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# Correlation Study of the Biological Activity of Sulfa Drugs and Theoretical Calculation NMR Spectra of the Parent Anilines

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## Abstract:-

Isotropic $^{1}H$, $^{13}C$ and $^{14}N$ nuclear magnetic shielding constants of anilines that used to synthesize sulfa drugs were calculated. The geometry of each compound has been optimized using 6-31G(d,p) and B3lyp/6-31G(d,p) basis sets at levels HF and DFT. The optimized geometries were used to estimate the chemical shifts which then correlated with biological activity of the drugs against bacteria.

## Introduction:-

Sulfa drugs were the first synthetic compounds to be used against bacterial infections [1]. They still in wide use due to their low cost and efficient action against common bacterial and microbial diseases despite that newer antibacterial and antimicrobial drug have been synthesized [2-7]. These drugs are synthesized mainly from anilines [8,9]. It had been shown that there is an approximately linear relationship between the $NH_2$ stretching frequencies of the amino group of the parent anilines and the minimum inhibition concentration (MIC) of these drugs [10]. Since C-N bond of the parent anilines behave as a descriptor for the activity of the sulfa drugs that derived from them [11, 12]. The aim of this work is to theoretically calculate the $^{1}H$, $^{13}C$ and $^{14}N$ chemical shifts and correlate them with biological activity with sulfa drugs.

## Materials and Methods:-

The calculations performed with Gaussian 03 [13] package with restricted Hartree Fock and B3LYP methods. All structures were fully optimized using the 6-31G (d,p) basis set. The optimized structures then used to calculate the chemical shifts of the C-NH2 group $^{1}H$, $^{13}C$ and $^{14}N$ atoms with GIAO method [14, 15]. All computations were done using a pentium IV computer has 3G processor.

## Results and discussion:-

The experimental values of the chemical shifts of the NH2 protons, $^{13}C$ and $^{14}N$ atoms of the C-NH2 linkage in aniline are 6.79, 147.9 and 57.76 respectively [16]. The calculated chemical shifts in the HF and DFT methods are displayed in Tables 1 and 2 respectively. From these tables it could be seen that the chemical shifts of the NH2 protons by the two methods are 2.118 and 2.223 ppm which means that the values are underestimated by the two methods, although their still a clear relationship between the calculated chemical shifts and MIC values. For $^{13}C$ the values are 148.082 ppm for the case of HF and 138.114 ppm for the case of DFT method indicating that the chemical shifts of this nucleus is best calculated by the HF level of theory. On the other hand, the calculated chemical shifts of the nitrogen atom are 51.483 and 58.820 ppm respectively. It is clear that the density functional theory is better to estimate the chemical shifts in this case.

Despite the underestimated values of the amino group protons chemical shifts, there appears a general correlation between their values and the MIC values of the sulfa drugs, as could be seen in Tables 1 and 2. From these tables it is clear that the chemical shift of the amino group protons in the para, meta and ortho positions are increase with increasing biological activity of the drugs. The shift in para substituent increases from 1.993 ppm in *p*-methoxyaniline to 2.759 ppm in *p*-nitroaniline. This increase parallels the change of the nitrogen atom from sp3 hybridization to a state with higher s:p ratio when the lone pair electrons become more localized over the aromatic ring [10]. This behavior accounts for the increase in the NH2 chemical shift because of the increasing double bond character. This is also true for the case of the ortho and meta substituents. Tables 1 and 2 also reveal that there is the same correlation between the estimated $^{13}C$ chemical shifts and the MIC values where the chemical shifts move to downfield as the biological activity increases (MIC decreases). The values, calculated by HF method, increase from 143.511 ppm in *p*-methoxyaniline to 148.082 ppm in aniline to 156.124 ppm *p*-nitroaniline which parallels the increase of biological activity. This could be rationalized on the basis that as the N atom becomes more s character the C-N bond becomes more double bond character which reflected on the chemical shifts of the carbon atom. The nitrogen chemical shifts are best expressed by the values that calculated by DFT method and table 2 shows that the estimated chemical shifts are in accordance with the foregoing discussion and there could be seen a progressive increase in the chemical shift values with increase of the biological activity from 57.299 ppm in *p*-methoxyaniline to 58.082 ppm in aniline to 64.944 ppm in *p*-nitroaniline. The same trends are seen for the ortho and the meta substituted anilnes. This is illustrated in the increase of the double bond character of the C-N bond as the electron withdrawing character of the substituent increase. In general this behavior is connected with the σ-Hammet values of the substituents since the double bond character increases as the substituent becomes more electron withdrawing, which correlate with the activity of the sulfa drugs as they become more active with increasing electron withdrawing character of the substituent.

