A New Approach to the Calculation of N-15 Chemical Shifts of Cyclic Compounds

Emad A. S. AL-HYALI

Chemistry Department, College of Education, Univiversity of Mosul, Mosul-IRAQ
e-mail: emadabd2006@yahoo.com

Two sets of additive parameters used previously for the calculation of C-13 chemical shifts of mono and poly six-membered cycloalkanes were applied for the prediction of N-15 chemical shifts of some methyl piperidine derivatives. These sets are based on 2 principles: the p-character (substituents electronic effect) of the atom under consideration and the steric effect that reflects the spatial arrangement of the molecule. An additional parameter, namely the ring angle of the studied atom, was added to the other parameters to define the structural distortion that is due to large steric interactions.

The p-character in set (1) is represented by the number of carbon atoms; primary, secondary, tertiary, and quaternary types at α-position to the nitrogen, while in set (2) it 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-lone pairs in both sets. Quantum mechanical and regression analysis methods were employed for this investigation.

The results showed that both sets were good for the prediction of N-15 chemical shifts. The parameters of set (2) were more consistent with the theory of nuclear magnetic resonance (NMR) spectroscopy; therefore, they are considered for further research. 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 were tested by the estimation of the chemical shifts of other systems. Deviations were observed only in positions that were involved in large steric interactions.

Key Words: N-15 chemical shift, Additive parameters, Regression analysis.

Introduction

The chemical shift behavior of N-15 NMR is often very closely parallel 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 greater than that of C-13 and reaches about 500 ppm. The feature that distinguishes nitrogen from carbon is the presence of an 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 becomes very difficult. Accordingly, correlations should be based, as much as possible, on data obtained under comparable conditions.

Treatment of N-15 NMR chemical shift data, when eliminating the solvent effect by using non polar solvent, could be based (like C-13 chemical shifts) on 2 factors:[5−7] the p-character (paramagnetic term) and the 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 considers the effects that come through the bond (inductive). The steric effect is represented by proton-proton (H-H) and proton-lone 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 2 factors, several sets of additive parameters have been suggested in order to treat N-15 chemical shifts by statistical and semi-empirical methods.

Duthaler and Robert[3] treated the N-15 chemical shift data for some primary, secondary, and tertiary amines and their hydrochlorides in a similar manner to that employed by Grant and Paul[6] to treat the C-13 chemical shifts of analogous compounds. The p-character is introduced in terms of the types of primary, secondary, and tertiary amines. Substituent parameters for carbon atoms 2 and 3 bonds away from the nitrogen atom are introduced. Correction terms are also added in cases in which large deviations 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 has been studied.[7] That investigation showed that in such compounds, both ring and nitrogen inversion allow a larger number of conformational possibilities than are present in the corresponding hydrocarbons. The axial-equatorial lone pair orientation is found to have a great effect on the value of the chemical shift, which likely arises from the interactions between the lone pair and anti-periplanar C-C or C-H orbitals. The experimental results indicated that the trend displayed by alicyclic amines were quite analogous to those of acyclic compounds.

Khalil[10] refined the parameters contributed 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 that contribution, Shahab and Al-Wahab directed their 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 α, β, γ, δ, and ε-positions. The p-character is described as the number of carbon atoms at α-position of primary, secondary, tertiary, and quaternary types.

Despite the great efforts undertaken to date by the authors mentioned in the literature, none of the employed methods could treat the N-15 chemical shifts satisfactorily. Therefore, there appears to be a lack of information regarding this field of investigation and that more research is required in order to provide a clear picture of the causative factors affecting the N-15 chemical shifts.

A recent study[12] succeeded in developing a new set of parameters for the calculation of C-13 chemical shifts of mono and poly six-membered ring cycloalkanes. More recently,[13] the later parameters were further 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 experiences. The (H-H) interactions are calculated manually by means of building a model compound. The mentioned parameters are proven to be conformational dependent and could be used successfully to predict unknown chemical shifts with acceptable errors.

