Computer-Assisted Structure Elucidation of Two Isomeric, Highly Symmetrical Helical Molecules

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Introduction

Computer-Assisted Structure Elucidation (CASE) applications are widely used today to characterize chemical structures from both natural and synthetic products. In the past decade, multiple reviews have been published to illustrate that ACD/Structure Elucidator Suite [1-4] is capable of identifying the chemical structure of very complex molecules with the aid of NMR and MS information.

The development of Structure Elucidator Suite is derived primarily by continuously challenging the application with new structural problems. With this study we intend to investigate the performance of the software for the structural elucidation of two highly symmetrical, hydrogen-deficient helical molecules.

Results and Discussion

The two compounds were synthesized by Rh(I)-catalysed cycloisomerisation of a triyne substrate as shown in Figure 1.

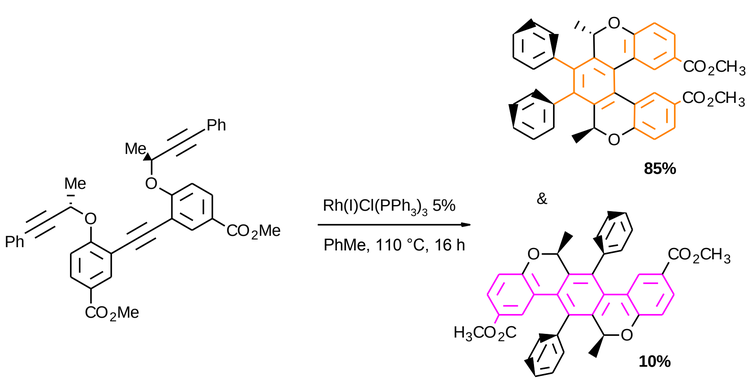

Figure 1: Reaction scheme for the synthesis of the two isomers in question.

Both isomers are derived from the reaction in Figure 1, and these were subsequently separated by preparative scale liquid chromatography. Approximately 10 mg of each isomer was dissolved with deuterated chloroform and placed in an NMR tube in order to record NMR spectra.

A 1D ^{1}H NMR spectrum, 1D ^{13}C, ^{1}H-{^{13}C} HSQC, ^{1}H-{^{13}C} HMBC and a ^{1}H-DQF-COSY were recorded for each compound, at a minimum. The spectra showed exactly half the number of peaks for a compound with a molecular formula of $C_{38}H_{30}O_6$, i.e., only 19 signals were observed in the ^{13}C spectrum, confirming the symmetry of the structure.

Moreover, the very close spacing of several of the ^{13}C peaks, the relatively poor H content of the molecule, along with some mild overlap of the (few) ^{1}H signals, presented a new challenge in the accurate assignment of the observed peaks. In order to resolve the ambiguities caused by these band-selective versions of the ^{1}H-{^{13}C} HSQC and ^{1}H-{^{13}C} HMBC, experiments were recorded limiting the ^{13}C observation to the region between 110-145 ppm (Figure 2). In addition, two ^{1}H-{^{13}C} HMBC spectra were recorded each time, one optimized for a ^{1}H-^{13}C long range coupling constant of 8 Hz and the other for 5 Hz. The ambiguities resulting from the overlap in the ^{1}H spectra were resolved by the ^{1}H-DQF-COSY experiments. The 1D and 2D NMR data used for the elucidation are presented in Table 1.