**Table (1) $^{1}H$, $^{13}C$ and $^{14}N$ chemical shifts in anilines used to synthesized sulfa drugs calculated by GIAO at HF/6-31G(d,p) level of theory**

| Substit. | $^{1}H$ | $^{13}C$ | $^{14}N$ | MIC* |
|---|---|---|---|---|
| *p*-OMe | 1.993 | 143.511 | 49.513 | 34.5 |
| *p*-Me | 2.008 | 145.578 | 50.227 | 27.2 |
| *p*-Cl | 2.149 | 147.305 | 72.094 | 16.0 |
| *p*-Br | 2.180 | 148.085 | 51.452 | 11.25 |
| *p*-COMe | 2.478 | 153.758 | 55.227 | 1.40 |
| *p*-NO2 | 2.759 | 156.124 | 57.640 | 1.40 |
| H | 2.118 | 148.082 | 51.483 | 16.0 |
| *m*-Me | 2.080 | 148.814 | 51.486 | 22.5 |
| *m*-Br | 2.211 | 148.987 | 51.623 | 11.25 |
| *m*-OMe | 2.164 | 160.769 | 52.628 | 11.2 |
| *o*-OMe | 2.320 | 142.072 | 41.079 | 45 |
| *o*-Cl | 2.554 | 145.395 | 49.532 | 2.8 |
| *o*-NO2 | 4.978 | 149.488 | 61.798 | 1.4 |

**MIC*: minimum inhibitor concentration.**

**Table (2) $^{1}H$, $^{13}C$ and $^{14}N$ chemical shifts in anilines used to synthesized sulfa drugs calculated by GIAO at B3LYP/6-31G(d,p) level of theory**

| Substit. | $^{1}H$ | $^{13}C$ | $^{14}N$ | MIC* |
|---|---|---|---|---|
| *p*-OMe | 2.116 | 134.82 | 57.299 | 34.5 |
| *p*-Me | 2.127 | 136.078 | 57.676 | 27.2 |
| *p*-Cl | 2.236 | 136.655 | 58.270 | 16.0 |
| *p*-Br | 2.250 | 137.134 | 58.507 | 11.25 |
| *p*-COMe | 2.559 | 141.157 | 62.966 | 1.40 |
| *p*-NO2 | 2.800 | 142.212 | 64.944 | 1.40 |
| H | 2.223 | 138.114 | 58. 820 | 16.0 |
| *m*-Me | 2.195 | 138.28 | 58.342 | 22.5 |
| *m*-Br | 2.277 | 139.183 | 59.027 | 11.25 |
| *m*-OMe | 2.257 | 139.763 | 59.295 | 11.2 |
| *o*-OMe | 2.439 | 128.932 | 47.863 | 45 |
| *o*-Cl | 2.638 | 143. 918 | 56.965 | 2.8 |
| *o*-NO2 | 4.800 | 135.252 | 68.989 | 1.4 |

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# دراسة ترابطية للعلاقة بين الفعالية البيولوجية لأدوية السلفا مع أطياف الرنين النووي المغناطيسي المحسوبة نظريا للأمينات الأم


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## الخلاصة:-

لقد تم حساب ثوابت الحجب النووي المغناطيسي الايزوتروبية للنوى $^{1}H$ و $^{13}C$ و $^{14}N$ في الانيلينات المستخدمة لتحضير أدوية السلفا. أن التراكيب الجزيئية المثلى للانيلينات تم التوصل إليها خلال الحسابات النظرية عند المستويين النظريين HF و DFT و باستخدام المجموعتين الأساسيتين 6-31G(d,p) و B3lyp/6-31G(d,p) . لقد تم استخدام التراكيب المثلى لحساب الإزاحات الكيميائية لأطياف الرنين النووي المغناطيسي و التي تم ربطها بالفعالية البايولوجية للأدوية المشتقة منها ضد البكتريا.