In addition to the success in applying these parameters to the calculation of C-13 chemical shifts of

cyclic compounds, since the p-character (EG) is presented as numbers only (no matter what type of atom is studied) it is possible that these parameters could be applied to the calculation of the N-15 chemical shifts of compounds with an analogous structure, but additional parameters regarding (H-Lp) interactions need to be included.

In the present work, the last 2 sets of parameters mentioned above were applied to calculate the N-15 chemical shifts of methyl derivatives of piperidines and N-methyl piperidine compounds. Comparison between the results of applying the 2 sets was carried out. The study also included an attempt to develop a general set of parameters that could be employed to calculate the C-13 and N-15 chemical shifts for cyclic hydrocarbons.

Experimental

Two sets of additive parameters were applied in this investigation for the prediction of the N-15 chemical shifts. Those parameters were based on 2 factors: the p-character of the nitrogen atom under consideration, which reflects 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 geometry of the studied molecules.

In set (1) of the applied parameters, the p-character was introduced in terms of the number of α-carbons of primary (α-pri), secondary (α-sec), tertiary (α-ter), and quaternary (α-quat) types. The (H-H) and (H-Lp) interactions were represented by the actual number of the interactions in the β- and γ-positions. The β- interactions were divided into 2 types, depending on the distance and angle[14] between the interacting protons or proton-lone pair. The first type was β^a and refers to the interactions between 2 protons or proton-lone pairs located in the same plane, either axial or equatorial. The other is given the symbol, β^{ae}, and explains the interaction between (H-H) or (H-Lp), one of them in the axial position and the other is equatorial (Figure 1).
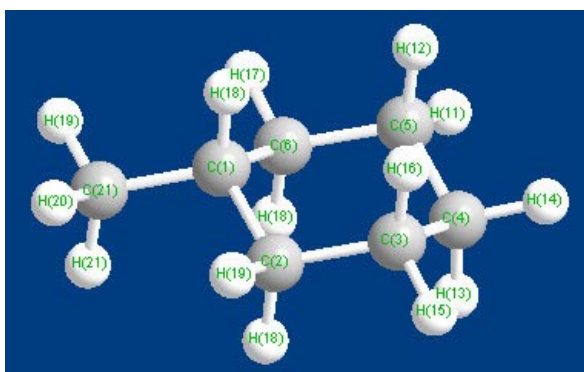

Figure 1. Methyl cyclohexane. Examples of α-(H-H) interactions on C(2) are (H(19)-H(16) and H(19)-H(15)). Example of β^a – (H-H) interaction on C(2) is (H(19)-H(20)). Example of β^{ae} – (H-H) interaction on C(2) is (H(19)-H(21)).

In 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 were treated in a similar way to that of set (1). Additional structural parameters, such as the ring angle ($<$ C-N-C) of the

studied molecule was used in some cases of this treatment. The number of interacting (H-H) and (H-Lp) were calculated as follows:

1. A model structure was constructed for the most stable (least energy) conformation of the studied compound. Energy minimization was carried out by employing the ChemOffice program of Cambridge University (v.2000).

2. For compounds of definite conformation (existing in one energetically favored conformation), a single model was used for the calculation.

3. For compounds that exist in 2 interconvertable conformations of equal energies, the number of interacting (H-H) and (H-Lp) are the weight average of the 2 conformations.

The values of the EG ($<$ C-N-C) and TE were calculated by employing the ChemOffice program as follows: The structure of the studied molecule was plotted by the CS ChemDraw program. The molecule was transferred into the CS Chem3D program in order to convert it into a 3-D molecule. This process was followed by molecular dynamic simulation using the MM2 program and then energy minimization was carried out. The TE and ($<$ C-N-C) of the investigated molecule were recorded and the charge was determined by the extended Hückel method. Their values, as well as the other parameters, were used for the formulation of the matrix that was employed for the multi-parametric linear regression analysis used to calculate the N-15 chemical shifts. The well-known statistical program SPSS was used for this purpose.