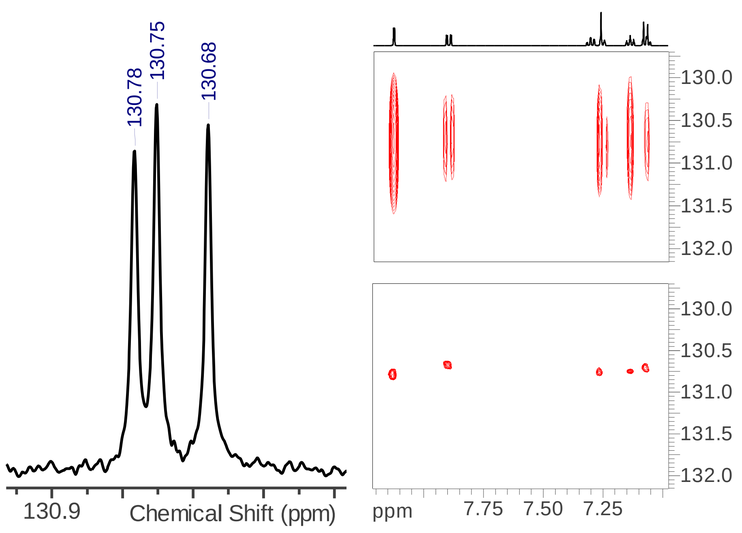

Figure 2: Expansion of 1D-^{13}C (left), normal ^{1}H-{^{13}C} HMBC (top right) and band-selective ^{1}H-{^{13}C} HMBC (bottom right) spectra of the first isomer.

Table 1: 1D and 2D NMR data used for the structure elucidation.

^{13}C label	δ_C (ppm)	Type	^{1}H label	δ_H (ppm)	HMBC	COSY
1	18.52	CH_3	1	0.99	C-3, 17	H-3
2	51.65	CH_3	2	3.70	C-6, 19	
3	73.39	CH	3	5.33	C-1, 7, 16, 17, 18	H-1
4	119.21	CH	4	7.07	C-16	H-5
5	122.19	C				
6	122.95	C				
7	124.70	C				
8	126.91	CH	5	7.13	C-8, 9, 15	H-4, 7
9	127.84	CH	7	7.30	C-10, 11, 13	H-5, 9
10	127.91	CH	6	7.06	C-5, 6, 7, 12, 18	H-10
11	129.10	CH	8	7.25	C-8, 13, 18, 19	H-9
12	130.67	CH	9	8.12	C-10, 15	H-7, 8
13	130.75	CH	11	6.78	C-7, 14	
14	130.78	CH	10	7.89	C-12, 18, 19	H-6
15	137.37	C				
16	137.53	C				
17	138.46	C				
18	157.67	C				
19	166.40	C				

Two approaches were used in order to deal with the symmetry problem. In the first approach, each signal was deliberately set to correspond to two atoms and the molecular formula set to the complete one of $C_{38}H_{30}O_6$. In the second approach each signal was set to correspond to one atom, and one additional C and three Br atoms were added to compensate for the problem of symmetry. The molecular formula used in the second case was $C_{19}H_{15}O_3Br_3$. The resulting Molecular Connectivity Diagrams (MCD) for the two approaches are shown in Figures 3 and 4 respectively.

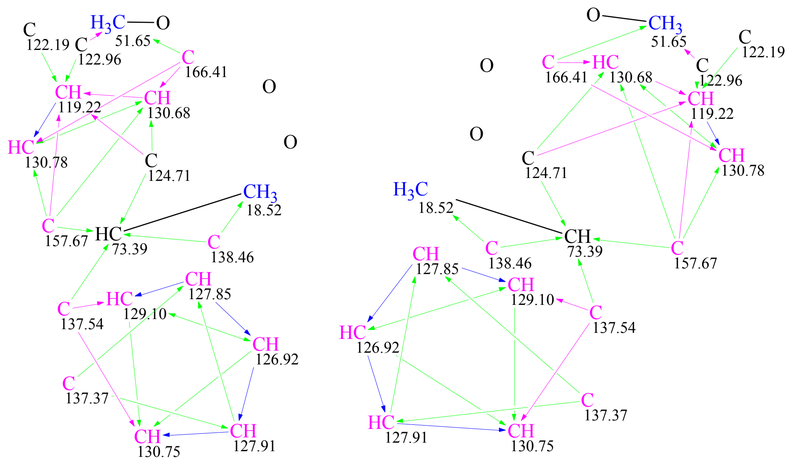

Figure 3: The Molecular Connectivity Diagram (MCD) of the first isomer, using the first elucidation approach. The ^{13}C chemical shifts are shown below the corresponding atoms. Black is a single bond and blue is 1, green is 1-2, and purple is 1-3 bond connectivity.

