EDITORIAL

NMR Structure Elucidation of Natural Products and Synthesized Compounds in Nigeria

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Structure elucidation using Nuclear Magnetic Resonance Spectroscopy (NMR) is one of the greatest milestones of spectroscopy. NMR is matchless in the elucidation and confirmation of structures of organic compounds. The chemical shifts of the protons and carbons in the structure reveal a lot about chemical environments and reactivity as well as exploitable properties of the compounds. Although NMR has certain weaknesses such as poor sensitivity compared to mass spectrometry, UV and IR spectrophotometry, it is nevertheless most informative in terms of structure and chemical properties of compounds. NMR requires a high concentration of material for a good spectrum and even a higher concentration for the advanced experiments such as 2D COSY, TOCSY, HMBC, INADEQUATE, HSQC and NOESY. The information and structural properties that could be obtained from these advanced experiments are priceless. A proper use of a compound's NMR data will reveal the structure of the compound under investigation and confirm its identity to a known compound or similarity to a known compound or class of compounds or its novelty. The desire for novelty or newness of a structure is one of the main aims of isolating and synthesizing compounds but proof of this can only come from the proper acquisition and interpretation of a compound's NMR data. It is also this desperation to obtain a new compound that drives many to propose and publish structures that are hardly supported by the NMR data or decipherable from the published data.

Proton NMR spectra are quite simple; signals appear as singlets, doublets, triplets, quartets, doublets of doublets, multiplets, etc depicting the number of neighbouring protons though some long-range spin-spin coupling such as meta coupling on aromatic rings can occur. However, these couplings can be rationalised on the basis of their coupling constants (J values). Trans coupled olefinic protons have a J value of 15-16 Hz, cis coupled olefinic protons, 9-11 Hz while for the aromatic protons, ortho coupled protons have a J value of 8-9 Hz and meta coupled have J value of 2-3 Hz. Other coupling constants have been well tabulated and they can be worked out easily. NMR signals are also accompanied by their chemical shift values. This gives information on the chemical environment of the protons or carbons with respect to the electronegativity, the degree of unsaturation and hybridization of the atoms to which they are bonded and anisotropy. For protons, the spatial disposition in chiral, prochiral and stereogenic centers could also affect the chemical shifts, thus protons that would normally be equivalent now possess different chemical shifts and different splitting patterns. Deuterated solvents used to acquire the spectra could also affect the chemical shifts but not by a ridiculous amount (^{13}C signals are not so affected by solvents). A final information that is obtained from an NMR spectrum is the integration of the proton signals to give a relative number of protons under the peaks. A good integration is based on a well-chosen signal that represents a specific number of protons. The solvent, water or an impurity peak should never be used as a reference for integration.

Carbon-13 NMR spectra are even simpler. All signals appear as single lines as the peaks are all decoupled (C-H coupling are jammed). Carbon spectra can be phased or J modulated to give C and CH_2 on one side and CH and CH_3 on the opposite side. Depending on the angles used, some signals may disappear e.g. a DEPT-135 will not show any quaternary C signals. With some few rules of the thumb, carbon multiplicities can be ascertained without the need to run a 2D HSQC spectrum. However, any doubts about an -OH, -NH or other protons not attached to a carbon can be cleared from the 2D HSQC spectrum for the compound. A 2D HMBC will confirm the long-range correlations and the structure especially identifying the chemical shifts of quaternary carbons. A 2D COSY will identify coupled protons and a TOCSY will identify spin systems. A passionate consideration of these data will certainly give the structure of the compound and even if the structure cannot be established, the NMR data will indicate that the structure drawn is incorrect. So **even if we don't know what the structure is, we must know what it is not.**

With so much spectral data in the literature and so many structures elucidated and chemical shifts for the protons and carbons provided, it is easy to identify well-known or previously isolated and synthesized compounds. Thus, it is advisable to accompany NMR structure elucidation reports by a citation of a previous report for the compound or a very similar compound/analogue or if novel, a compound in the same class that is similar or has identical or peculiar chemical environments to support the chemical shift assignments for the new compound(s) being reported. Spectral data for known compounds can be obtained from databases such as SciFinder, Dictionary of Natural Products (DNP), Aldrich Spectral database or Spectral database for Organic Compounds (SDBS), Reaxys and any other NMR spectral database or simply google "Compound name NMR pdf" for free access journals. It is also possible to simulate the NMR data for the compound using ChemDraw or ChemSketch or online NMR simulation resources and compare to experimental values. Large deviations from the calculated and experimental values should not be ignored but considered pertinently.

However, with these available opportunities, our Universities and Research Institutes have refused to subscribe to these databases and once there is no hit from Google, it is assumed that the compound is new, then

a structure is proposed and the NMR data is made to fit the new structure. Often times signals from impurities are made to be part of the structure thus giving rise to strange substitutions. The compounds are usually not purified especially if synthesized, a 100% conversion is expected or the by-products of the initial reactions are assumed to be inactive in the subsequent steps of the reaction sequence. This leads to a mixture of compounds being analyzed and the NMR data cannot be for a pure single compound. Sometimes, NMR data that is clear or obvious for a known compound or a common impurity is passed for another compound or even a novel one. Often the compounds structures are not numbered or improperly drawn. Yet references to proton and carbon numbers or positions are made in the structure elucidation. The question to mind now is "**How many incorrect structures or how many structures with the wrong spectral data or assignments are out there?**"

Although numerous fruitful reports and laudable achievements have been made in this area of research in Nigeria and Nigerian plants have contributed a lot of novel compounds, some natural products and synthetic chemists in Nigeria have contributed significantly to the number of bogus compounds and NMR data found in the literature. Some of the compounds isolated or structures proposed have never been re-isolated or re-synthesized even by the same investigators. These phony compounds have become debris or chaff dumped in the atmosphere of organic compounds and there are no retrievals or rebuttals to these structures. This methodology or lack of it has become a bottleneck hindering dereplication studies for the identification of known or novel natural products or synthesis of new compounds in Nigeria. It is time we consider this aspect of our organic chemistry research and organize workshops and seminars to teach the principles of NMR and structure elucidation. Reviewers, especially for Nigerian based journals should take time to ascertain the proposed structures and any glimmer of a doubt should lead to rejection of the manuscript. We should not as students, supervisors, reviewers or investigators help in contributing to the publication of incorrect NMR data and structures thus polluting the rich and laboriously attained library of organic compounds. As editors, we should insist on authors including chromatographic evidence for purity, NMR spectra and MS results as supplementary data and clearly stipulate this as a precondition for publication of any paper based on structure elucidation of novel compounds or identification of known compound(s).

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Prof. John Igoli is avid and passionate about structure elucidation using NMR and other spectroscopic techniques. He has organized and participated in several NMR and spectral structure elucidation workshops in Nigeria, UK, Malaysia and Thailand.

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