In the regression analysis the observed chemical shifts ($\delta_{N-15obs}$) were considered as the dependent variable (Y in Eq. 1), while the parameters were applied as independent variables (X_1, X_2, ..., Xn). The matrix (Tables 1 and 2) was generated on the basis of a linear model, according to the following equation.
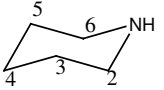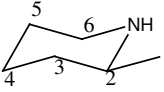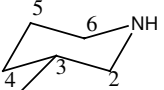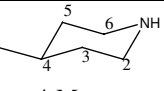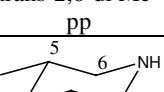
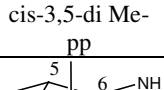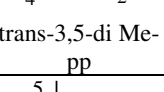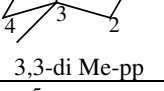$$Y = B + a_1 X_1 + a_2 X_2 + \cdots + a_n Xn \tag{1}$$
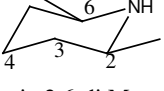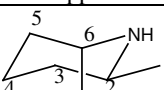
The coefficients of the parameters (a_1, a_2,...., a_n) and the constant (B) were obtained as a result of regression analysis. The success of the selected parameters was estimated in terms of the correlation coefficient (R) and standard deviation (SD).

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 significance 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 affecting the N-15 chemical shifts; therefore, more detailed research may be required to clarify the ambiguity in this field.
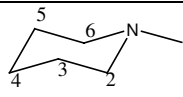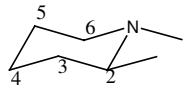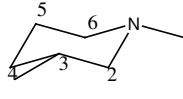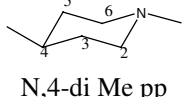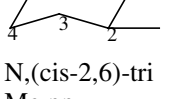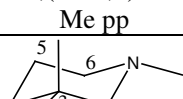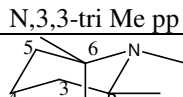
The compounds selected for the present study (listed in Tables 1 and 2) were methyl derivatives of piperidine and N-methyl piperidine. These compounds were chosen because of their conformation analogy to cyclohexanes, so that comparison between the 2 systems could be achieved. The effect of axial-equatorial lone pair inversion, which may create variou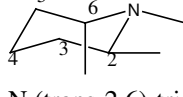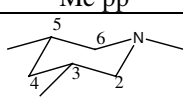s conformations that affect the N-15 chemical shifts[3] could be investigated. The experimental N-15 chemical shifts of the studied compound[7] are obtained under the same medium conditions and measured in an inert solvent (cyclohexane) in order to reduce or eliminate the solvent effect, and so that the suggested parameters could be applied without any restriction and used for structural correlation.

Table 1. The parameters of sets (1) and (2) applied to the piperidine compounds.

*Compound	Charge on N	No. of carbon			No. of interacting				No. of interacting			
		-α sec	-α ter	-α quat	-α H-H	-βᵃ H-H	-βᵃᵉ H-H	-γ H-H	-α H-Lp	-βᵃ H-Lp	-βᵃᵉ 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
2,2,6,6- Tetra Me-pp	-0.232	0	0	2	0	4	2	0	0	4	4	0

*N-15 chemical shifts were considered the dependent variable.

Table 2. The parameters of sets (1) and (2) applied to the N-methyl piperidines.

*Compound	Charge on N	Angle < C-N-C	**No. of carbon			No. of interacting			
			-α sec	-α ter	-α quat	-α H-Lp	-β[a] H-Lp	-β[ae] H-Lp	-γ 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 (α-pri) = 1 for all the compounds.

The idea for this study emerged from the point of similarity of the behavior of N-15 and C-13 chemical shifts of analogous compounds. A preliminary correlation between selected piperidines and N-methyl piperidines with their corresponding methyl cyclohexanes produced good correlation coefficients with relatively high values of standard deviations, which may have been due to the difference in some geometrical

aspects. This inspired the continuation of these investigations.