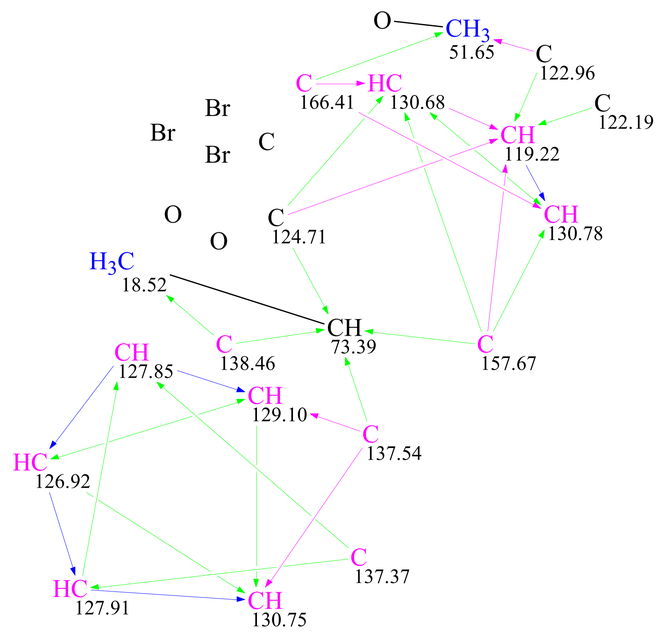

Figure 4: MCD of the first isomer using the second elucidation approach. Details as in Figure 3.

The elucidation with the first approach took ca. 12 hours for the first isomer, and produced ca. 3000 structures. The top 3 are shown in Figure 5 (structures 1a, 2a, and 3a), and ranked according to the lowest difference of predicted and observed ^{13}C chemical shifts. Interestingly the mono-substituted aromatic ring shows 5 distinct signals instead of the normally expected 3, clearly a result of the restricted rotation. The elucidation of the second structure with the first approach took ca. 15 seconds after manually defining the mono-substituted aromatic ring in the MCD.

