Chemical Reaction Feedstock Troubleshooting with Benchtop NMR

Benchtop NMR has many advantages over similar analytical techniques due to its high degree of chemical specificity, especially when combining information from multiple chemical nuclei. Minimal or no sample preparation and quick data generation allows the deployment of benchtop NMR in QA/QC environments without the need for operation by R&D scientists. This saves significant time and money. One example is in the quality control of reaction feedstocks which are the raw chemical materials required to supply large-scale chemical manufacturing processes.

To confirm that lab technicians in a QA/QC environment as well as organic, polymer and pharmaceutical chemists can identify good or bad feedstock from a single, quick measurement, our applications team investigated a specific industrial use case. A manufacturer of fluorochemical products sent us two samples from different suppliers. Both samples were reported to be the same reaction feedstock compound. One of the samples worked as a reaction feedstock but the second one did not. Could the samples be efficiently screened to identify the ineffective failed chemical? Importantly, was this failure due to degradation of the material, contamination, or was there another explanation?

One advantage of multi-nuclei broadband benchtop NMR is that a straightforward pass/fail or fingerprinting method can be often developed selecting a nucleus that gives very simple spectrum. The compound in question was 2,3-Dichloro-1,1,1-trifluoropropane, a relatively simple molecule that generates a surprisingly complex 1H NMR spectrum given that it has only three hydrogen atoms. The proton spectra for both the known and unknown samples are shown in figure 1, along with the molecular structure.

The complex splitting pattern makes very rapid analysis potentially challenging to the untrained eye. Although there are some clear similarities between the samples, such as the two main groups of peaks, there are also some obvious differences, such as the splitting patterns and the chemical shifts. As there are few minor peaks and the major peaks are quite different, this initial result immediately suggested that we had two different molecules rather than contamination. To verify this result and to see if other methods might quickly provide additional information, we decided to further characterise the molecules.
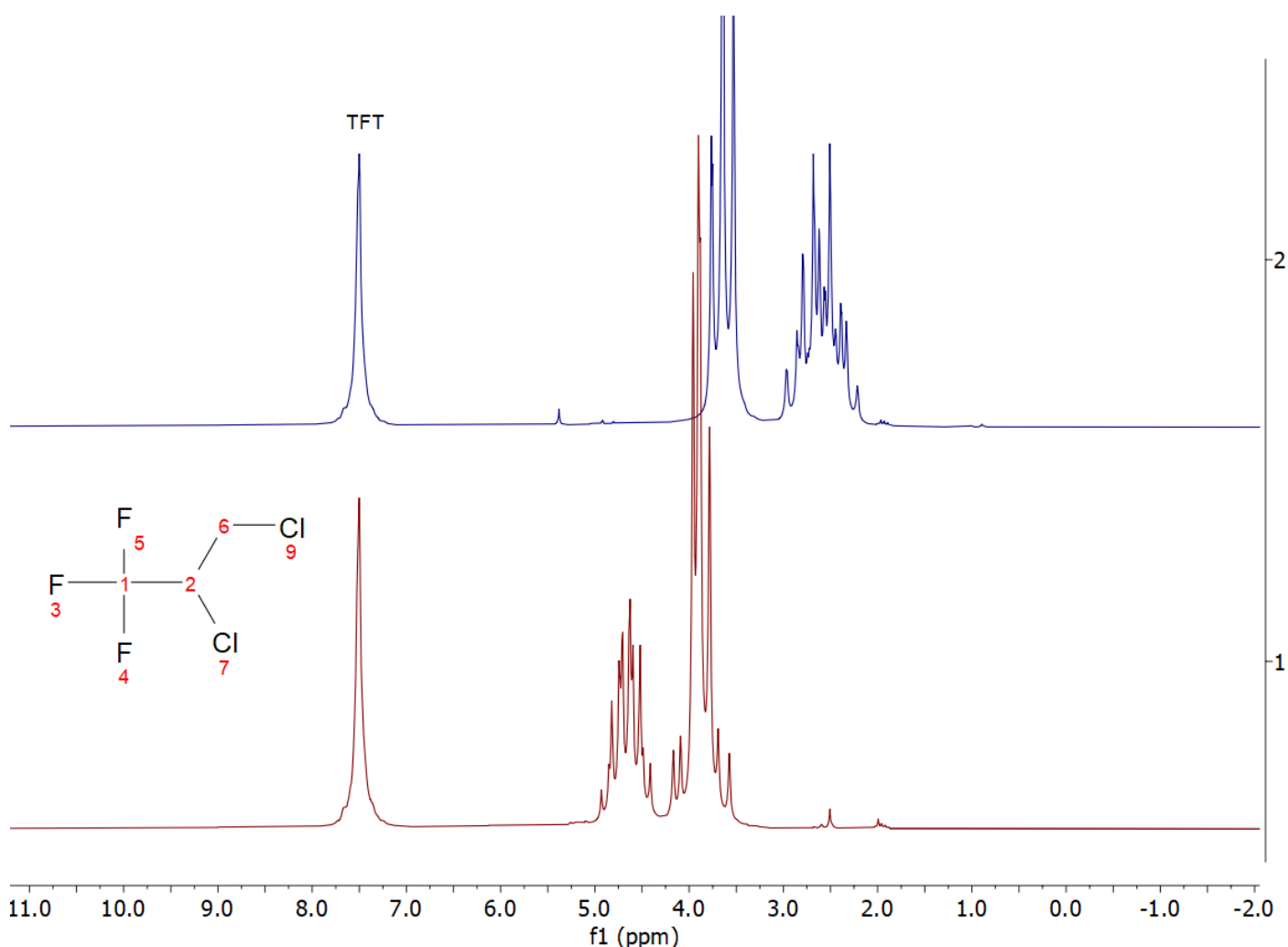