The piperidines and N-methyl piperidines were treated separately by applying set (1) and set (2) parameters, as mentioned previously. Since the application of the suggested parameters, especially the number of (H-H) and (H-Lp) interactions, required (according to this method) the building of model compounds in order to count them manually and formulate the matrix for the regression analysis, and since the lone pair could occupy axial and equatorial positions, knowledge about the conformations must be available to do this work.

The total energy of each of the considered compounds was estimated with the lone pair being in the axial and equatorial positions. Tables 3 and 4 show the values obtained for piperidines and N-methyl piperidines, respectively.

Table 3. Value of the total energy (in Kcal/mole) of the piperidines with a lone pair in the axial and equatorial positions.

Compound	TE with axial lone pair	TE with equatorial Lone 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
2,2,6,6- Tetra Me-pp	14.619	14.670	0.051

Table 4. Value of the total energy (in Kcal/mole) of the N-methyl piperidines with a lone pair in the axial and equatorial positions.

Compound	TE with axial lone pair	TE with equatorial Lone 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

The results of Tables 3 and 4 indicate that the piperidines exist in 2 conformations of nearly equal energy; therefore, the number of interacting (H-H) and (H-Lp) were weight averaged over the 2 conformations. The great (H-Lp) interactions of the γ-gauche type[6] in the N-methyl piperidine compounds when the methyl group was located in the axial position created a relatively high difference in the total energy of the molecule, as compared to the same molecule in the equatorial position. This suggests that the studied N-methyl piperidines exist in one favorable conformation. For this reason the (H-Lp) interactions were calculated by considering the conformation of the lower energy (more stable one).

Piperidines

The 2 sets of additive parameters (sets 1 and 2) stated in the experimental part were applied for the estimation of N-15 NMR chemical shifts of the piperidine compounds considered in this study. The results obtained from multiple regression analysis when employing the parameters of set (1) are presented by Eq. 2 (r = 1, SD = ±0.41), while the result of applying set (2) is given by Eq. 3 (r = 1, SD = ± 0.54).

$$\delta_{N-15calc} = \quad 96.964 - 1.773\alpha_{ter} - 7.632\alpha_{quat} - 9.500\alpha_{(H-H)} - 6.582\gamma_{(H-H)} - 10.245$$
$$\alpha_{(H-Lp)} - 15.473\gamma_{(H-Lp)}. \tag{2}$$

$$\delta_{N-15calc} = \quad 83.414 + 85.886Charge - 4.324\alpha_{(H-H)} + 9.106\beta_{(H-H)}^{ae} - 6.488\gamma_{(H-H)}$$
$$-4.917\alpha_{(H-Lp)} - 15.074\gamma_{(H-Lp)} \tag{3}$$

Comparison between the observed and calculated N-15 chemical shifts obtained by using the results of Tables 1 and 2 are portrayed in Table 5.

Table 5. Comparison between the experimental[3,7] and calculated value of N-15 chemical shifts of piperidines calculated from the results of sets (1) and (2).

Compounds	$\delta_{N-15obs}$	$\delta_{N-15calc}$ (set1)	*Res.	$\delta_{N-15cal}$ (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
2,2,6,6- Tetra Me-pp	81.70	81.70	0.0	81.70	0.0

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

The application of sets (1) and (2) parameters on the piperidine (Table 5) compounds gave comparable results, suggesting 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 (Eqs. 2 and 3) 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 the shielding effect, which is inconsistent with 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 NMR spectroscopy, in which the increase in electronic charge increases the non-spherical distribution of electrons (in the p-orbital) around the nucleus, leading to a greater 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 the shielding effect. This can be explained in terms of the repulsion among protons of nitrogen and carbon atoms, which depend on their spatial arrangements. Such repulsions may further push the valence electrons of N-H towards the nitrogen nucleus, and therefore, this would extend the shielding around it. The β-interactions exhibited a 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 previously reported C-13 NMR results[6,11,14].

