Validating Automated Structure Confirmation in a Blind Study

INTRODUCTION

In previous work, we have presented several findings on the automated evaluation of chemical structures using 1H, 13C, and 2D NMR verification algorithms.1-2 These studies have shown that these systems have performed extremely well through numerous challenges.

The current study focuses not only on the performance of the verification algorithms but also on the automated preparation of experimental data through a blind test. This study was designed to prove that such a system would hold up in an industrial environment without any human intervention.

This study consisted of two distinct sets of structures and spectra. The first contained 19 spectra sets each dataset contained 1D (1H and 2D HSQC) spectra that were provided ahead of time for adjustment of processing settings and options. This step was necessary to identify the best software settings based on the instrument and data collection practices for the laboratory where the samples were prepared and run. Once the first set was run through the system and results of the verification procedure obtained, the second, blind test, was performed on 10 distinct datasets (with chemical structures) that were not available to the software or the software operators in advance. The details and results of these two tests are presented here, along with a comprehensive look at the structures that could not be confirmed.

Setting Up Ideal Processing and Evaluation Parameters

In order to have a system that can run without human intervention, automated processing and structure verification procedures (macros) must be created in the software to perform these tasks. The raw 1D and 2D NMR datasets for 19 Aldrich compounds were first evaluated using ACD/Labs’ standard macros. These settings proved to be non-sufficient as the datasets contained several abnormally broad water peaks and low signal-to-noise ratios. These macros were then modified to exclude these water peaks and set more stringent peak picking guidelines to combat the S/N issue. The second attempt was improved but had some issues with the referencing in one of the 2D datasets. In addition, the 1D spectra were not well-resolved, resulting in an inaccurate evaluation of some multiplets. These issues were rectified by decreasing the line broadening setting in the software by a factor of 10. Following this modification, the settings were then deemed to be sufficient.

Results of the First Test

An explanation of the combined verification algorithms used to evaluate spectrum-to-structure matches have been previously reported.3 Following the modification of ACD/Labs standard macros explained in the previous section, the raw data of the 19 Aldrich compounds were fully processed and evaluated automatically.

Looking closer at the failed samples provides some insight to the nature of the failure. ID #3 failed specifically because of an unassigned 2D peak appearing at 17.8 ppm and 2.2 ppm. It was determined that this peak was due to the aromatic methyl group in the structure. The reason for a lack of consistency between the predicted and experimental chemical shifts in this case was due to a slow rotation around the N-CO bond. As a result, this rotamer produces an experimental spectrum that looks like a mixture. The software was unable to accurately predict this mixture of forms based on the experimental conditions; the predicted spectrum did not match the experimental and the sample was flagged for manual analysis.

Table 1 - The results of the 19 Aldrich datasets. For this dataset, 13 of the 19 datasets (69%) were automatically evaluated by the software.

Table 2 - The results of the 10 blind Aldrich datasets. For this dataset, 7 of the 10 datasets (70%) were automatically evaluated by the software.

CONCLUSIONS

The goal of this study was to evaluate a fully automated NMR processing and structure verification workflow for a blind test set of compounds. The processing and evaluation settings for a typical group of samples was set up using a pilot set of 19 compounds. Once these settings were adjusted, they were used to automatically process and evaluate a blind set of 10 compounds that were prepared under the same conditions. The results revealed that this completely automated system could reduce the interpretation workload of a spectroscopist by up to 90% if problems with rotomers and impurities are filtered out before the NMR Verification step, up to 70% when these problem samples are left in.

This study highlighted several examples where datasets were flagged by the software for closer inspection by a spectroscopist. These particular examples illustrate the software’s discrimination ability that help reduce the risk of false positives. The results of this blind study suggested that a fully automated processing and interpretation system can perform sufficiently in an industrial environment.

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REFERENCES