Figure 1: ¹H 1D NMR spectra of 2,3-Dichloro-1,1,1-trifluoropropane (bottom, red) and the unknown sample (top, blue).

Next, we looked at the ^{13}C spectrum of the molecule so that we could better understand any potential structural difference between the two samples. As can be seen from figure 2, using ^1H-decoupled ^{13}C 1D NMR spectra allows easy identification of structural differences. Without decoupling, a single ^{13}C peak would be split into multiple peaks by neighbouring ^1H nuclei, as well as by ^{19}F nuclei. For these nuclei, the general rule is that n equivalent neighbours will split a signal into n + 1 peaks. In other words, if a ^{13}C nucleus has 3 nearby ^{19}F neighbours, it will be split by them into a quartet. This effect generally becomes less pronounced as the nuclei become more distant from each other on the molecular chain. This splitting can provide useful information but can also make spectra more complex and difficult to interpret. To obtain the information we need without unnecessary complexity, we can use decoupling, which removes this connection. By decoupling on ^1H, only splitting due to ^{19}F is seen in the ^{13}C spectrum.

Comparing the unknown molecule with known assignments from the 2,3-Dichloro-1,1,1-trifluoropropane, we see that the CF_3 quartet centred near 125 ppm is essentially unchanged between the two molecules, but there is a significant upfield (towards the right) shift of the other quartet from the sample, suggesting a change in the chemical environment strongly affecting that carbon. Again, there are significant differences but also similarities; in this case both molecules have two quartets, indicating two carbon atoms coupled to three ^{19}F atoms each, one apparently a single-bond coupling (as in a CF_3 group), and one more consistent with a two-bond coupling (as would be seen on a carbon neighbouring a CF_3 group). They also each have one singlet carbon peak, suggesting very similar structures. The singlet shows some difference in chemical shift from that of 2,3-Dichloro-1,1,1-trifluoropropane, but not as much as the upfield-shifted quartet. While the ^{13}C spectrum is very useful to gain information about the overall structure, it is impractical for a rapid yes/no test due to the low sensitivity of ^{13}C, which requires relatively long data acquisition times.
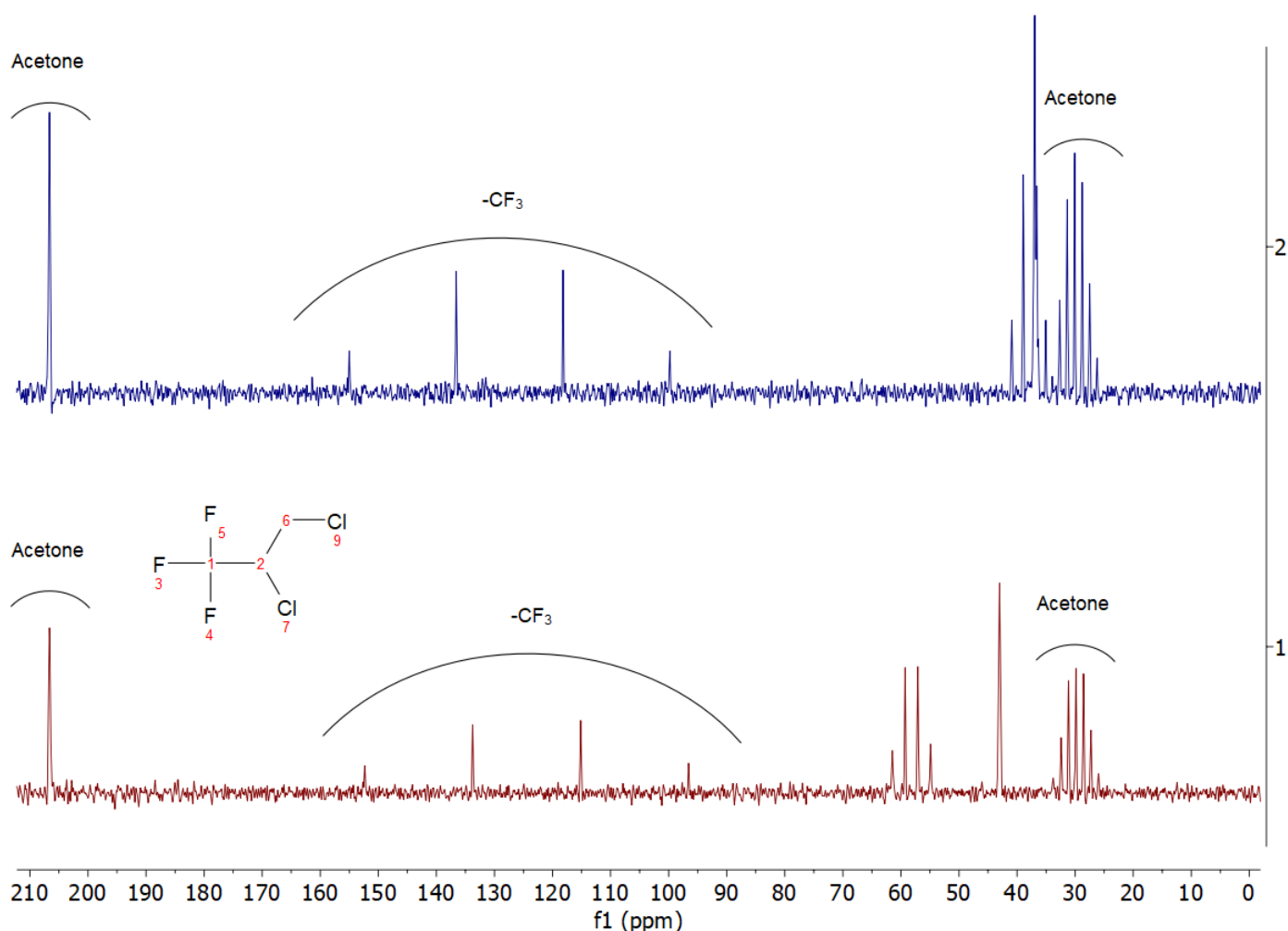