3. The coefficient value of α- (H-Lp, a = -4.917) was slightly higher than that of (H-H, a = -4.324), while the coefficient value of the γ- (H-Lp) interactions parameter (a = -15.074) was nearly double that of the γ- (H-H) interactions (a = –6.582). This may have been 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 2 protons or proton and lone pair of electrons are directed toward each other, while the α-protons are not (Figure 2). Since the space occupied by the free lone pair is relatively larger than that of the valence electrons of the C-H bond, the γ- (H-Lp) interactions will be greater than those of γ- (H-H) interactions.

4. The values of the correlation coefficients and standard deviations are good indications of the correct choice of parameters that were selected for this study.
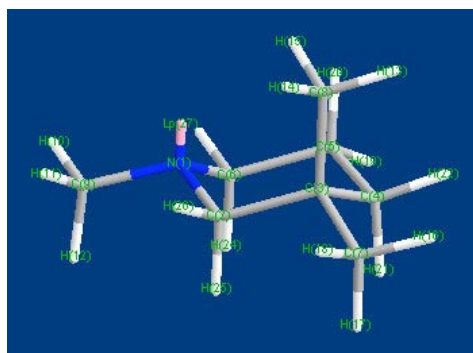

Figure 2. This model shows an example of the γ-interaction, in which the (H(16) and loan pair (Lp (17)) are directed toward each other, while the α-interacting (H(10) and Lp(17) are not.

N- Methyl Piperidines

The methyl piperidines were treated in a similar way as the piperidine compounds. The main difference was that the protons in the latter were replaced by a methyl group; therefore, only (H-Lp) interactions were observed in these compounds.

The result of regression analysis when applying set 1 parameters to N-methyl piperidines is given in Eq. 4 (r = 0.9999, SD = ± 0.44).

$$\delta_{N-15calc} = 36.843 - 4.957\alpha_{ter} - 10.543\alpha_{quat} + 17.471\beta^{ae}_{(H-Lp)} - 4.243\gamma_{(H-Lp)} \tag{4}$$

Regression analysis results of applying set (2) to the N-methyl piperidines and then adding the ring angle (< C-N-C) parameter to the regression are indicated by Eq. 5 (r = 0.9960, SD = ± 3.36) and Eq. 5 (r = 0.9999, SD = ± 0.58).

$$\delta_{N-15calc} = -124.814 - 1347.619 Charge + 0.990\alpha_{(H-Lp)} - 5.684\gamma_{(H-Lp)} \tag{5}$$

$$\delta_{N-15calc} = 365.743 + 545.169 Charge + 16.966\beta^{ae}_{(H-Lp)} - 3.785\gamma_{(H-Lp)} - 2.372 \text{ Angle } (< C-N-C). \tag{6}$$

The results of Eqs. 4 and 6 show the same trend as the results of the regression analysis of Eqs. 1 and 2 for the piperidine compounds, which could be interpreted in the same way. The difference in the values of proton interaction coefficients of the 2 types may refer to the structural dimensions that reflect the dependence of such interactions on the size and distance between the interacting atoms or lone pairs. The angle (< C-N-C) value, presented as a parameter, and 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 obtained from the regression analysis results of Eqs. 4 and 6 are shown in Table (6).

Table 6. Comparison between the observed and calculated chemical shifts obtained from the results of Eqs.4 and 6.

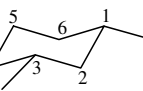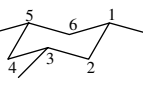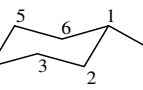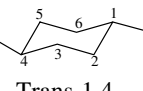| Compound	$\delta_{N-15obs}$	$\delta_{N-15calc}$ (Eq. 4)	*Res.	$\delta_{N-15cal}$ (Eq. 6)	*Res.
N-Me-pp	37.4	36.84	-0.56	37.20	-0.20
N,2-di Me pp	48.9	49.36	0.46	49.52	0.62
N,3-di Me pp	36.4	36.84	0.44	36.31	-0.09
N,4-di Me pp	37.0	36.84	-0.16	37.44	0.44
N,(cis-2,6)-tri Me pp	62.1	61.87	-0.23	61.71	-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
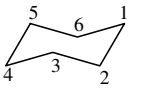
*Res. $= \delta_{N-15calc} - \delta_{N-15obs}$

The values in Table 6 show good agreement between the observed and calculated chemical shifts when applying the parameters of sets (1) and (2). 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 NMR spectroscopy.

