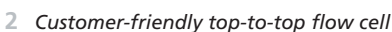


1 Flow cell installed in benchtop NMR spectrometer



2 Customer-friendly top-to-top flow cell



3 Bottom-to-top flow cell for long-term installation inside the NMR spectrometer

NMR ON-LINE ANALYSIS FOR CONTINUOUS CHEMICAL PROCESSES

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Advancing analysis of fluorine fine chemicals

The use of Nuclear Magnetic Resonance (NMR) Spectroscopy for on-line industrial process monitoring has not been well established, largely owing to the steric and economic realities of current high-field NMR spectrometer technology. The recent development of benchtop NMR spectrometers has offered an interesting alternative, which enables developing reliable continuous flow analytical methods, and incorporating this technique into improving chemical processes. Especially an analysis method for fluorine (^{19}F) as non-standard NMR-active nucleus would be very useful for industrial applications since fluorine and fluorine-containing groups have become „must-have“ functional ingredients in modern synthetic organic chemistry. This status is indeed justified when looking on fluorine’s exquisite and unique properties as part of an active pharmaceutical ingredient.

In consequence, many of today’s Life Science products contain fluorinated groups for increasing the biological activity of pharmaceutical drugs. This desired high activity of the fine chemicals justifies a high level of safety standards during both the chemical synthesis and the analysis.

Flow synthesis and on-line NMR analysis

The fine chemical synthesis performed in reactors with small volume allows in combination with NMR spectroscopy as a contactless analysis method safe handling of fine chemicals, resulting in a reduction of the risk potential for the lab technician. This approach has now been realized by combining a versatile continuous flow reaction setup with a compact benchtop NMR system and an electronically regulated liquid control system.

IN COOPERATION WITH

Nanalysis Corp.
Hansa Fine Chemicals GmbH



Benchtop NMR with adjustable flow cells

The recent developments of permanent magnets meanwhile allow the construction of NMR spectrometer without any cost-intensive helium-based cooling system. Such very compact NMR spectrometer can now be used as powerful analysis tool directly at the point of synthesis, in other words in every lab fume hood. Beside the use of standard NMR tubes for conventional off-line analysis of chemical compounds, specially adapted flow-through cells have been developed for allowing NMR analysis of liquid streams from continuous flow reaction setup. The design of the top-to-top flow cell enables both the filling and the release of sample solution from the top of the spectrometer. This customer-friendly design can be used for medium to high concentrated reaction solutions (> 100 mM) and allows the quick exchange of the flow cell. In contrast, the bottom-to-top flow cell is dedicated for long-term application inside the benchtop NMR spectrometer. Its design provides a larger sample volume for quicker measurement and allows in consequence also the analysis of low concentrated sample solutions (>10 mM). Both flow cells are made of PEEK polymer capillaries and NMR-approved glass ware.

Liquid control system

One integral part of the whole analytical setup is the liquid control system. It is installed in-between the continuous flow reaction setup and the flow cells of the benchtop NMR spectrometer. Four electronically controlled magnetic valves are used to route the sample solution either

directly into the flow cells for real on-line NMR monitoring (continuous flow mode). But the liquid control system also allows stopped flow mode, which consists of three steps. At first, the flow cell is filled with sample solution. After that, the valves switch and redirect the incoming reaction solution into a bypass capillary outside the flow cell. Now the sample solution inside the flow can be used for NMR analysis under static conditions. This mode is especially important for process control and development with low concentrated samples. In a last step, the valves switch again for enabling the purging of the flow cells with pure solvent. This last step is especially important as the cleaning and the filling of the flow cell with pure solvent is the base for the shimming procedure of the NMR spectrometer between the analyses of two samples.

Current applications

In order to prove the concept of combining continuous flow synthesis with on-line NMR analysis, a multi-purpose lab plant was developed that allows the synthesis of fluorine containing fine chemicals. The outlet of the lab plant was directly connected to the liquid control system, whose program was also used for physical data read-out (pressure, temperature) and control of the lab plant. Four reactions were successfully performed with this setup: 1) Krapcho decarboxylation for CF_2H group generation, 2) the Ruppert-Prakash reaction for incorporation of a CF_2CF_3 group into an aldehyde, 3) the cyclisation of a diketone with hydrazine, and 4) the oxidation of a thioether with hydrogen peroxide. For the two last reactions, CF_3

groups were only used as probes for ^{19}F -NMR spectroscopy for reaction control. The attached benchtop NMR spectrometer was a valuable and powerful analytical tool for the process development directly at the point of synthesis.

4 Fully installed lab plant with benchtop NMR spectrometer and liquid control system