dimitris.argyropoulos@acdlabs.com ENC 2021 Poster Session 5 Wednesday, March 31st 08:00-09:30 am EDT

Evaluation of the Benefit and Informing Capability of 2D NMR Experiments for Structure Elucidation Using CASE Software

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Introduction

Computer Assisted Structure Elucidation (CASE) has been developed over 50 years ago and it's still going through modifications. Meanwhile, experiments in NMR spectroscopy have evolved significantly offering many options for extracting new information. Here we see how a modern CASE system, ACD/Structure Elucidator, benefits from these type of experiments.

Elucidation of Simple Structures

How much data is really required by a modern CASE system to elucidate a simple structure? A complete set of experiments would include 1D ^{1}H and ^{13}C and 2D HSQC, HMBC and COSY. But not all of these may be available for specific cases. Table 1 shows the results obtained using combinations of these for 2, Ethyl Indanone (Fig. 1).

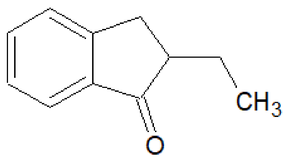

Figure 1: 2-Ethyl Indanone

^{1}H	^{13}C	HSQC	HMBC	COSY	Time	Structures
	X	X			4h 33m 17s	4319
X	X	X			29m 47s	626
		X		X	9m 44s	5354
		X	X		9s	7
X	X	X	X	X	<1s	7

Table 1: Elucidation time and reported non-duplicate structures for combinations of standard NMR experiments for 2-Ethyl Indanone

A modern CASE system can solve this simple structure using a 1D ^{13}C and an HSQC spectrum and without any >1 bond correlation experiments. It can also solve it using an HSQC and a COSY, without any information about quaternary carbons. However, once >1 bond correlation experiments (COSY, HMBC) are added the elucidation time drops dramatically.

Elucidation of Complex Structures

The previous results illustrate the capabilities of a modern CASE system. For complex natural product structures, the elucidation time may be prohibitively large, even with all the standard experiments available. In this case, more advanced experiments, as well as proper adjustment of the options for non-standard correlations, hybridization and connectivity with heteroatoms are required. To explore this, we changed the input to the CASE system for Spirodactylone (Fig. 2), where both HMBC and LR-HSQMBC experiments were available. The results are shown in Table 2.

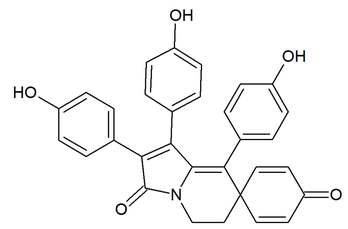

Figure 2: Spirodactylone

HMBC length	COSY	H-O-C	C=O	Hybrid.	LR	Time	Structures
2-3	X		X	sp^2		2h	10
2-3	X	X	X	sp^2		23s	48
2-3		X	X	sp^2		32s	48
2-3	X	X	X	sp^2	4-6	1s	2
2-3	X		X	sp^2	4-5	7m 51s	24
2-3	X	X	X	not sp	4-5	6s	2
2-3	X	X		not sp	4-5	90s	6
2-3	X			not sp	4-6	14h	766
2-4*	X	X	X	sp^2	4-5	9h 3m	2
2-3	X	X	X	sp^2	2-6	17s	18
2-3	X		X	sp^2	2-6	1h 50m	438

Table 2: Effect on elucidation time of Spirodactylone. The HMBC correlations were set to be 2-3 bonds or 2-4 bonds if a peak was present in the LR-HSQMBC. COSY correlations were set to 2-3 bonds. H-O-C, i.e. obligatory connection to heteroatoms and manual definition of carbonyls were set as shown.

INADEQUATE?

The INADEQUATE experiments is considered the holy grail of NMR spectroscopy. But is it really needed? To explore this, we varied the input to the CASE system for the heterodimer structure in Fig. 2. Can the CASE system elucidate the structure without INADEQUATE? The results are shown in Table 3.

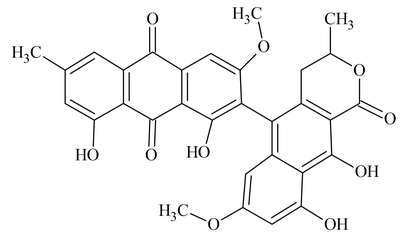

Figure 3: The heterodimer structure studied..

HMBC	INAD.	Hybridiz.	Hetero.	Manual bonds	NSCs	Time	Structures
X		Set	Manual	Yes	4	28m	1
X		Set	Manual	Yes	2-4	49m	1
X	X	Not Set	No	No	Auto	0.3s	1
X	X	Auto	no	No	Auto	0.4s	1

Table 3: Effect on elucidation time of heterodimer structure. The hybridization of the 31 non-sp^3 carbons, obligatory connectivity to a heteroatom, manual carbonyl, ester and hydroxy bonds as well as NSCs were set as shown.

While INADEQUEATE helps with reduce the elucidation time, the correct result can be obtained in a reasonable time with just the HMBC and careful adjustment of other parameters as well as identification of NSCs.

Conclusions

A modern CASE system can work properly, with the chemist allowing solutions to problems without requiring extra, difficult experiments.

References

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