Combination of C-13 and N-15 chemical shifts

Based on the success of applying the parameters of set (2) for the prediction of N-15 chemical shifts of six-membered ring compounds, as well as the previous success of the application of these parameters on mono and poly six-membered rings cycloalkanes,[12] and according to the assumption made earlier, in which the partial atomic charge is expressed in terms of its value (no matter which atom), 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 was carried out (using the parameters of set (2)) on a number of selected cyclohexanes of definite conformation and least strain (listed in Table 7) combined with the N-methyl piperidines listed in Table 2. The choice of the later compounds was based on their structural similarities to the methyl cyclohexanes and their presence in one favorite conformation. The results of the regression analysis are given by Eq. 7 (r = 0.9998, SD = ± 0.56).

Table 7. Cyclohexanes employed for regression analysis in combination with the compounds in Table 2.

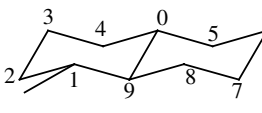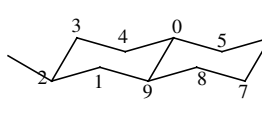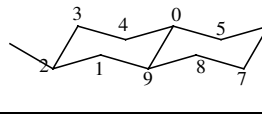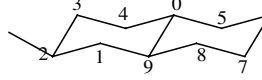| *Compound	C_{No}	$\delta_{C-13\,ob}$	Charge	< C-N-C	No. of interacting (H-H)			
					-α	-β^a	-β^{ae}	-γ
Cyclohexane	1	27.06	-0.057	110.948	6	2	0	0
	2	27.06	-0.057	110.948	6	2	0	0
	3	27.06	-0.057	110.967	6	2	0	0
	4	27.06	-0.057	110.967	6	2	0	0
	5	27.06	-0.057	110.969	6	2	0	0
	6	27.06	-0.057	110.958	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
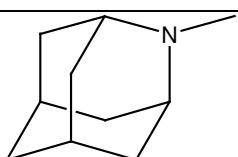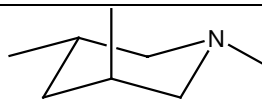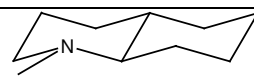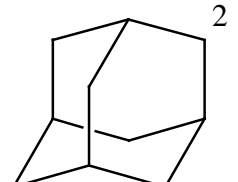
*D = di, M = methyl, T = tri, and C= cyclohexane.

$$\delta_{N-15calc} = 257.861 + 14.018 Charge - 1.88\alpha_{(H-H)} + 2.954\beta^{ae}_{(H-H)} + 12.899$$

$$\beta^{ae}_{(H-Lp)} - 4.310\gamma_{(H-Lp)} - 1.975 \text{ Angle } (< C - N - C)$$

(7)