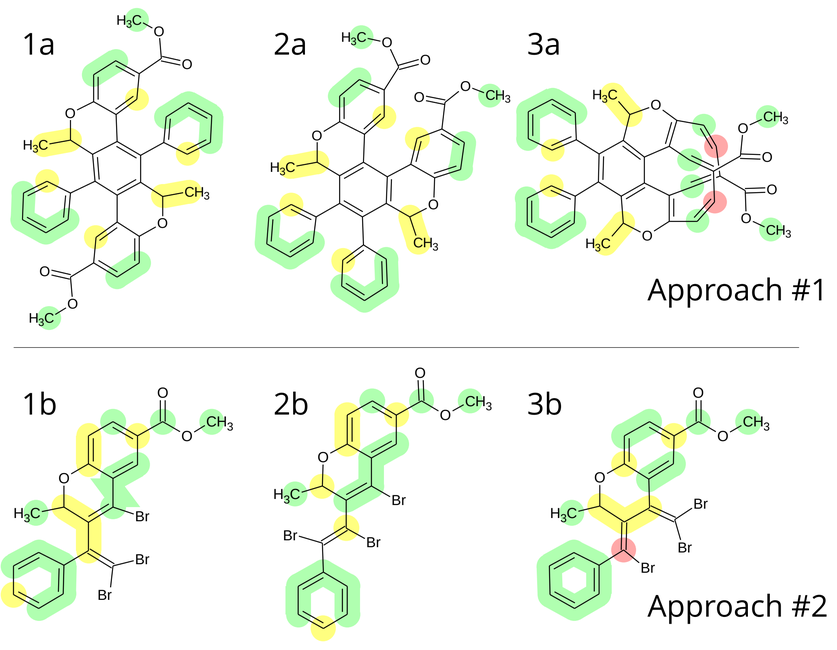

Figure 5: The top 3 structures predicted with the first approach (top row) and second approach (bottom row) for the first isomer, ranked in descending order by ^{13}C chemical shift deviations. The colouring indicates the quality of the match between the predicted and experimental ^{13}C chemical shifts, green indicating a deviation of less than 3 ppm, yellow less than 15 ppm and red more than 15 ppm. The mean ^{13}C chemical shift deviation for the first two structures on the top row is 1.475 and 1.583 ppm respectively, and it jumps to 2.454 for the third. The final structure for the second approach is derived when the extra C and Br are removed and the fragment is duplicated.

The elucidation of the first structure with the second approach took ca. 6 minutes and produced ca. 800 structures. The best three are shown at the bottom of Figure 5 (structures 1b, 2b, and 3b). The final structure can be obtained by removing the extra C and Br atoms and manually closing the aromatic ring.

The final issue that needs to be resolved is the unambiguous assignment of each structure to a sample. This is not possible to achieve with standard structure elucidation NMR experiments, as the structural differences between the two isomers are further away from what experiments like HMBC can show (maximum 5 bonds under very favourable conditions). The solution to this is given by recording a ^{1}H-^{1}H NOESY spectrum for the two isomers.

An expansion of the NOESY experiment for the second isomer is shown in Figure 6. It can clearly be seen that the methyl protons of the acetyl group (3.70 ppm) correlate not only to the aromatic ring on which the acetyl group is attached, but also to the other mono-substituted aromatic ring (broad peaks due to restricted rotation). Correlations to the mono-substituted ring are absent for the first isomer. This clarifies that the first isomer has a plane of symmetry perpendicular to the aromatic ring in the centre (structure **2a** in Figure 5) while the second isomer has a C_2 symmetry axis passing through the centre of the middle aromatic ring (structure **1a** in Figure 5).

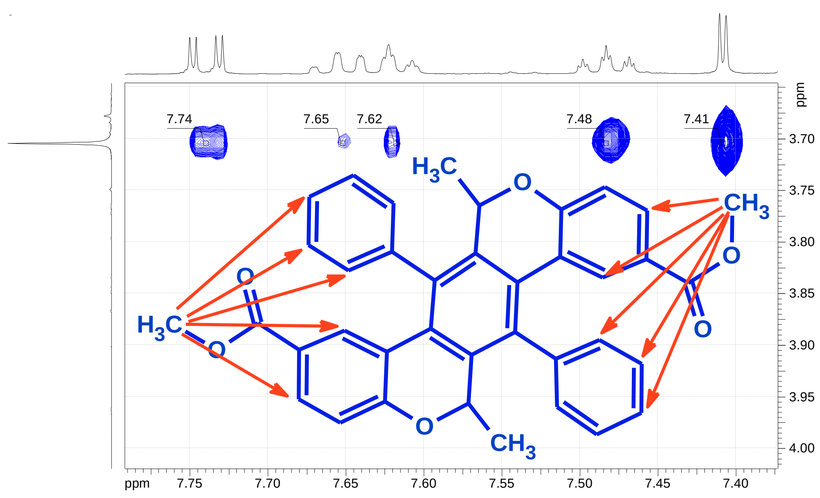

Figure 5: Expansion of the NOESY spectrum of the second isomer around the region of the acetyl methyl signal at 3.70 ppm. The correlations to both the aromatic rings are visible.

Conclusions

The structure elucidation of complex symmetric molecules is possible using CASE methods, but sometimes the strategy used should be optimized for the problem. It is very important to have high quality, well-resolved 2D NMR spectra that will help avoid ambiguous assignments and extended calculation time. For this reason the now routine 2D band-selective experiments are a very powerful tool. The ability to solve such complex, proton deficient structures using only NMR methods can be a very valuable option in cases where single crystal X-ray diffraction may not be applicable.

References

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