# When does Computer-Assisted Structure Elucidation (CASE) spare you from recording (IN)ADEQUATE?

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## Introduction

The INADEQUATE[1] experiment was first reported in the literature in 1980 and has since been considered the holy grail for determining the C-C connectivity of organic molecules. In 1996, the creation of the 1,1-ADEQUATE[2] experiment and its variants allowed the observation of the C-C bonds through their attached protons.

During the same period, Computer-Assisted Structure Elucidation (CASE) has evolved quite significantly[3-5] allowing scientists to elucidate large and complex structures using 1D and 2D NMR data.

Here, we investigate how relevant experiments like (IN)ADEQUATE truly are, given the existence of powerful tools like CASE.

## Results and Discussion

We analyzed a series of published examples in which (IN)ADEQUATE information was stated as being vitally necessary for unambiguous structure elucidation. We looked to determine whether using HMBC and COSY data within a CASE system could elucidate the structure(s) in a reasonable amount of time without using (IN)ADEQUATE data. We focus mostly on proton deficient and/or challenging carbon skeletons. For all the CASE work, we used ACD/Structure Elucidator v. 2021.2.1. In all cases, if (IN)ADEQUATE data was included, the correct result was obtained in less than 1 sec.

## 1. A Simple Natural Product

First, we look at a natural product[6] with a large "silent" fragment and molecular formula (MF) $C_{22}H_{28}O_5$. Even though this is not a proton deficient structure, it has an interesting fused ring system. The investigators had recorded an ADEQUATE over 48 hours on a 700 MHz NMR spectrometer. A CASE system solved the structure in 35 sec, using an HSQC and an HMBC spectrum. (Figure 1)

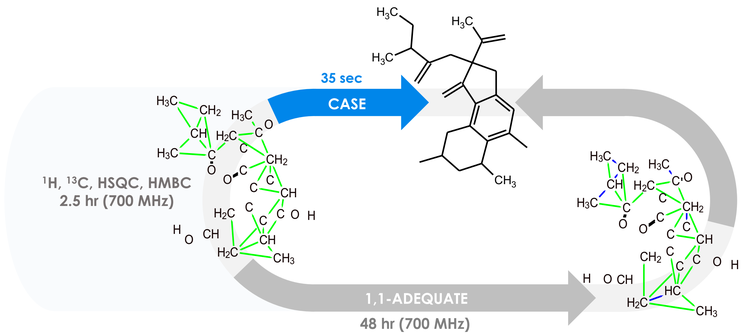


*Figure 1: Comparison of the structural information and experimental/elucidation times for the natural product. Green lines indicate HMBC and blue lines represent ADEQUATE correlations.*

## 2. Penicillactone A

The second example is a more complex natural product[7] with many NMR-invisible oxygen atoms and an MF of $C_{25}H_{32}O_{10}$. The authors had to record an INADEQUATE over a couple of days on an 800 MHz system. A CASE system solved the structure in 8 min 53 sec using an HSQC, and HMBC, and a COSY.

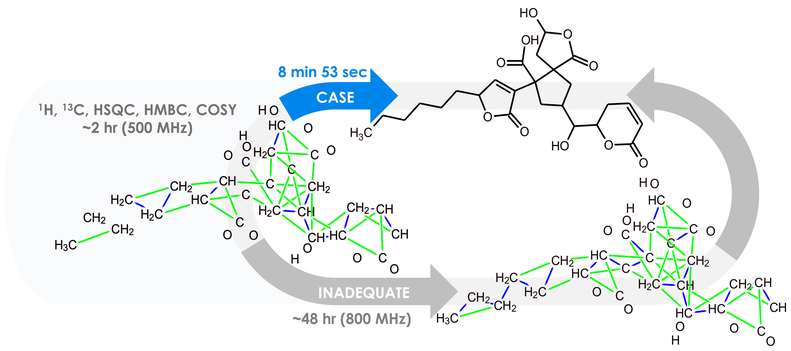


*Figure 2: Comparison of the structural information and experimental/elucidation times for Penicillactone A. Green lines indicate HMBC and blue lines represent ADEQUATE correlations.*

## 3. A Synthetic Heterocycle

The third example is a hydrogen-deficient heterocyclic compound[8] with an MF of $C_{15}H_{10}N_4O$. Moreover, there are many possible tautomers. An INADEQUATE was recorded over 28 hours. The CASE system solved the structure in 35 min 11 sec using H-C and H-N HSQC and HMBC spectra, as well as a COSY.

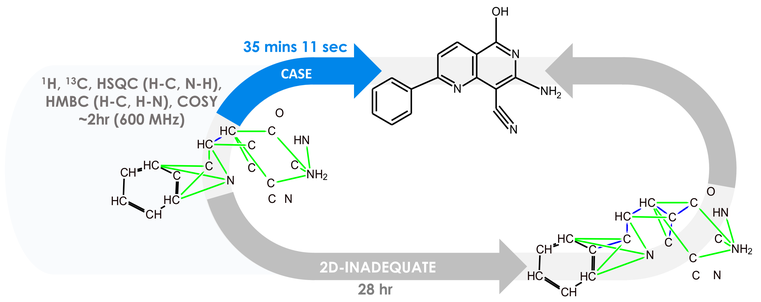


*Figure 3: Comparison of the structural information and experimental/elucidation times for the synthetic heterocycle. Green lines indicate HMBC and blue lines represent ADEQUATE correlations.*

## 4. A Large Natural Product

This is a very large proton deficient natural product[9] with an MF $C_{31}H_{24}O_{10}$. An INADEQUATE on a 950 MHz was recorded over a period of 3 days and 7 hours. A CASE system could solve it in 2h 11 min using only HSQC and HMBC data.

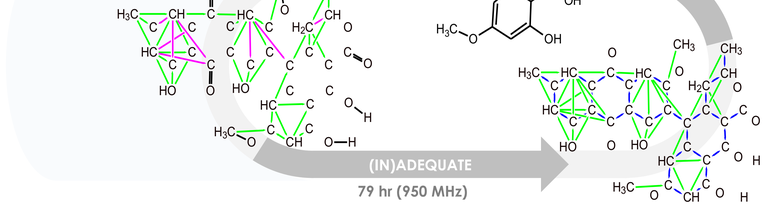


*Figure 4. Comparison of the structural information and experimental/elucidation times for the large natural product. Green lines indicate 2-3 bond HMBC, magenta lines 4 bond HMBC, and blue lines INADEQUATE correlations. Only 1 C-C bond was not visible in INADEQUATE.*

## Conclusions

A modern CASE system can elucidate proton deficient structures in quite a few examples without the need for an (IN)ADEQUATE spectrum. It will never substitute these experiments, but it is something to try before endeavoring in recording them, or right after you started to do so.

## References

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