The results of Eq. 7 agree, in terms of their trend and coefficient values, with those obtained earlier (Eq. 6). The high correlation coefficient and relatively low standard deviation indicate the agreement between the observed and calculated C-13 and N-15 chemical shifts of the considered compounds (Table 8). Deviations were observed only in cases of large steric interactions, due to ring flattening.[7]
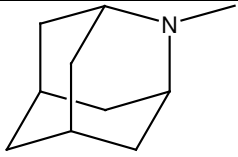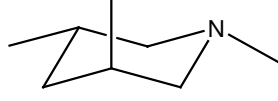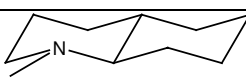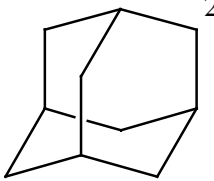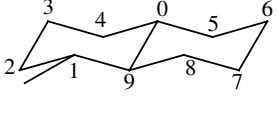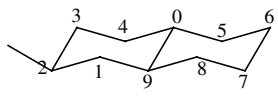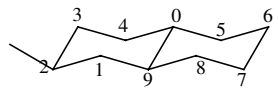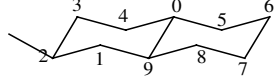
Table 8. Comparison between the observed and calculated C-13 and N-15 chemical shifts obtained from the results of Eq. 7.

Compound	$C_{No.}$	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
Compound	$C_{No.}$	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 success of the suggested parameters for such treatment could be further tested by using the results of Eq. 7 for estimation of the C-13 and N-15 chemical shifts of compounds other than those considered in the regression analysis. A number of compounds of some rigid systems were selected for this purpose and
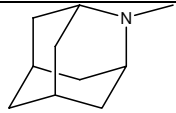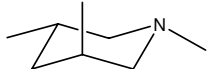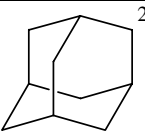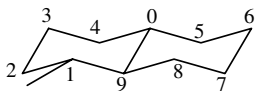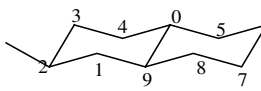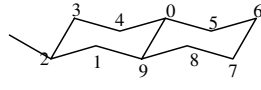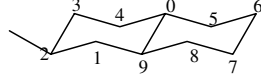
are listed in Table 9. Table 10 shows a comparison between the observed and calculated C-13 and N-15 chemical shifts that were obtained from using the regression analysis results of Eq. 7.

Table 9. Parameters of some rigid systems used for testing the success of the results of Eq. 7.

Compound	$C_{No.}$	Charge	< C-N-C	No. of interacting (H-Lp)			
				$-\alpha$	$-\beta^a$	$-\beta^{ae}$	$-\gamma$
	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
Compound	$C_{No.}$	Charge	< C-C-C	No. of interacting (H-H)			
				$-\alpha$	$-\beta^a$	$-\beta^{ae}$	$-\gamma$
	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 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 their geometrical conformation data are available. Since the compounds selected for the regression analysis were chosen to have minimum strain, the deviation between the observed and calculated chemical shifts may be used as an indication of the geometrical distortions, which result in cases of steric congestion.

Table 10. Observed chemical shifts of the compounds in Table 9 and their calculated values estimated using the results of Eq. 7.

Compound	Atom No.	$\delta_{\text{N-15 or C-13 obs}}$	$\delta_{\text{N-15 or C-13 calc}}$
	N	*38.0	37.6
	N	*28.9 **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).

The overall results obtained and discussed thus far could 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-15 NMR chemical shifts by a common parameter, and may be used to calculate the chemical shifts of other nuclei when information concerning the geometrical structures of the treated compounds are available. Such data are currently easily obtainable because of the availability and wide spread use of theoretical programs regarding this field of study.

References

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

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

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

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

5. George C. Levy and Robert L. Lichter, **"Nitrogen-15 Nuclear Magnetic Spectroscopy"**, John Wiley and Sons, New York, 1979.

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

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

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

9. F. M. H. Al-Abady, **"Calculation of C-13 Chemical Shifts and the Spatial Arrangement Effect in Cyclo-organic 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 and H. A. Al-Wahab, **J. Chem. Soc. Perkin Trans 2,** 255 (1988).

12. Emad A. S. Al-Hyali and Faiz M. H. Al-Abady, **JJC 2,** 1, 21-44 (2007).

13. Emad A. S. Al-Hyali, **Turk. J. Chem. 31**,479-490 (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 and J. D. Roberts, **J. Am. Chem. Soc. 99**, 8406, (1977).

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