Figure 2: ^{13}C 1D NMR spectra of 2,3-Dichloro-1,1,1-trifluoropropane (bottom, red) and the unknown sample (top, blue).
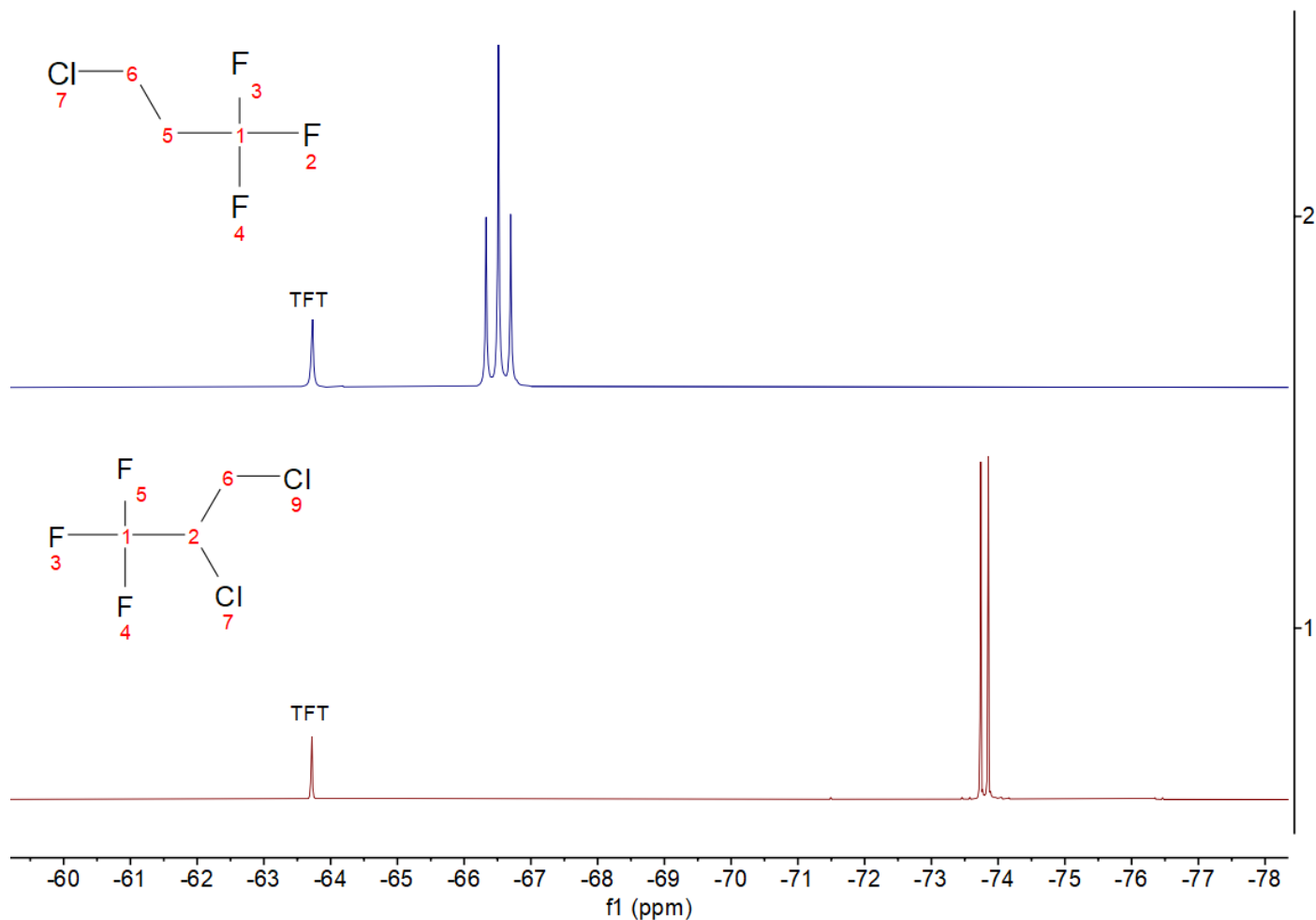
Figure 3: ^{19}F 1D NMR spectra of 2,3-Dichloro-1,1,1-trifluoropropane (bottom, red) and the unknown sample (top, blue), now assigned as 3-Chloro-1,1,1-trifluoropropane.

Since the molecule is fluorinated, we also acquired ^{19}F NMR data.

In figure 3, we see the fluorine spectra for each molecule. Immediately the differences are clear! We have significant chemical shift, and we have a triplet instead of a doublet. This suggests an obvious change in in the molecular structure; in the unknown sample, the CF_3 is now neighboured by a CH_2 rather than a CH.

Taken together, these spectra allow us to complete the picture of the structural differences between the molecules. The ^1H spectra are consistent with a similar overall structure. From the ^{13}C spectra, we know that the CF_3 group is still present and that the neighbouring carbon (-CHCl- group) has had a much greater change in electronic environment than the other two carbons. From this evidence, as well as published NMR data of the respective molecules, we concluded that instead of 2,3-Dichloro-1,1,1-trifluoropropane, the unknown sample was actually 3-Chloro-1,1,1-trifluoropropane, a chemical also used in reaction feedstocks, which had been mislabelled.

More importantly, because the key question is whether the compound could be screened by a technician with a single measurement, the answer is clearly yes. Because the full structural determination is not necessary to screen a compound, either the ^{1}H or the ^{19}F spectra alone would provide the answer. In particular, the differences in the ^{19}F spectrum were clear and extremely obvious, giving us an effective yes/no test for a user with no NMR background. More importantly, because both ^{1}H and ^{19}F are extremely sensitive in NMR, a measurement time of less than a minute could be used, giving us the perfect rapid analysis to ensure quality and consistency of feedstocks. Using benchtop NMR at the point where the feedstock is received, or where the feedstock is added to the reactor will save hours of reaction time and substantial cost of product.

If you have any questions about this application note, please contact our experts:
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