}}$ | $\delta_{N\text{-}15\text{ or }C\text{-}13\text{ calc}}$ |
|---|---|---|---|
|  | N | *38.0 | 37.6 |
|  | N | *28.9<br>**32.3 | 32.39 |
|  | N | | 48.49 |
|  | 2 | | 33.198 |
|  | 1 | #38.42 | 39.61 |
|  | 2 | #33.06 | 33.07 |
|  | 1 | #43.31 | 41.44 |
|  | 3 | #35.66 | 35.40 |

*Measured[15] in $C_6H_{12}$(solvent), **Measured[15] in $CH_3OH$, #Taken from reference[16]

shifts of compounds other than those considered in the regression analysis. A number of compounds of some rigid systems are selected for this purpose and portrayed in TABLE 14. TABLE 15 shows a comparison between the observed and calculated C-13 and N-15 chemical shifts which obtained from using the regression analysis results of TABLE 12.

The agreement between the measured and experimental values in the above TABLE suggests that, this set of parameters could be used successfully for the prediction of C-13 and N-15 chemical shifts of cyclic compounds when data of their geometrical conformations are available. Since the compounds selected for the regression analysis are chosen to be with minimum strain, the deviation between the observed and calculated chemical shifts may be used as an indication of the geometrical distortions which result in case of the steric congestion.

The overall results obtained and discussed so far may lead to the conclusion that, the representation of the p-character by the electronic charge could be employed to treat the C-13 and N-15NMR chemical shifts by a common parameters and may be used to calculate the chemical shifts of other nuclei when information of the geometrical structures of the treated compounds are available. Such data are easily obtainable now days because of the availability and wide spread of the theoretical programs regarding this field of study.

## REFERENCES


[1] E.D.Decker; J.Magn.Resonance, **4**, 142 **(1971)**.

[2] R.L.Lichter, J.D.Roberts; J.Am.Chem.Soc., **94**, 2495 **(1972)**.

[3] R.O.Duthaler, J.D.Roberts; J.Am.Chem.Soc., **100**, 3889 **(1978)**.

[4] J.P.Warren, J.D.Roberts; J.Phys.Chem., **78**, 2507 **(1974)**.

[5] George C.Levy, Robert L.Lichter; 'Nitogen-15 Nuclear Magnetic Spectroscopy', John Wiley, Sons, New York, **(1979)**.

[6] D.M.Grant, E.G.Paul; J.Am.Chem.Soc., **86**, 2984, **(1964)**.

[7] R.O.Duthaler, J.D.Roberts; J.Am.Chem.Soc., **100**, 3882, **(1978)**.

[8] R.J.Abraham, M.Edgar, R.P.Glover, L.Griffiths, M.A. Warne; J.Chem.Soc.Perkin Trans, **2**, 333 **(1996)**.

[9] Faiz M.H.Al-Abady; 'Calculation of C-13 Chemical Shifts, the Spatial Arrangement Effect in Cycloorganic Compounds', M.Sc.Thesis, College of Education, Mosul University, Mosul, Iraq, **(2001)**.

[10] R.A.Khalil; 'A Study of the Factors Affecting the N-15 NMR chemical shifts', Ph.D.Thesis, College of Science, Mosul University, Mosul, Iraq, **(1994)**.

[11] Y.A.Shahab, H.A.Al-Wahab; J.Chem.Soc.Perkin Trans, **2**, 255 **(1988)**.

[12] Emad A.S.Al-Hyali, Faiz M.H.Al-Abady; Jordon Journal of Chemistry, **2(1)**, 21-44 **(2007)**.

[13] Emad A.S.Al-Hyali; Turkish J.Chem., **(2007)**.

[14] Emad A.S.Al-Hyali; 'Development of A New Set of Additivity Parameters for the Calculation of C-13 Chemical Shifts', Ph.D.Thesis, College of Science, Mosul University, Mosul, Iraq, **(1994)**.

[15] R.O.Duthaler, K.L.Williamson, D.D.Giannini, W.H.Bearden, J.D.Roberts; J.Am.Chem.Soc., **99**, 8406, **(1977)**.

[16] D.K.Dalling, D.M.Grant; J.Am.Chem.Soc., **96**, 1827, **(1974)**.